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Active Methylene Compounds in Asymmetric Organocatalytic Synthesis of Natural Products and Pharmaceutical Scaffolds

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Abstract: Last decades have witnessed the golden rush of organocatalysis, which opened an effective and efficient way to high yielding, metal free, stereoselective strategies toward the synthesis of a plethora of natural products. The present review provides an overview of the current achievements of those organocatalytic methodologies in which active methylene compounds have been used as key intermediates. Ranging from covalent to non-covalent activation mode, from monofunctional to bifunctional catalysts, recent results suggest a variety of new powerful tools to accomplish the formal and total synthesis of both the simplest and the most complex natural compounds with facile procedures in high yields and excellent stereoselectivities. At the same time, it is clear how the organocatalytic approach might offer an outstanding and impressive answer to unsolved longstanding synthetic challenges. Finally the possible application to industrial protocols and to the preparation of novel potential drugs has been highlighted.

Keywords: Natural products, Organocatalysis, Methylene compounds, Total synthesis, Multi-step synthesis, Stereoselection.

1. INTRODUCTION

"Ein von der Natur organisiertes Erzeugnis ist ein Erzeugnis, in dem alles gegenseitig Mittel und Zweck ist; in ihm gibt es nichts Unnuützes, Zweckloses oder von einem blinden Naturmechanismus Herruührendes". (A natural element is one in which everything is simultaneously a means and an end. It contains nothing useless, pointless, or which is fruit of a blind natural mechanism) [1].

Since the first reports on organocatalyzed processes have appeared in 2000 [2, 3], enormous efforts have been devoted to this field in order to develop original transformations that could be fruitfully employed in recalcitrant synthetic problems. Rapidly, a cornerstone set of new reactions that stands out of such studies have appeared and have been successfully used to excel over unsolved longstanding synthetic challenges. Therefore, new retrosynthetic disconnections have been made possible, providing impressive new opportunities in the synthesis of natural product and active pharmaceutical ingredients. Thanks to the vast organic chemistry processes directly related to the growing impact of organocatalysis, many natural products syntheses have become achievable so far. Indeed, since the first total synthesis of a natural product in which an organocatalyzed step was involved, many other examples have followed and the Fig. (**1**) summarizes the increase in publications containing the words "organocatalysis" and "total synthesis" from 2003-2011 timeframe.

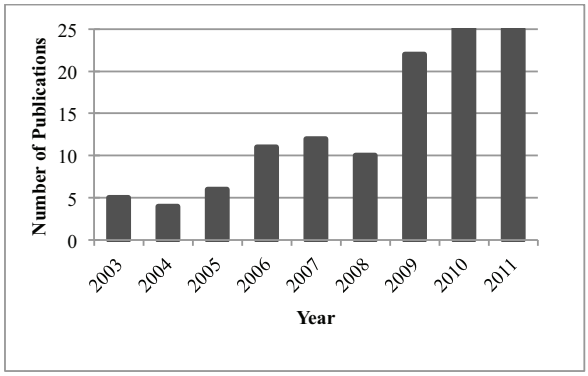

Fig. (1). Publications on organocatalysis and total synthesis (SciFinder®).

Among the major challenges in which chemists are currently involved with, a mention should be made to the synthesis of complex molecular structures *via* highly selective chemical transformations. Indeed, to devise stereoselective and straightforward ways to the preparation of chiral chemical entities remains a field of paramount importance in both academia and industry. By using the advantages of organic molecules-mediated transformations, chemists are inspired by lessons of Nature (where complex biochemical reactions are catalyzed by enzymes) and exploited organocatalysis towards the synthesis of natural products. Thus, organocatalysis has emerged as a new tool in organic chemistry, which, over the years, has been employed alone or, more recently, in combination with transition-metal catalysis for carrying on exceptional reactions. Many advantages are associated with the use of organocatalytic systems: (*i*) generally, the catalysts are less expensive than metal-based ones, they are also more stable and most of them are easily

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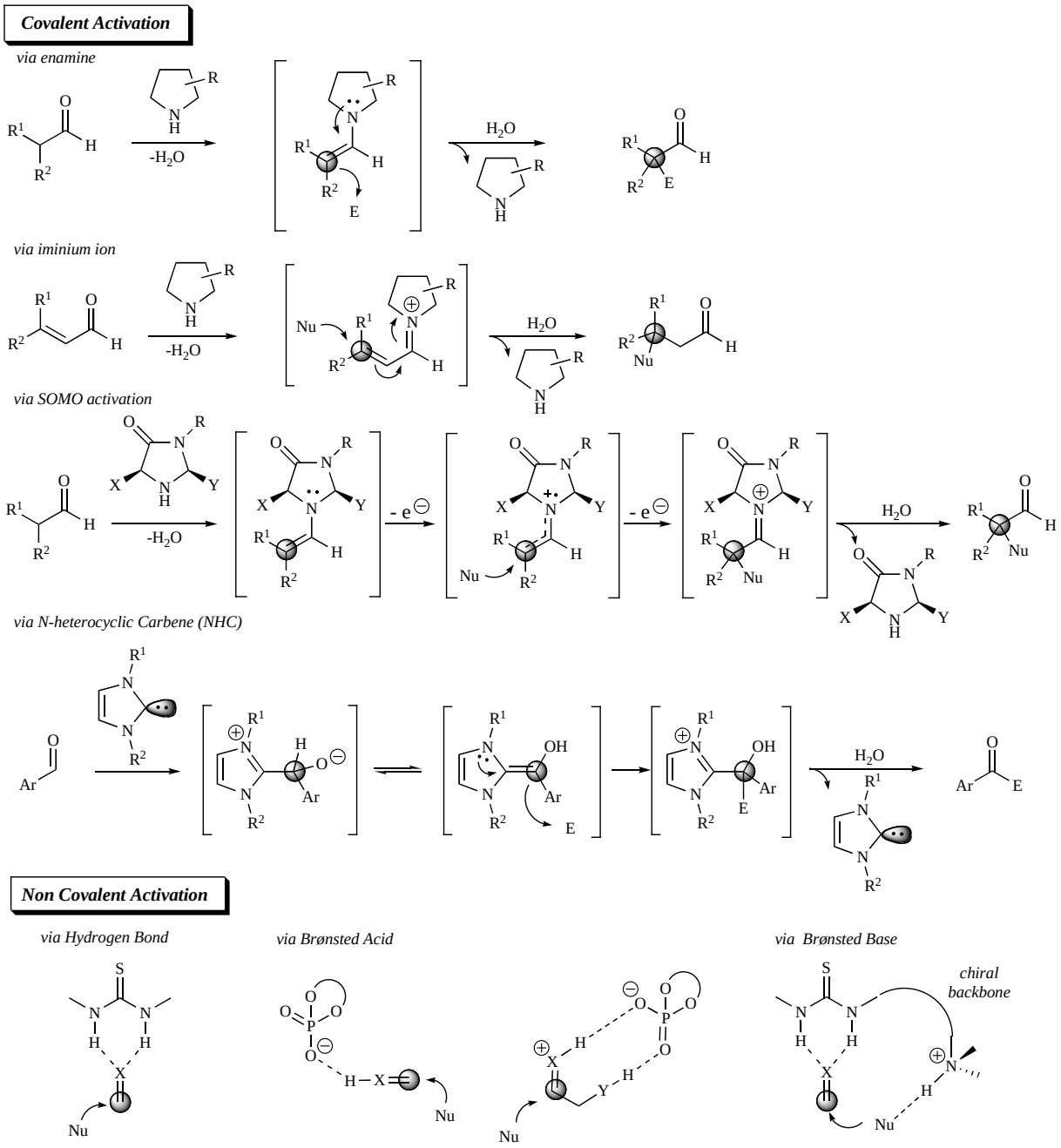
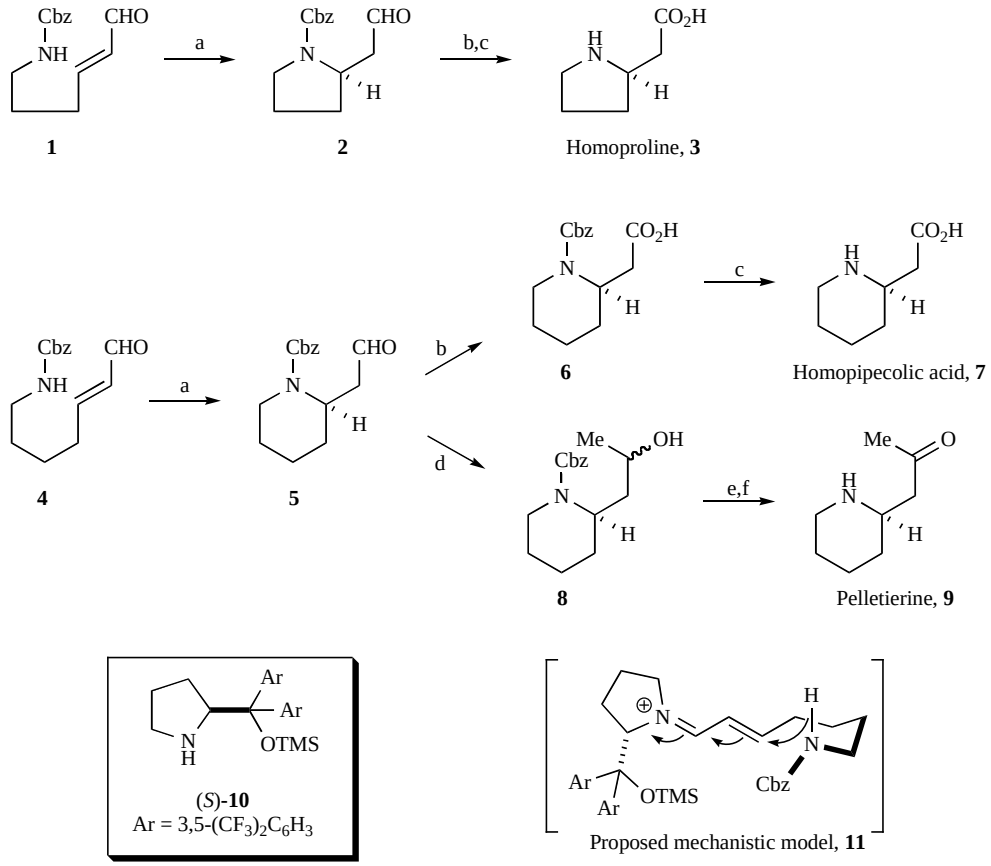


Scheme 1. Selected covalent and non-covalent activation modes.

synthesized, (*ii*) the reactions can be run under standard conditions without the need for inert atmosphere or dry solvents, and most importantly, (*iii*) different activation modes are possible by means of this kind of catalysis (covalent and non-covalent interactions with the substrates). Indeed, one of the biggest attractiveness of organocatalysis relies on the fact that these organic molecules can variously interact with substrates according to the accurate choice of the organocatalyst chemical structure and properties. To date, the main classes of organocatalysts that have been used are imidazolidinones, diarylprolinol ethers, cinchona alkaloids, phosphoric acids, and thiourea derivatives. Basically, these organic molecules activate one of the substrates either (*i*) by the reversible formation of iminiums/enamines (covalent activation) when aldehydes and ketones are employed with secondary or primary amines, or (*ii*) *via* hydrogen-bond formation (non-covalent activation) when chiral catalysts bearing hydrogen-bond donors/acceptors are used. It is noteworthy mentioning that dual and cooperative catalysis (that allows the catalyst to bind to more than one substrate by using different activation modes) and SOMO-organocatalysis have also paved the way to original reactions giving access to novel useful scaffolds, while activation *via* heterocyclic carbenes (NHC) has furnished one of the most elegant expression of *umpolung* concept where the key intermediate species represent an active aldehyde or ketone with an inverted reactivity at the carbonyl carbon. In all cases, the similarity between these different modes of activation relies on a passage through an active methylene compound intermediate as shown in Scheme **1**.

Whereas many excellent reviews appeared on the recent applications of organocatalysis in total synthesis of natural compounds [4-12], the present review updates the employment of those meth-



Scheme 2. Synthesis of pyrrolidine and piperidine ring systems. Reagents and conditions: (a) (*S*)-**10** (20 mol%), MeOH/DCE (1:1), -25 °C, 2-3d (69%, 95% *ee* determined over the alcohol analogue); (b) $NaClO_2$, NaH_2PO_4 buffer, 2-methyl-2-butene, *t*-BuOH, H_2O; (c) H_2, Pd/C, MeOH (54%, 2 steps for homoproline; 75%, 2 steps for homopipecolic acid); (d) MeMgBr, Et_2O/THF, -78 °C to rt; (e) DMP, $NaHCO_3$, CH_2Cl_2 (71%, 2 steps); (f) H_2, Pd/C, EtOAc (99%).

odologies that exploit an organocatalytic activation in which active methylene compounds have been used as key intermediates. We have chosen to divide the very recent literature (from 2009 to April 2012) according to the publication year and far to be comprehensive and exhaustive only a few representative examples by different authors are going to be covered. Finally, we apologize for relative omissions.

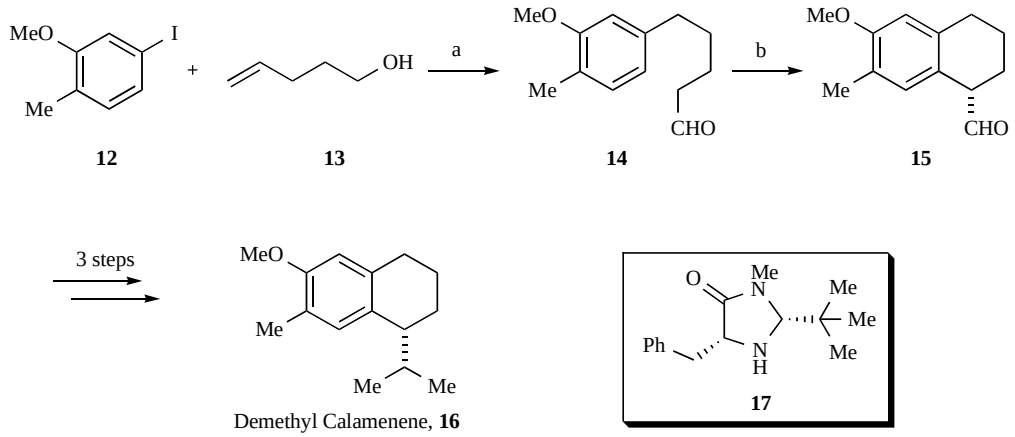
2. 2009

2.1. Homoproline, Pelletierine and Homopipecolic Acid

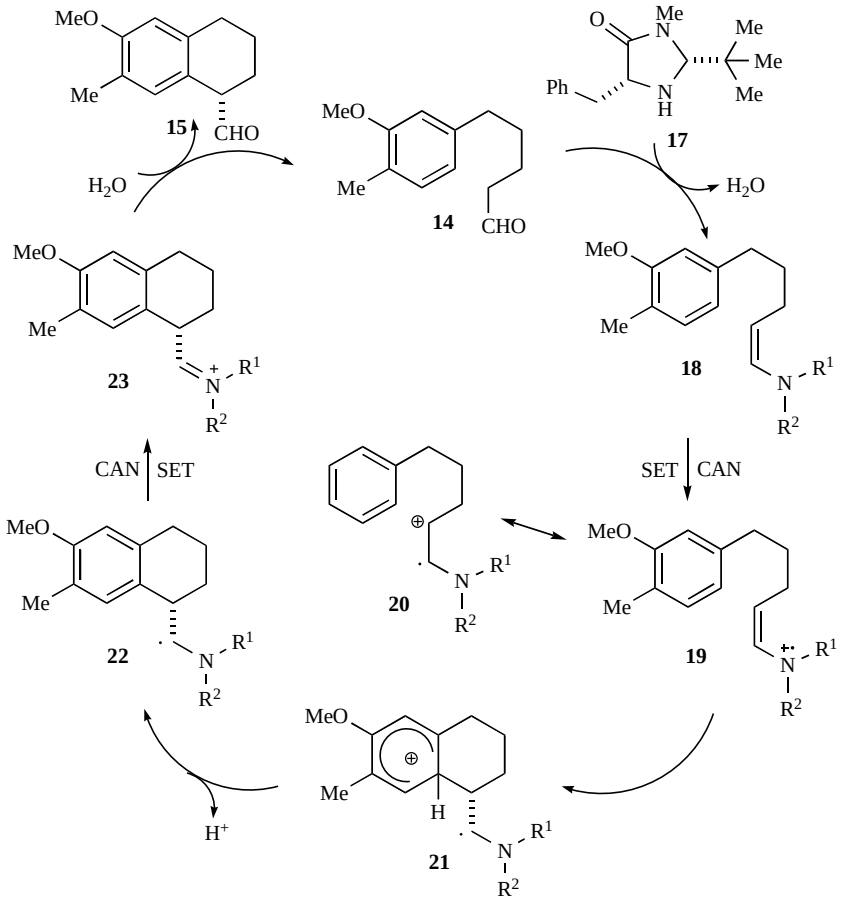
Carter and co-workers have devised a versatile strategy which allows the enantioselective preparation of pyrrolidine, indoline and piperidine ring systems *via* an intramolecular aza-Michael reaction (IMAMR) by using secondary amines as catalyst [13]. They have illustrated the synthetic potential of their methodology with the syntheses of homoproline (**3**), used in medicinal chemistry as well as in organocatalysis, homopipecolic acid (**7**), a cyclic β-amino acid derivative, and pelletierine (**9**), a natural alkaloid found in the bark of the pomegranate. The key organocatalyzed step in the preparation of each heterocycle was the intramolecular conjugate addition of carbamates bearing an α,β-unsaturated aldehyde catalyzed by diaryl prolinol silyl ether (*S*)-**10** (20 mol%), in methanol and 1,2-dichloroethane (1:1) as solvent system at –25 °C at prolonged reaction times (two to four days). The required products were obtained in good yields and selectivities (up to 95% *ee*). It is noteworthy to mention that two years earlier pioneering work on similar organocatalyzed IMAMR was described by Fustero and co-workers [14, 15].

2.2. Demethyl Calamenene

Recently, the organo-SOMO (Singly Occupied Molecular Orbital) catalysis [16, 17] in which enamine catalysis is combined with single-electron transfer (SET) reactions has allowed a great number of novel and unique transformations in the field of the α-functionalization of simple aldehydes (*e.g.* α-allylation, α-enolation, α-vinylation, α-oxyamination, α-arylation). This newly developed concept was, in 2009, successfully used for the synthesis of two natural products so called demethyl calamenene and (–)-tashiromine *via* well-designed strategies. In both cases, intramolecular Friedel-Crafts (F-C) type α-arylations of simple aldehydes incorporating electron-rich aromatic nuclei were the key step. The Nicolaou's group applied this concept during the preparation of demethyl calamenene **16**, a potent cytotoxic agent against human adenocarcinome A 549 [18]. Their sophisticated five-step-strategy started with a Heck reaction between aryl iodide **12** and 4-penten-1-ol **13** that gave rise to aldehyde **14** in 63% yield. Next, reaction of **14** under the previously optimised intramolecular F-C α-arylation [*e.g.* catalyst **17** (20 mol%), CAN (2 eq.), H_2O (2 eq.) in 1,2-dimethoxyethane as solvent at –30 °C] led to bicyclic aldehyde **15** in 56% yield and 90% *ee*. Subsequent one-pot oxidation/esterification of the aldehyde moiety, and sequential Grignard addition/reductive deoxygenation gave the desired demethyl calamenene (**16**) in three further steps (17% overall yield) (Scheme **3**).



Scheme 3. Synthesis of Demethyl Calamenene. Reagents and conditions: (a) $Pd(OAc)_2$ (3 mol%), *n*-Bu_4NCl (2 eq.), $LiOAc{\cdot}2H_2O$ (3 eq.), LiCl (1 eq.), DMF, 25 °C, 72h (63%); (b) **17** (20 mol%), TFA (20 mol%), CAN (2 eq.), H_2O (2 eq.), DME, – 30 °C, 24h (56%, 90% *ee*); (c) NIS (3.1 eq.), K_2CO_3 (3.1 eq.), MeOH (104 eq.), CH_3CN, dark, 25 °C, 24h, (84%).

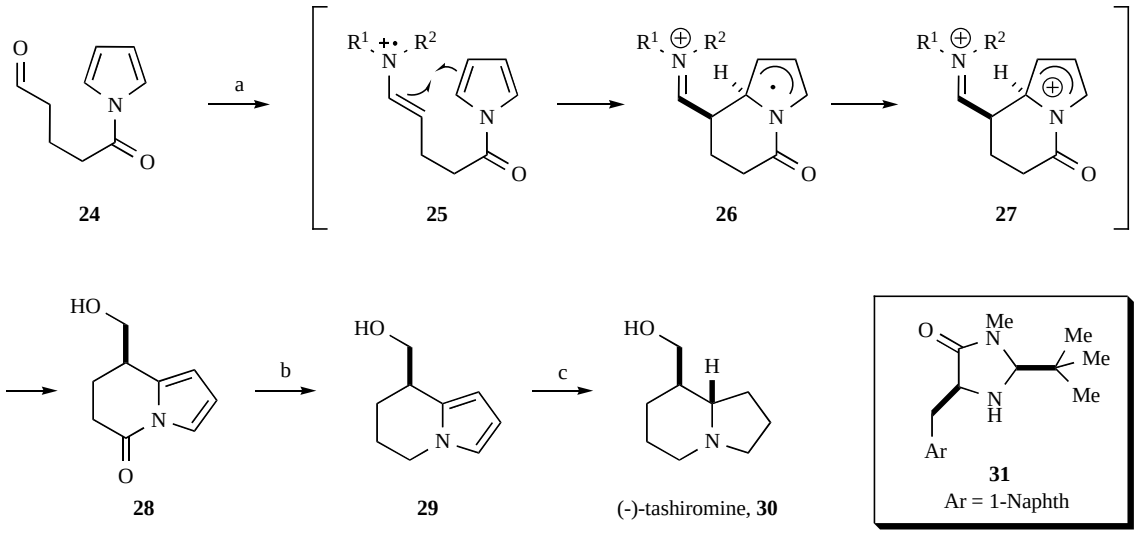


Scheme 4. Proposed catalytic cycle for the synthesis of demethyl calamenene *via* organo-SOMO catalysis.

The proposed mechanism goes through, in a first instance, enamine activation of aldehyde **14** with imidazolidinone **17**. Then, single electron transfer (SET) oxidation mediated by CAN afforded intermediate radical cation **19** (that is in equilibrium with **20**) and rapidly evolves intramolecularly to the more stable Wheland- or σ-complex **21**, a characteristic intermediate in F-C type reactions. Proton elimination followed by a second SET oxidation CAN-mediated gave rise to iminium **23** that over hydrolysis furnished the bicyclic aldehyde **15** and reconstituted the organocatalyst.

2.3. (–)-Tashiromine

Another elegant example of organo-SOMO catalysis in the total synthesis of natural compounds was published by MacMillan and co-workers [19]. Indeed, they have rationalized a highly ortho-selective arylation reaction *via* a radical-mediated addition pathway where exposure of electron-rich aromatics that carry an alkyl-tethered aliphatic aldehyde to imidazolidinone catalysis in the presence of an appropriate oxidant would render the radical-cation **25** formation possible (Scheme **5**). Thus, addition of the aromatic ring system to the 3π-electron species could evolve in to bicyclic radical



Scheme 5. Synthesis of (-)-Tashiromine. Reagents and conditions: (a) **31** (20 mol%), TFA (20 mol%), CAN, $NaHCO_3$, NaO_2CCF_3, -30 °C, acetone then $NaBH_4$ (72%, 93% *ee*); (b) $AlCl_3$, $LiAlH_4$, THF, 0 °C (83%); (c) Rh/Al_2O_3, H_2, 4 atm, MeOH, rt (62%).

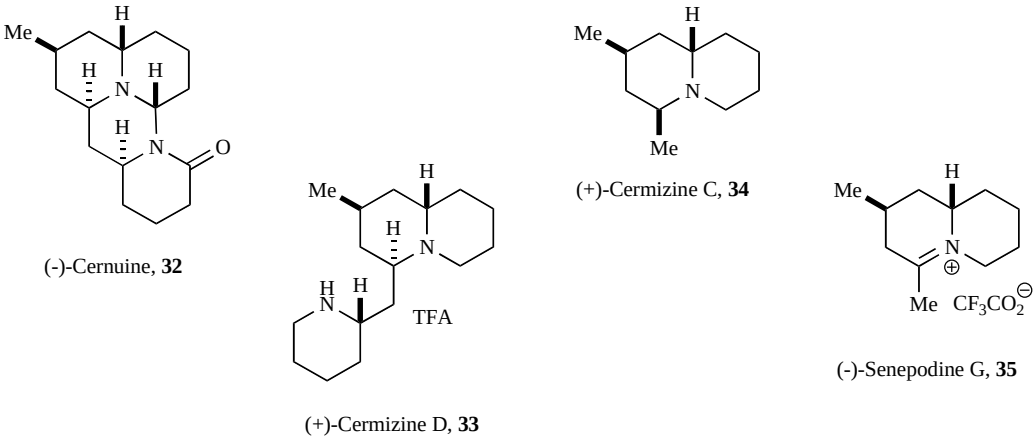


Fig. (2). Examples of cernuane-type *Lycopodium* alkaloids.

cation **26**, that after an additional oxidation step could give rise to the dienyl cation intermediate **27**. At last, the required product could be obtained upon rearomatization *via* proton elimination followed by iminium hydrolysis, and then, set free the organocatalyst. Hence, they were able to apply their novel carbonyl α-arylation strategy in to the three-step total synthesis of (–)-tashiromine (**30**), an indolizidine isolated from the Asian deciduous shrub, *Maackia tashiroi* [20].

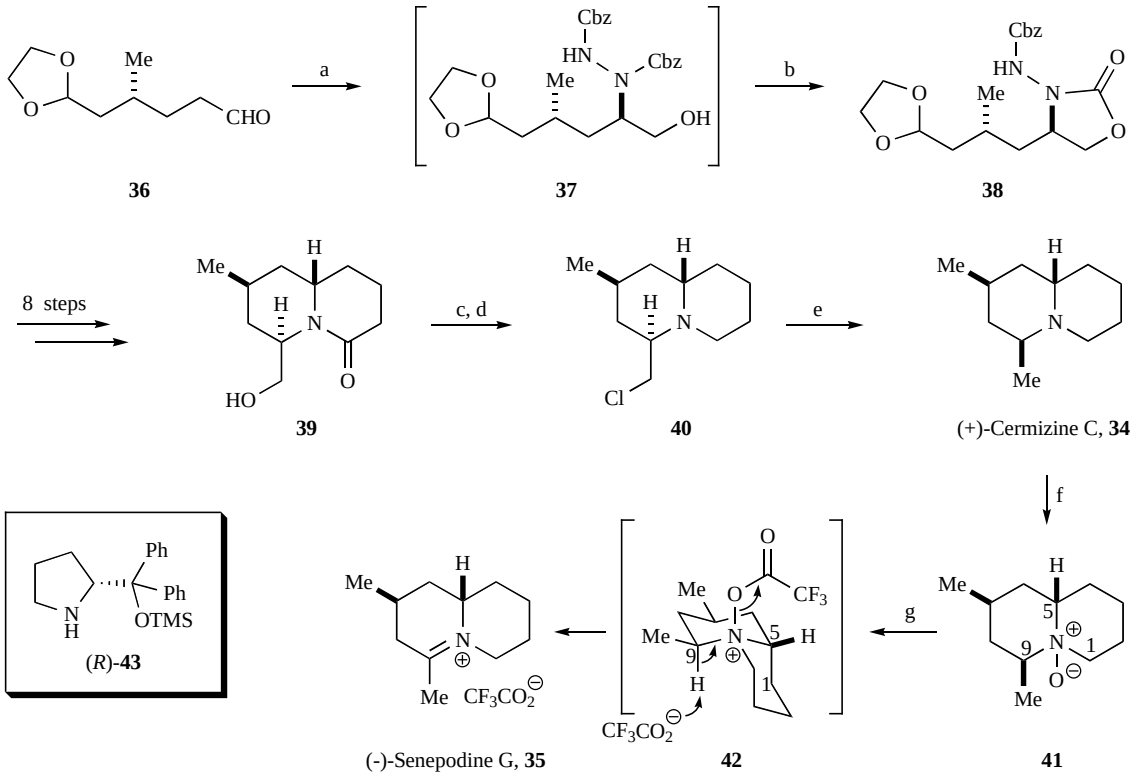
The organocatalyzed step takes place with pyrrole amide tethered aliphatic aldehyde **24** in the presence of catalyst **31** (20 mol%) and CAN as oxidant. The desired bicyclic compound **28** was isolated in good yield (72%) and selectivity (93% *ee*). Reduction of the amide moiety with $AlCl_3/LiAlH_4$ and pyrrole hydrogenation with Rh/Al_2O_3 gave rise to (–)-tashiromine (**30**) in 37% yield over three-steps.

2.4. (+)-Cermizine C and (–)-Senepodine G

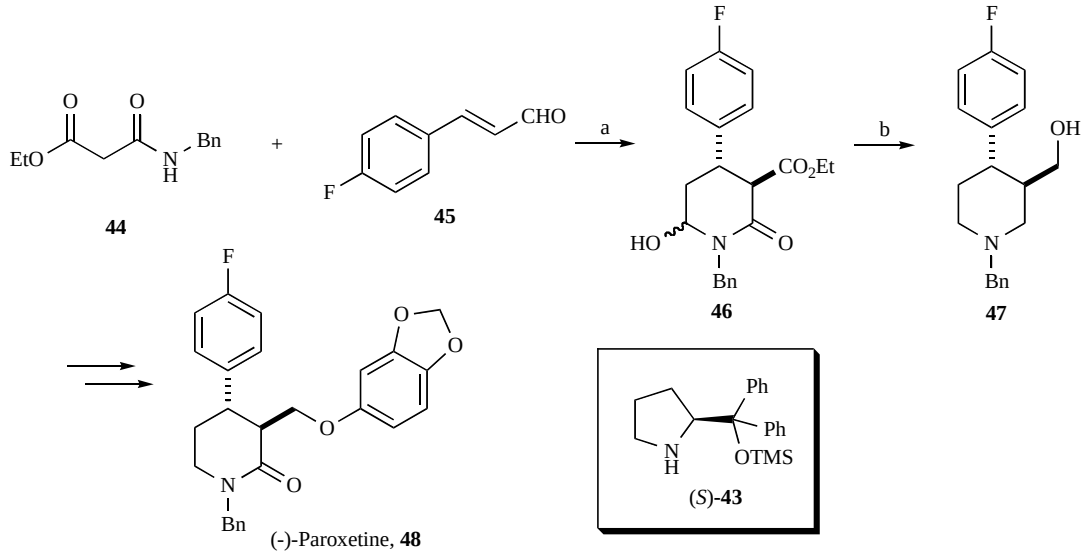
Alkaloids isolated from plants of the genus *Lycopodium* are known for having a broad range of biological activities - as for instance, acetylcholine esterase (AchE) inhibition - in addition of very tricky and varied polycyclic chemical structures [21, 22]. Cernuine (**32**), isolated in 1948 by Marion and Manske [23], is a representative of cernuane-type *Lycopodium* alkaloids. Its complex fused tetracyclic structure bearing an aminal moiety was elucidated only 19 years later by Ayer and co-workers [24, 25]. Several total syntheses of different types of *Lycopodium* alkaloids have been reported, nevertheless none is about that of cernuane-type alkaloids. In 2004, Kobayashi's group reported the isolation of other cernuane-type and quinolizidine-type *Lycopodium* alkaloids from *Lycopodium cernuum*: cermizine D (**33**), cermizine C (**34**) and senepodine G (**35**) [21], among which cermizine D (**33**) and senepodine G (**35**) showed cytotoxicity against murine lymphoma L1210 cells with IC_{50} of 7.5 μg/mL and 7.8 μg/mL respectively (Fig **2**).

In 2008 and 2009 Takayama's group accomplished the first total syntheses of the reported cernuane-type *Lycopodium* alkaloids and then established their chemical structures as well as their absolute configuration [26, 27]. Among the key steps on these syntheses, organocatalyzed α-amination of aldehyde **36**, obtained in 2 steps from commercially available (+)-citronellal, allowed the elaboration of oxazolidinone **38** (Scheme **6**).

The best reaction conditions requested the use of catalyst (*R*)-**43** (10 mol%), dibenzyl azodicarboxylate (1 eq.), in dichloromethane at room temperature followed by *in situ* reduction with $NaBH_4$ giving rise to intermediate **37**. Oxazolidinone **38** was isolated after stirring of **37** in the presence of K_2CO_3 under toluene reflux in 94% yield and 84% *ee*. Further 8 steps led to the formation of the key



Scheme 6. Syntheses of (+)-Cermizine C and (-)-Senepodine G. Reagents and conditions: (a) (*R*)-**43** (10 mol%), CbzN=NCbz, CH_2Cl_2, rt, 30 min, then $NaBH_4$ in MeOH; (b) K_2CO_3, reflux (2 steps, 94%, 84 % *ee*); (c) BH_3·THF, THF, reflux; (d) $SOCl_2$, $CHCl_3$, reflux; (e) $LiAlH_4$, THF, reflux (52%, 3 steps); (f) *m*CPBA, CH_2Cl_2, 0 °C (89%); (g) TFAA, CH_2Cl_2, 0 °C (quant.).

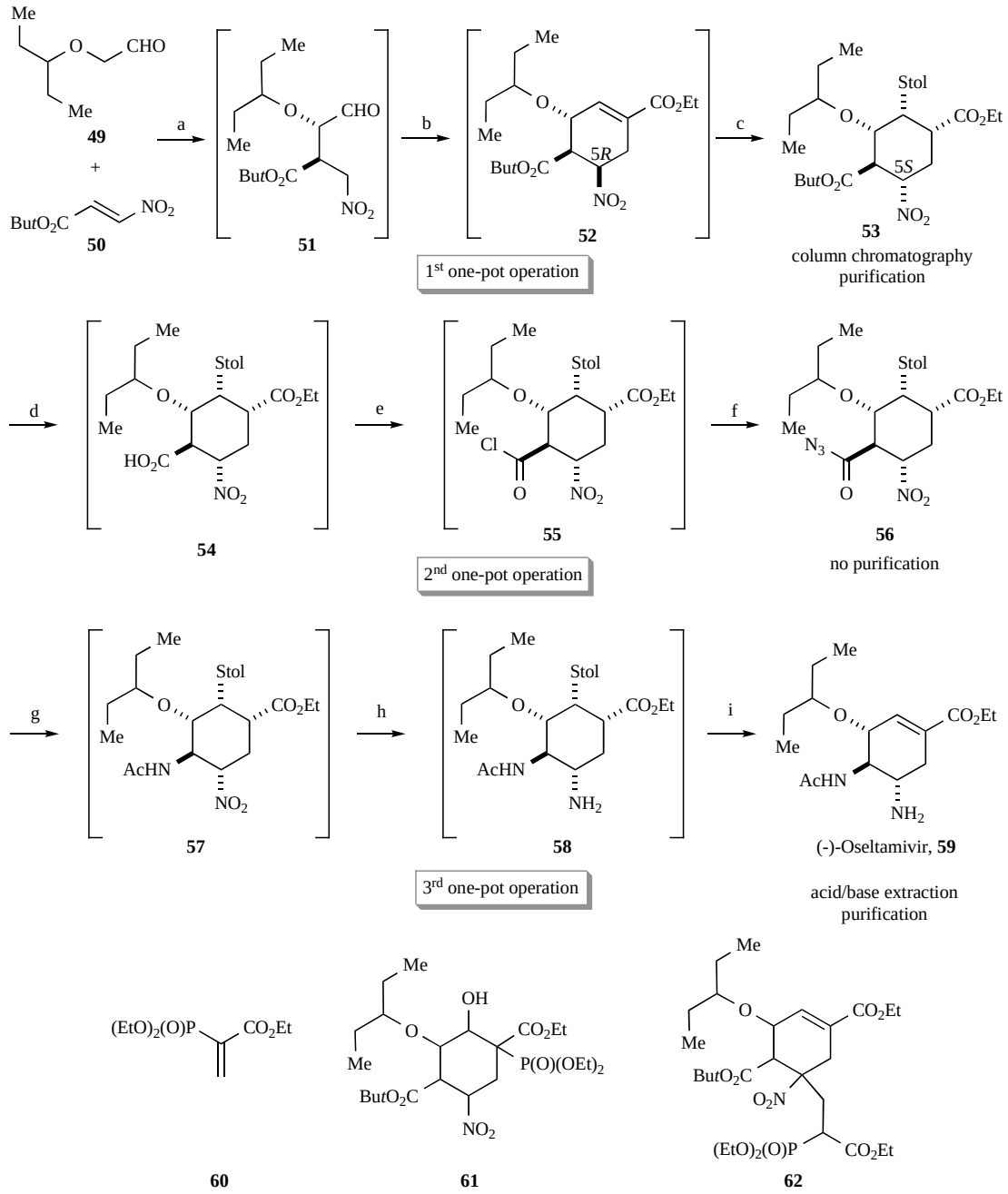


Scheme 7. Synthesis of (-)-Paroxetine. Reagents and conditions: (a) (*S*)-**43** (20 mol%), KOAc (1.2 eq.), CF_3CH_2OH, rt (84%, d.r. = 5:1, 90% *ee*); (b) BH_3, THF, (76%).

intermediate ketone **39**, from which sequential reduction/chlorination/reductive dehalogenation allowed the isolation of (+)-cermizine (**34**). Afterwords, its subsequent regioselective *N*-oxidation followed by the Polonovsky-Potier reaction straightforwardly furnished the desired (–)-senepodine G (**35**).

2.5. (–)-Paroxetine

When devising an enantioselective organocatalytic route to piperidines, Moyano and Rios provided a formal synthesis of (–)-paroxetine (**48**), a blockbuster antidepressive drug [28]. Their method relies on coupling amidomalonate derivatives and α,β-unsaturated aromatic aldehydes (Scheme **7**) in the presence of Hayashi catalyst (*S*)-**43** (20 mol%) for preparing piperidine analogs in good yields and enantioselectivities (up to 5:1 d.r. and up to 99% *ee*). Starting from amidomalonate **44** and aromatic aldehyde **45**, the desired hemiacetal intermediate **46** was obtained *via* spontaneous cyclization of the Michael adduct in the presence of (*S*)-**43** in 2,2,2-trifluoroethanol as solvent. The authors have shown that the addi-

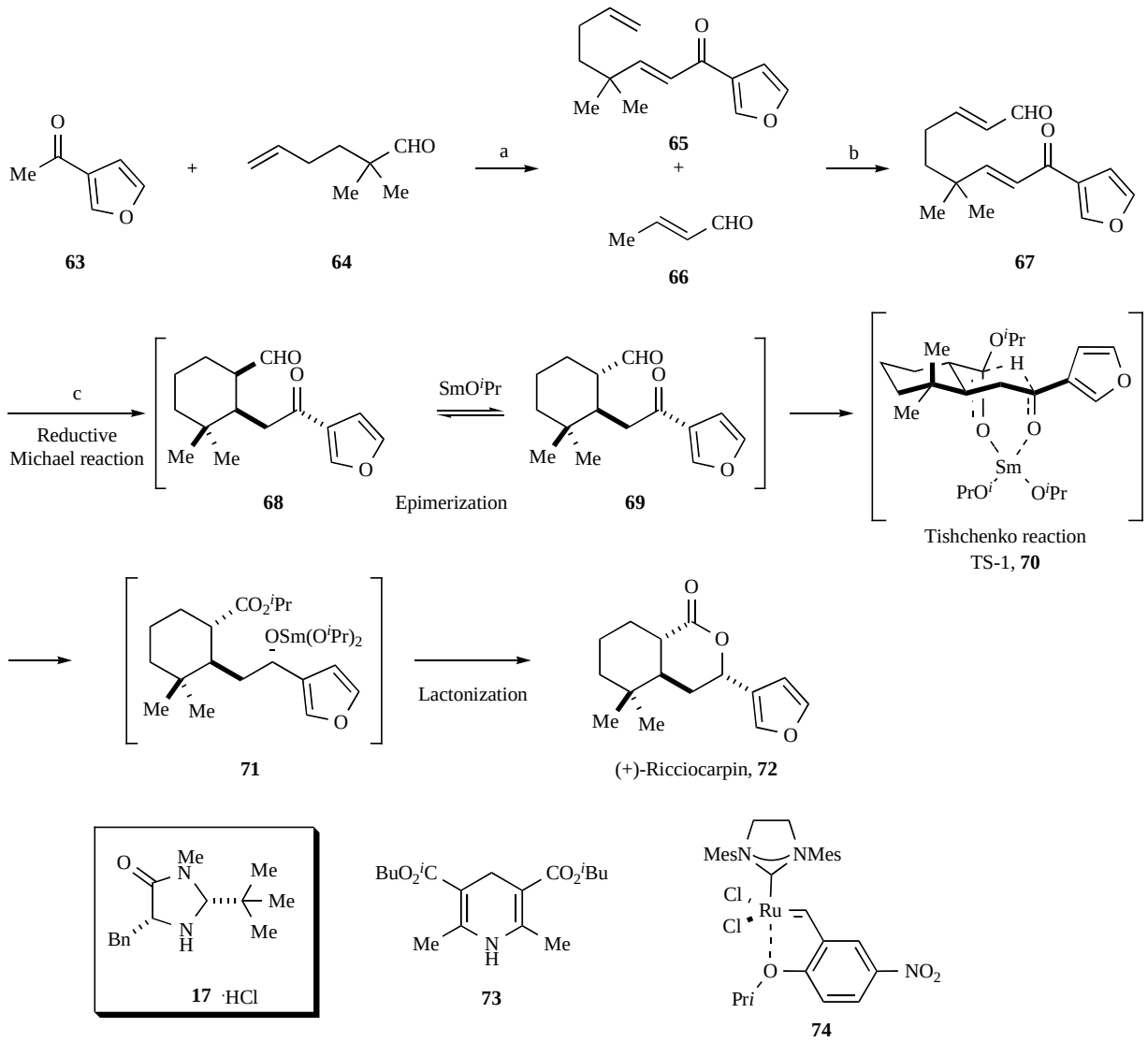


Scheme 8. Synthesis o**f** (-)-Oseltamivir and -15°C. Reagents and conditions: (a) (*S*)-**43** (5 mol%), $ClCH_2CO_2H$ (20 mol%), CH_2Cl_2, rt, 40 min (100%, major *syn* isomer: 96% *ee* and minor *anti* isomer: 87% *ee*); (b) **60**, Cs_2CO_3, 0°C, 3h, evaporation, then EtOH, rt, 15 min; (c) tolSH, EtOH, -15°C, 36h (70%, 3 steps); (d) TFA, CH_2Cl_2, 2h; (e) $(COCl)_2$, cat. DMF, CH_2Cl_2, 1h; (f) NaN_3, H_2O/acetone, 0°C, 20 min; (g) AcOH, Ac_2O, rt, 49h; (h) Zn, TMSCl, EtOH, 70°C, 2h; (i) NH_3 then K_2CO_3, EtOH, 6h (82%, 6 steps).

tion of a stoichiometric amount of a base (KOAc) could allow higher yields for this transformation. After reduction of **46** with BH_3 in THF the absolute configuration of compound **47** was assigned as (3*R*,4*S*) by analogy with optical rotation described within the literature data.

2.6. (−)-Oseltamavir

An outstanding example in total synthesis that well illustrates the potential of diphenylprolinol silyl ether (*S*)-**43** on one-pot operations was published by Hayashi and co-workers during the synthesis of (−)-oseltamivir [29]. (−)-Oseltamivir phosphate (Tamiflu®) is a neuraminidase inhibitor used in the treatment of both type A and type B human influenza. Ranked among the most promising therapeutics worldwide due to possible influenza outbreak, intensive efforts for devising efficient routes towards this drug, and also analogs owing to the emergence of Tamiflu-resistant virus strains, are currently required. With this in mind the group of Hayashi developed a very efficient total synthesis of this promising drug in which only nine steps (a total of three separate one-pot operations and sole one column chromatography purification step) were used. The overall yield reported for this synthesis is 57% and inexpensive reagents were employed, which renders this sequence suitable for multi-gram scale (Scheme **8**). The synthesis starts with the enantioselective preparation of the highly functionalized cyclohexane



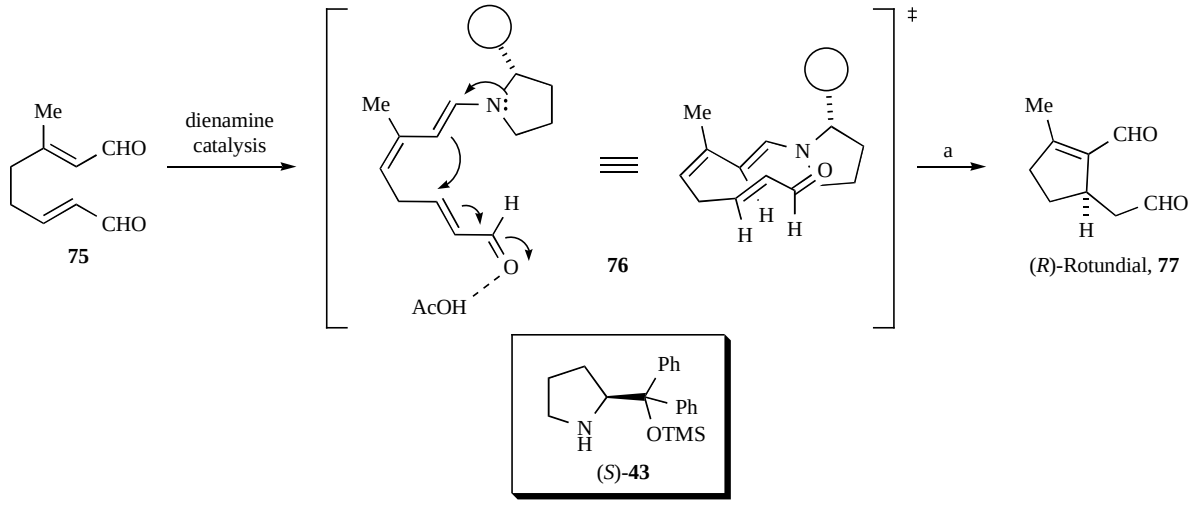
Scheme 9. Synthesis of (+)-Ricciocarpin. Reagents and conditions: (a) NaH, EtOH (65%); (b) **74** (2 mol%), CH_2Cl_2, 40°C (90%); (c) **17**•HCl (20 mol%), **73** (1.1 eq.), dioxane, 22°C, 72h, $Sm(O^iPr)_3$, 4h (43%, 84% *ee*).

moiety (first one-pot operation). *Via* a conjugate addition between alkoxyaldehyde **49** and nitroalkene **50** in the presence of diphenyl prolinol silyl ether (*S*)-**43** (5 mol%), the Michael adduct **51** was obtained in quantitative yield and excellent enantioselectivity. This intermediate was, thus, engaged without purification into a domino process (Michael reaction/Horner-Wardsworth-Emmons reaction) by reaction with vinylphosphonate **60** affording cyclohexenecarboxylate **52**. It is noteworthy mentioning that on this stage of the synthesis, by-products such as **61** and **62** were also obtained. By treating the mixture of **52**, **61** and **62** *in situ* with Cs_2CO_3 in EtOH, the desired **52** intermediate can be successfully isolated as single compound *via* a retro-aldol/ Horner-Wardsworth-Emmons reaction of **61** and a retro-Michael reaction of **62** respectively. The diester **52** was obtained in a (5*R*)/(5*S*) 5:1 mixture and the authors have shown that the treatment of this mixture with *p*-toluenethiol in the presence of Cs_2CO_3 gives the Michael product **53** with the (5*S*)-isomer being the major product. This base-mediated isomerization step ends the first domino one-pot operation. Additional two one-pot transformations were then necessary to finally accomplish the synthesis. The second one takes profit from a sequence of three classical transformations for converting the *tert*-butoxycarbonyl group (**53**) into an acetylamino (**57**) framework. Finally, (–)-oseltamivir (**59**) could be isolated after the last one-pot operation that also needs three steps: (*i*) a Curtius rearrangement and amide formation, (*ii*) a reduction of the nitro group to an amine, and (*iii*) a retro-Michael reaction of the thiol.

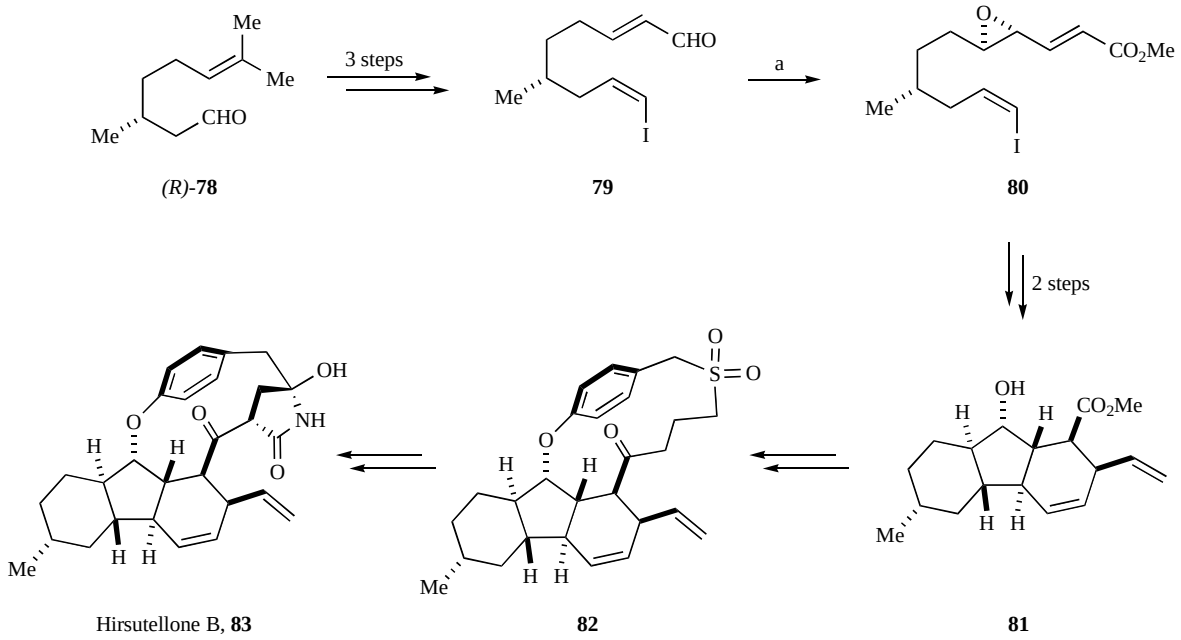
The synthetic route proposed here by Hayashi's group is quite different from all the others and allows the preparation of high amounts of this prized drug. In addition, the use of an organocatalyzed domino transformation in the first stage of the synthesis should authorize the preparation of novel derivatives by simple modification of the starting materials' nature and thus be a valuable tool in the search for new agents effective against Tamiflu-resistant strains.

2.7. (+)-Ricciocarpin A

An outstanding example of cascade transformations in the synthesis of natural products was published by MacMillan and Michrowska [30]. Indeed, by using a combination of reductive Michael-Tishchenko reactions, they have successfully devised a very short and efficient route to (+)-ricciocarpin (**72**), a furanosesquiter-



Scheme 10. Synthesis of (*R*)-Rotundial. Reagents and conditions: (a) (*S*)-**43** (20 mol%), AcOH (20 mol%), CH_2Cl_2, rt, 22h (36%, 86% *ee*).



Scheme 11. Synthesis of Hirsutellone B. Reagents and conditions for the organocatalytic reaction: (a) (*S*)-**43** (10 mol%), CH_2Cl_2, H_2O_2, 0°C, 8h then $Ph_3P{=}CHCO_2Me$, 0°C, 1h (80% 2 steps, *Z*/*E* 5:1).

pene that exhibits promising activity against schistosomiasis (also called bilharziasis). In their three-step synthesis, the key organocatalytic step takes place in the presence of MacMillan's imidazolidinone catalyst *ent*-**17**•HCl (20 mol%) and Hantzsch ester **73** (1.1 eq.) with samarium triisopropoxide $Sm(OiPr)_3$ (Scheme **9**).

The desired Michael adduct **68** was predominantly obtained as the 'undesired' *cis*-isomer intermediate. However, they have observed that the *cis*-isomer isomerizes to the more thermodynamically stable *trans*-isomer, and this isomerization is strongly accelerated in the presence of $Sm(OiPr)_3$, the catalyst of the Tishchenko reaction. The authors proposed that this highly diastereoselective Tishchenko cyclization may be explained by the transition state TS-1 (70), in which the two carbonyl compounds are chelated by the samarium complex during the hydride-transfer step. It is noteworthy to mention that this method has also paved the way to the preparation of analogs in which one of them has shown higher biological activities than the naturally occurring (+)-ricciocarpin.

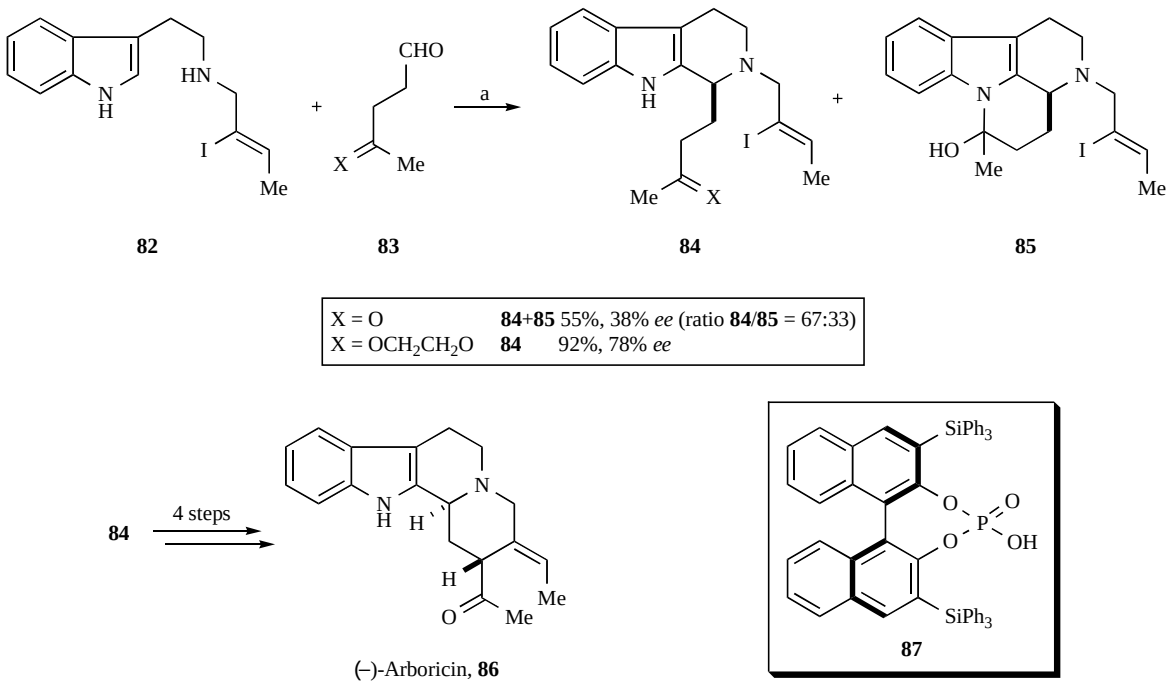
2.8. (+)-Rotundial

Christmann and co-workers developed a straightforward way to iridoid frameworks by developing an intramolecular Rauhut-Courrier (RC) reaction *via* electron rich dienamines [31]. The intramolecular RC-reaction gives rise to chiral cycloalkenes (**77**) from acyclic tethered Michael acceptors (**75**) (Scheme **10**). Their synthesis takes place under secondary amine ((*S*)-**43**) catalysis and an application of this strategy was illustrated with the six-step synthesis of (+)-rotundial (**77**) (25% overall yield, 86% *ee*), a mosquito repellent isolated from *Vitex rotundifolia*.

Interestingly, previous asymmetric versions of RC-reaction have relied on 1,4-additions of chiral nucleophiles whereas in this case the catalytic cycle is initiated by a 1,2-addition of the catalyst.

2.9. Hirsutellone B

Nicolaou and coworkers achieved the total synthesis of hirsutellone B [32], an antifungal and antibiotic natural product with a



82 **83** **84** **85**

X = O	**84**+**85** 55%, 38% *ee* (ratio **84**/**85** = 67:33)
X = OCH_2CH_2O	**84** 92%, 78% *ee*

Scheme 12. Synthesis of (-)-Arboricine. Reagents and conditions of the organocatalytic step: (a) 87 (1 mol%), toluene, 4 Å MS, rt, 18h (92%, 78% *ee*).

complex and challenging chemical structure. Among the several novel cascade sequences and chemoselective reactions that made possible this tricky total synthesis, they used an organocatalyzed epoxidation step in the earlier stage of the construction of the tricyclic core **81** (Scheme **11**). The α,β-unsaturated aldehyde intermediate **79**, easily obtained from commercial available (*R*)-citronellal (*R*)-**78** in 3 steps, was submitted to organocatalyzed epoxidation using H_2O_2 in the presence of secondary amine (*S*)-**43** (10 mol%). The desired epoxy aldehyde is *in situ* treated with a suitable ylide ($Ph_3P{=}CHCO_2Me$) to furnish the epoxy ester iodide **80**. After several steps and outstanding transformations, they have succeeded on preparing hirsutellone B (**83**).

2.10. (–)-Arboricine

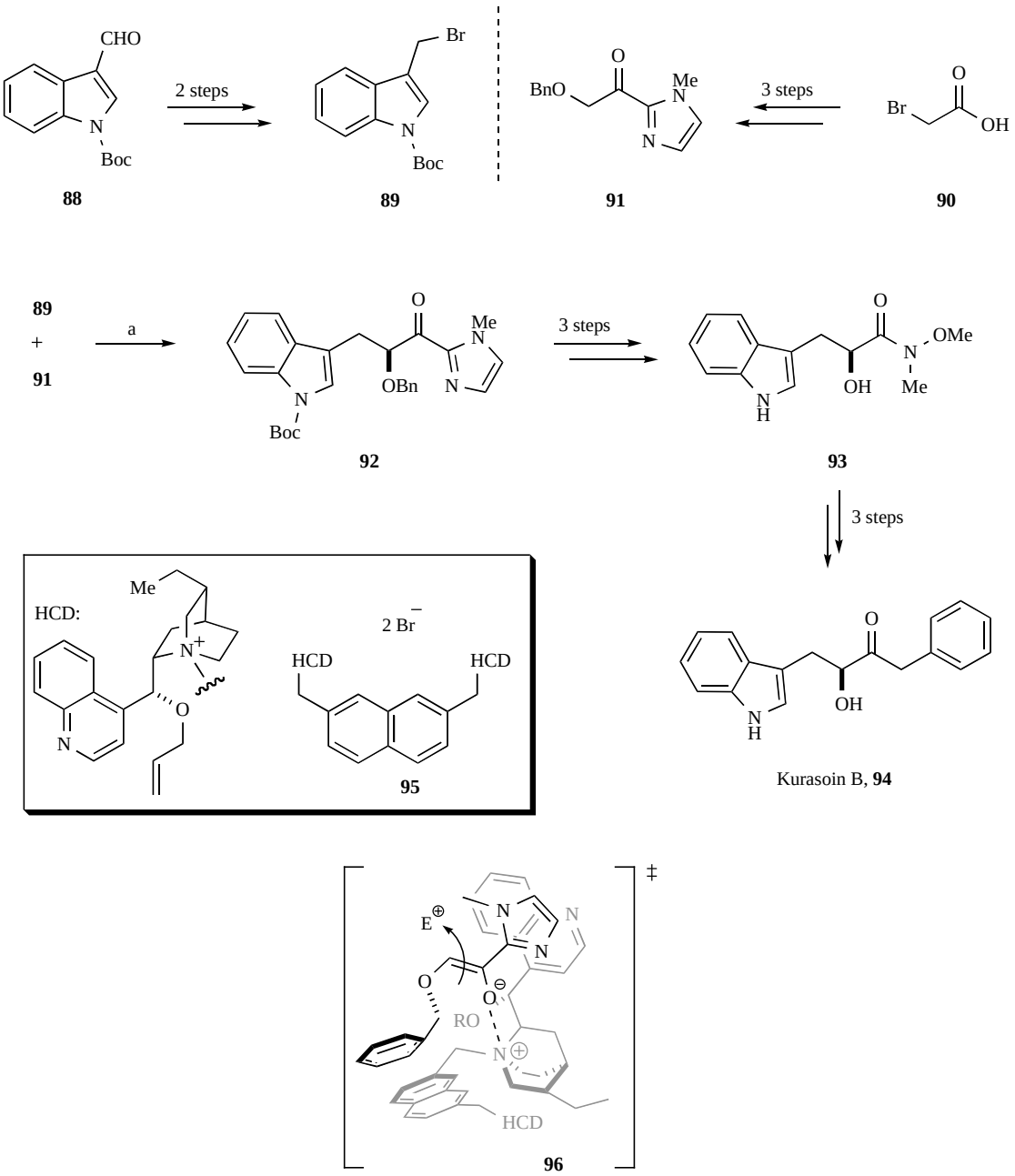
Enantioselective Pictet-Spengler reaction, named the intramolecular Friedel-Crafts alkylation of imines, can be considered a straightforward method for the preparation of enantioenriched tetrahydroisoquinolines and tetrahydro-β-carbolines building blocks. Indeed, the group of Hiemstra, Maarseveen and co-workers has devoted intensive efforts in this field by means of hydrogen-bond donor catalysis with binolphosphoric acid derivatives [33]. They have validated their method in the total synthesis of β-carboline arboricine (**86**), a tetracyclic indole alkaloid that exhibits a moderate ability to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells (Scheme **12**). The synthesis started with the known tryptamine **82**, which is submitted to the Pictet-Spengler key step by treatment with (*R*)-3,3'-triphenylsilyl-binol phosphoric acid **87** [(*R*)-binol-PA, 5 mol%)] in toluene in the presence of aldehyde **83** and 4Å molecular sieves at room temperature. The desired β-carboline intermediate **84** was isolated in 55% yield together with the aminal **85** in a 67/33 ratio respectively, and an unacceptable selectivity of 38% *ee* for both compounds. They validated that protection of the ketone as the dioxolane affords exclusively **84** (92%, 78% *ee*) avoiding the aminal formation. By simple installing the acetal protecting group, which remains quite remote from the iminium intermediate, better yield and higher enantioselectivity were achieved and lower catalyst loading (only 1 mol%) can be successfully employed.

Therefore, they have used a mild and efficient method for synthesizing arboricine **86** in six overall steps and with 33% overall yield. In addition, the absolute stereochemistry was proven by X-ray crystallographic analysis and a revised structure with opposite stereochemistry has been proposed based on the one published on the original paper.

2.11. Kurasoin B

Phase-transfer catalysis (PTC) was used by Andrus and co-workers for preparing Kurasoin B (**94**) [34] which is, together with its phenol-containing analogue Kurasoin A, protein farnesyltransferase (PFTase) inhibitor isolated from the fungus *Paecilomyces* sp. [35] . These compounds have potential as novel cancer drug leads due to the possible easy tuning of the aromatic functionalities around the central core structure [36, 37]. In this synthesis, they successfully employed their own previously developed method [38, 39] based on asymmetric phase-transfer catalytic alkylation of aryl ketone glycolate substrates giving rise to α-hydroxy esters, as the key step. As starting materials, benzyloxyacetyl imidazole **91** (prepared in 3 steps from bromoacetic acid) [39] and bromomethyl indole **89** (obtained *via* a modified Coelho's strategy) [40] were used for synthesizing the required (*S*)-acylimidazole **92** (Scheme **13**).

The key PTC alkylation reaction, catalysed by a biscinchonidinium dimethylnaphthalene catalyst **95**, was performed in the presence of **91**, **89** (2 eq.) and $CsOH{\cdot}H_2O$ under liquid-solid conditions at –40 °C giving rise to the intermediate **92** in 98% yield and excellent enantioselectivity (99% *ee*). Six-further steps allowed the incorporation of the benzylic-containing moiety. Concerning the rational for the mechanism, the transition state **96** was proposed for illustrating the *S*-stereoinduction. The oxygen of the *Z*-enolate situated between the quinoline and quinuclidine moieties on the catalyst is coordinated with the least hindered face of the catalyst am-



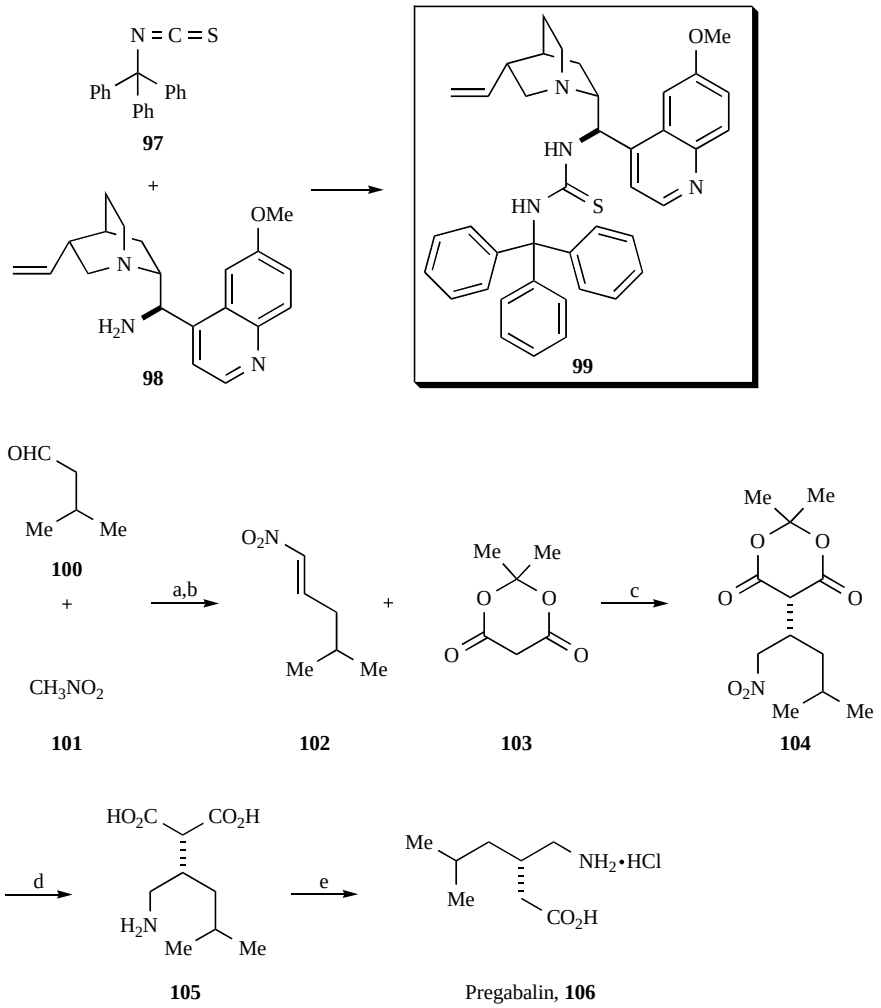
Scheme 13. Synthesis of Kurasoin B. Reagents and conditions: (a) HCD-dimer 95 (10mol%), CH_2Cl_2, -40°C then $CsOH{\cdot}H_2O$ (4 eq.), 28h (98%, 99% *ee*).

monium nitrogen (*"pocket" binding mode*) [39]. Thus, a nine-step direct route to Kurasoin B (**94**) (34% overall yield) was devised which takes profit from the newly efficient developed PTC alkylation reaction that sets up the *S*-hydroxy stereocenter present in the chemical structure of this natural product.

2.12. Pregabalin

Pregabalin (Lyrica®) is an anticonvulsant drug used to treat epilepsy and neurophatic pain [41, 42]. Its high and broad therapeutic activity places this compound among the 'drugs of the future'. Although many research groups have shown interest on its total synthesis devising simple and straightforward routes to this compound, it might be pointed out that only the (*S*) enantiomer exhibits the suitable pharmacological activity and that enantioselective strategies are highly suitable and demanded. Amongst the different total syntheses devised to date, we will highlight the one by Koskinen and co-workers in which an organocatalytic conjugate addition reaction of Meldrum's acid (**103**) to nitroalkene **102** gives rise to the single stereocenter (responsible for the medicinal activity) on the chemical skeleton of pregabalin [43]. After the screening of a broad range of thiourea-based catalysts, the authors have shown that quinidine derived thiourea **99** (10 mol%), previously synthesized in 79% yield by the same group *via* condensation of the free amine **98** derived from quinidine with commercial trityl isothiocyanate (**97**), provided the better compromise between reaction outcome and selectivity.

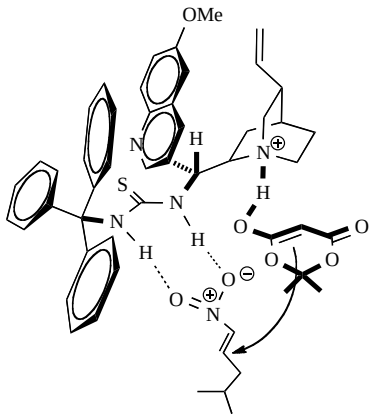
Thus, after preparation of nitroalkane **102** in 2 steps from isovaleraldehyde (**100**) and nitromethane (**101**) by a sequence of Henry reaction/dehydration this compound was subjected to the thiourea-mediated conjugate addition with Meldrum's acid (**103**).



Scheme 14. Synthesis of Pregabalin. Reagents and conditions: (a) 10M NaOH, EtOH, 0 °C to rt, overnight then AcOH, rt (88%); (b) $(CF_3CO)_2O$, CH_2Cl_2, then Et_3N, 0 °C to rt, overnight (70 °C); (c) **99** (10 mol%), CH_2Cl_2, rt (1^{st} batch 23h, 84% yield, 75% *ee*; 2^{nd} batch 24h, 82% yield, 75% *ee*); (d) H_2, Raney-Ni, AcOH, rt, 22h (75%); (e) 6N HCl, 100 °C, 28h (94%).

The desired intermediate **104**, bearing the (*S*) stereocenter, was thus obtained in 84% yield and 75% *ee*. Mention should be made that, during the purification of **104** *via* column chromatography, 55% of the catalyst **99** was recovered and reused in a second reaction cycle showing therefore the same activity and selectivity (82% yield and 75% *ee*). Pregabalin could be isolated in 80% *ee* after a crystallization of the free amino acid from 2-propanol/water. Concerning the origin of the enantioselectivity, the authors have envisaged a transition state model similar to that previously described by Takemoto and co-workers [44, 45]. They have proposed an activation of the two oxygen atoms of the Michael acceptor **102** through double NH hydrogen bonding with the monomeric organocatalyst **99**.

The quinuclidine moiety and the trityl group are placed on the same face but they are far away from each other in order to avoid steric interaction. They are orientated in the same direction than both NH groups. Owing to the product configuration, delivery of the enolate derived from Meldrum's acid from the top face of the *s-cis* nitroalkene gives rise to the product with the required (*S*) configuration.

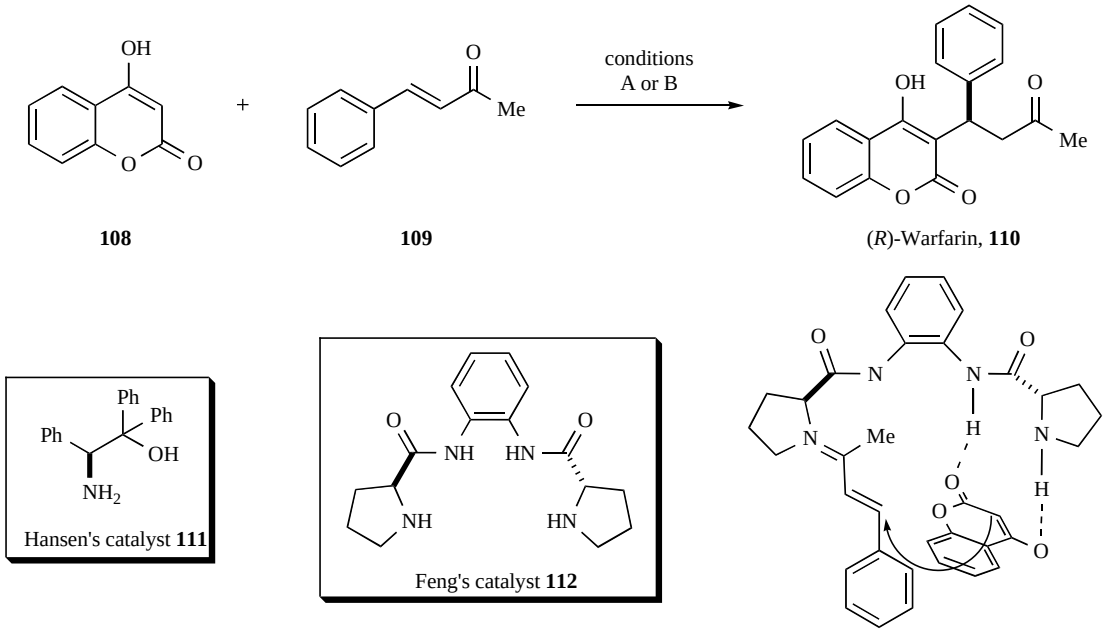


Proposed transition state intermediate, **107**

Fig. (3). Proposed transition state intermediate.

2.13. Warfarin

Warfarin (Coumadin®, Marevan®) is among the most effectively used anticoagulants for preventing thrombosis and embolism. For more than fifty years, it has been prescribed in its racemic form although the activity and metabolism are different for the two enantiomers: the (*S*) enantiomer being a better anticoagulant than the (*R*)-Warfarin (about 2-5 times) [46]. Although several efficient asymmetric synthesis of Warfarin has been described so far, the



Scheme 15. Synthesis of (*R*)-Warfarin. Reagents and conditions: (a) Hansen's conditions **108** (1.0 eq.), **109** (1.2 eq.), **111** (20 mol%), CH_3CO_2H (1.0 eq.), THF, rt, 24h (76%, 81% *ee*); (b) Feng's conditions: **108** (1.0 eq.), **109** (1.5 eq.), **112** (20 mol%), succinic acid (10 mol%), *n*butyl alcohol (1 mL), 50 μL H_2O, 40 °C, 12h (99%, 83% *ee*, after recrystallization >99% *ee*).

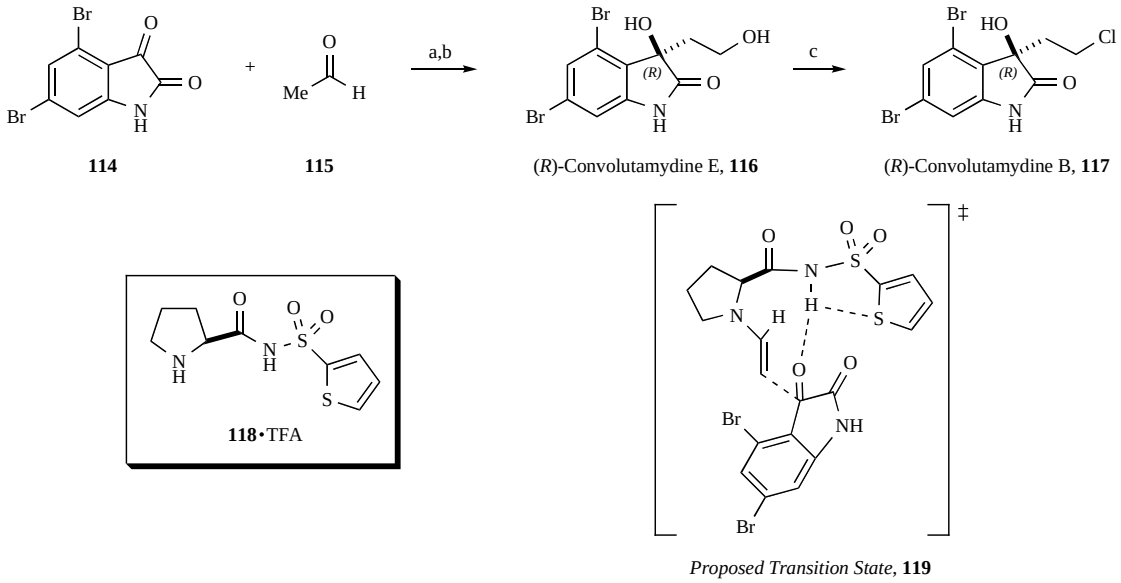
first example taking profit of asymmetric organocatalysis was described in 2003 by Jørgensen's group [47]. Three and four years later, Kim [48] and Deng [49] have respectively reported two additional total syntheses, both by means of iminium organocatalysis. More recently, work on this purpose also takes advantage of amine-catalyzed conjugate addition of 4-hydroxycoumarin **108** to α,β-unsaturated ketones **109**. Indeed, simultaneously the groups of Hansen [50] and Feng [51] have devised efficient and straightforward routes to both enantiomers of Warfarin. The first group have used as catalyst a new phenylglycine-derived primary amine **111** (20 mol%) with acetic acid (1 eq.) as co-catalyst in THF at room temperature [50]. The group of Feng reported their transformation by means of secondary amine amide catalyst **112** (20 mol%) in the presence of succinic acid (10 mol%) as co-catalyst in *n*-butyl alcohol as solvent with a small amount of water at 40 °C [51]. Both methods allowed the required products in good yields (up to 99%) and enantioselectivities (up to 89% *ee*, after a single recrystallisation step, >99% *ee*) and the reaction can be easily transposed to large-scale conditions. Feng's group postulated that model **113** might illustrate the plausible transition state intermediate *via* the required *Re*-face attack from 4-hydroxycoumarin (*via* hydrogen-bond activation) to the unsaturated ketone (activated *via* iminium ion intermediate) [47-49].

2.14. (R)-Convolutamydine B and E

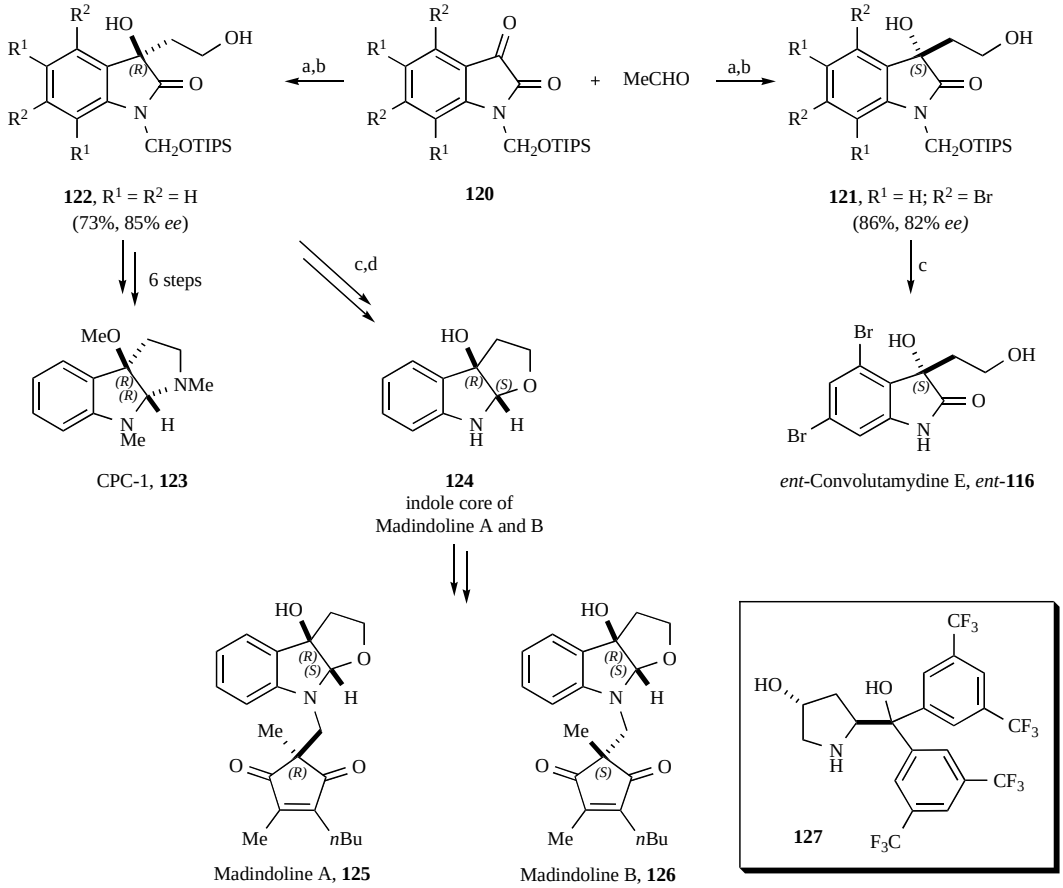
Convolutamydine A-E were isolated from the Floridian marine bryozoan *Amathia convoluta*. These alkaloids have in common a 4,6-dibromo-3-hydroxyoxindole skeleton and only differ from each other on the side chain moieties at the quaternary stereocenter at the C-3 position. Convolutamydine A and B exhibit a potent inhibitory activity against the differentiation of HL-60 human promyelocytic leukaemia cells at 0.1 and 12.5 μg mL^{-1} respectively. However, only very low quantities of convolutamydine E were isolated to date and a detailed annotation of its biological activity will await the availability of considerable quantities. Among the synthesis reported to date [52], we are going to highlight the one described by Toru, Nakamura and co-workers in where an enantioselective synthesis of convolutamydine B and E were reported taking profit of organocatalysis for building the quaternary stereocenter *via* aldol reaction between acetaldehyde and 4,6-dibromoisatin [53]. Thus, by using *N*-(2-thienylsulfonyl)prolinamide **118** as catalyst (10 mol%), they have achieved the synthesis of convolutamydine E in 94% yield and 92% *ee* (>99% *ee* after a single recrystallization). Convolutamydine B was obtained in 87% yield and 92% *ee* (98% *ee* after a single recrystallization) from convolutamydine E by simple chlorination of the alcohol function. Although more studies might be carried out concerning the mechanistic pathway of this enantioselective aldol reaction, the authors assumed, by using this catalyst, an intramolecular hydrogen bonding network between the sulfonamide NH proton, the sulfur atom and the carbonyl group. By using this method with catalyst **118** the authors have also provided various convolutamydine E derivatives in high yields and good selectivities.

2.15. (S)-Convolutamydine E, CPC-1 and an Indole Fragment of Madindoline A and B

Almost simultaneously, the group of Hayashi has also devised a straightforward route to 3-hydroxyindole alkaloids by means of asymmetric direct aldol reaction of isatin derivatives and acetaldehyde (also see previous sub-section). Following the methodology previously developed by the same group [29], they overcome the difficulties which are commonly encountered on aldol reaction when acetaldehyde is used as a nucleophile which are: (*i*) acetaldehyde is reactive as an electrophile which causes a self-aldol reaction; (*ii*) the aldol product formed, an α,α-unsubstituted aldehyde, can also act as both nucleophile and electrophile, promoting overreaction, and (*iii*) dehydration can be observed as a side reaction (Scheme **17**). Thus, by using catalyst **127** (30 mol%) they have successfully synthesized 3-hydroxyindole scaffolds that can be further transformed into alkaloids such as unnatural convolutamydine E (*ent*-**116**), CPC-1 (**123**), a new pyrrolidinoindoline alkaloid,



Scheme 16. Synthesis of (*R*)-Convolutamydine B and E. Reagents and conditions: (a) **118** (10 mol%), THF, rt; (b) $NaBH_3CN$, AcOH (94%, 92% *ee*, after a single recrystallization procedure >99% *ee*); (c) TsCl, Pyridine, 75°C, 7h (87%, 92% *ee*, after a single recrystallization procedure 98% *ee*).



Scheme 17. (*S*)-Convolutamydine E, CPC-1 and an indole fragment of madindoline A and B. Reagents and conditions: (a) **127** (30 mol%), $ClCH_2CO_2H$ (60 mol%), DMF, 4°C, 48h; (b) $NaBH_4$, MeOH (*R*-isomer 73%, 85% *ee*, *S*-isomer 86%, 82% *ee*) (c) NH_4F, MeOH, 70°C (76% convulamydine E, 88% madindoline A and B); (d) $NaBH_4$, THF, rt (47%).

and an indole fragment (**124**) of madindoline A (**125**) and B (**126**) (both selective inhibitors of interleukin-6). In contrast to Nakamura's work, they have used protected isatin derivatives as the electrophile and the required aldol adducts were obtained in very good yields and enantioselectivities.

It is noteworthy mentioning that the nature of the substituent on the C-5 position of the isatin derivative is crucial for the stereocontrol of the reaction. Based on previous work [29], the authors have assumed that the proton of the hydroxy group of the catalyst might activate the isatin derivative by coordination with the carbonyl

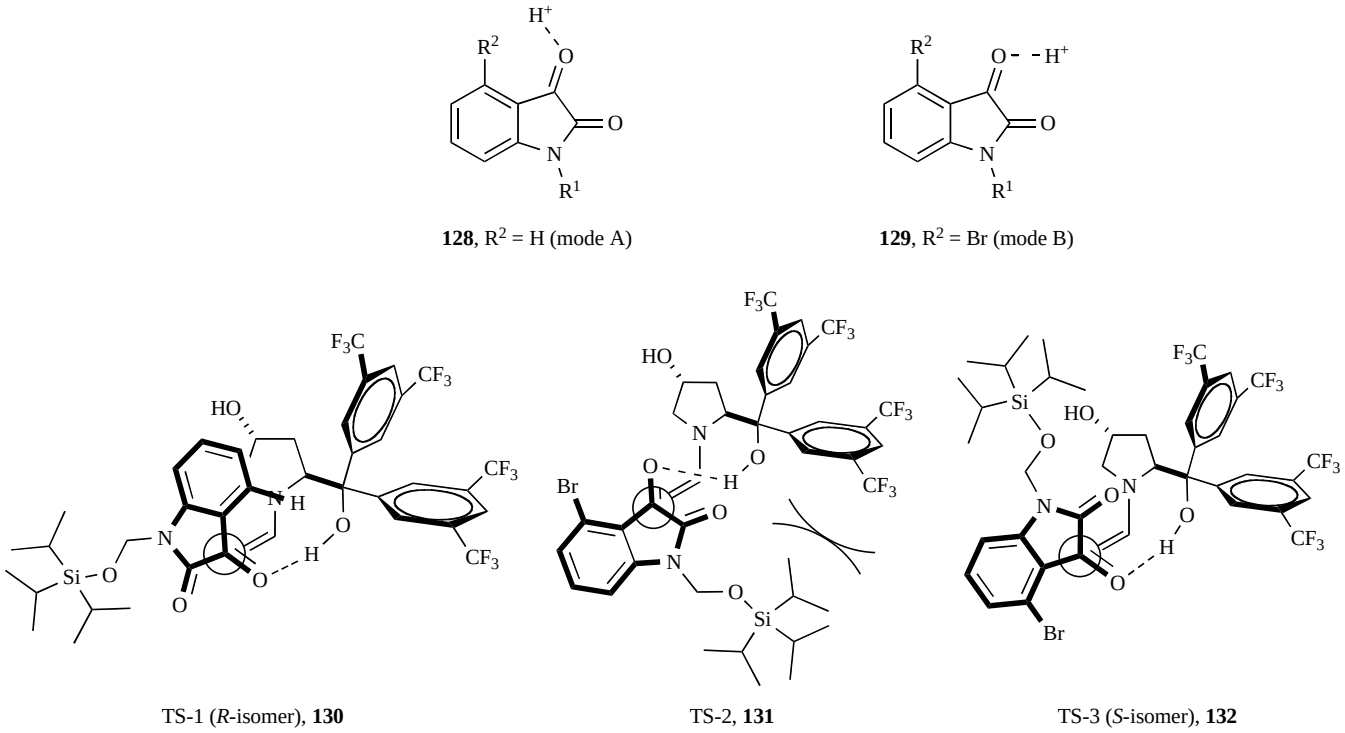


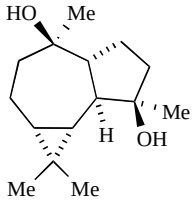
Fig. (4). Coordination modes to isatin derivatives (mode A and mode B) and transition state (TS) models.

group *via* two possible ways (A and B in Fig. **4**). Consequently, a hydrogen atom (small) on the C-5 position of isatin favors a transition state TS-1 (**130**) (based on patway A) that affords the *R*-isomer whereas a larger substituent (a bromine atom for example) would not be suitable *via* A owing to steric hindrance. In this case, for explaining the formation of the *S*-isomer, transition state TS-3 (**132**) is more suitable than TS-2 (**131**), both bearing a bromine atom on C-5, due to the steric repulsion between the substituent on the nitrogen atom of the isatin moiety and the aryl group of the catalyst **127**.

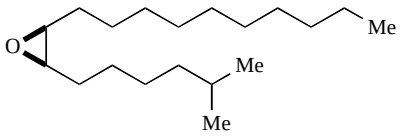
2.16. Other Selected Natural Products

Year 2009 was a very productive one concerning the total synthesis of natural products by means of organocatalysis in which active methylene compounds have played a very important role for reactions outcome and selectivity. Although some representative examples have been presented above, it might be pointed out that many other outstanding syntheses have also been published. Some selected structures of these natural compounds are illustrated below (Fig. **5**). During the synthesis of (−)- aromadendranediol (**133**), MacMillan and co-workers have used an elegant triple-cascade-catalysis sequence (*eg*. cross-metathesis/iminium/enamine cycles) for building a bicyclic butenolide intermediate which bears four of the six stereocenters and 12 of the 15 carbons found in the chemical structure of this natural sesquiterpene compound [54]. In the synthesis of (+) and (−)-disparlure (**134**) and their *trans*-isomers, Kim have employed a tandem asymmetric organocatalytic α-aminoxylation-allylation of dodecanal giving thus rise to chiral diols and cross-metathesis using Grubbs' catalyst [55]. Johnson and Campbell have started their total synthesis of the antimalarial agent (+)-polyanthellin A (**135**) by means of an enantioselective organocatalytic conjugate addition of isovaleraldehyde to methyl vinyl ketone (MVK) using diphenylprolinol methyl ether (5 mol%) and catechol (20 mol%) as co-catalyst. The use of this additive improved both, yield and reaction rate [56]. Kádas and co-workers have published an efficient stereoselective total synthesis of *ent*-(−)-7-deoxy-*trans*-dihydronarciclasine (**136**), an *ent*-form of highly potent antineoplastic agent constituent of the Amaryllidaceae alkaloids [57]. They have used a novel strategy based on the enantioselective nitromethane conjugate addition, under 4-(*S*)-bezyl-1-methylimidazolidinone-2-carboxylic acid catalysis, to synthesize an enantiopure form of a known arylcyclohexylamine typer precursor. (−)-Nakadomarin A (**137**), a marine alkaloid of the manzamine family with different biological activities (*eg*. cytotoxic activity against murine lymphoma L1210 cells, inhibition of cyclin dependent kinase 4 and antimicrobial) has a very tricky structural topology with a hexacyclic containing 8/5/5/5/15/6 ring system and 4 stereogenic centers in which one is quaternary. Among the key steps that were used by Dixon and co-workers during their total synthesis of (−)-Nakadomarin A, a bifunctional cinchona alkaloid/thiourea catalyzed nitro olefin Michael addition allowed the preparation of a sophisticated intermediate in good yield and high diastereoselectivity [58].

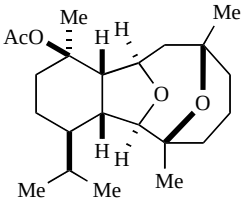
During the total synthesis of (+)-physostigmine (**138**), Barbas III and co-workers have devised a highly enantio- and diastereoselective methodology mediated by thiourea-catalysis for the additions of oxindoles to nitroolefins [59]. Another example that highlights the use of α-aminoxylation of an aldehyde as a key step was published by Kalkote and co-workers during the enantioselective synthesis of β-adrenergic blockers (*S*)-propranolol (**139**) and (*S*)-naftopidil (**140**) [60]. An efficient Michael addition between isovaleraldehyde and MVK was used by Chen and Baran in their syntheses of eudesmane terpenes **141** by using an atypical two-phase approach, in where site-selective C-H oxidations were exploited, inspired by terpene biosynthesis [61]. Hatakeyama and co-workers have devised a general strategy allowing the preparation of the phoslactomycin family of antibiotics (**142**), selective and powerful protein phosphatase inhibitors, by means of an asymmetric



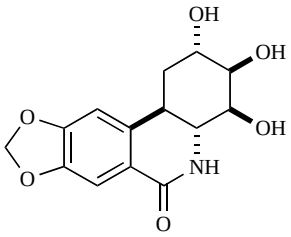
(-)-Aromadendranediol, **133**



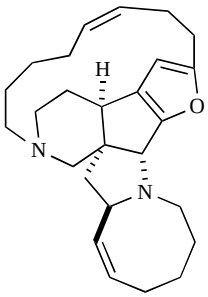
(+)-Disparlure,**134**



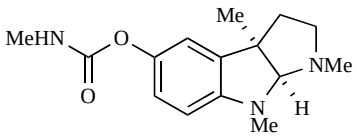
(+)-polyanthellin A, **135**



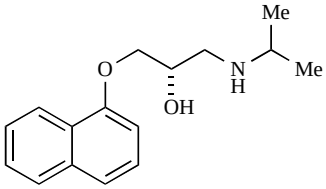
ent-(-)-7-deoxy-trans-dihydronarciclasine, **136**



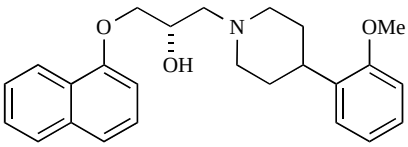
(-)-Nakadomarin, **137**



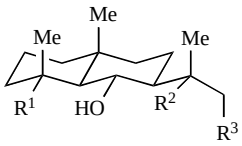
(+)-Physostigmine, **138**



(*S*)-propranolol, **139**

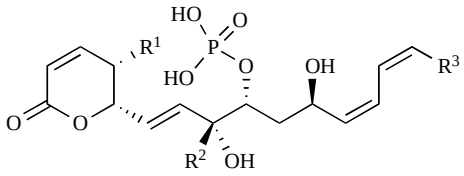


(*S*)-Naftopidil, **140**



Eudesmane terpenes, **141**

(R^1 = OH, R^2 = R^3 = H) 4-*epi*-ajanol
(R^1 = OH, R^2 = OH, R^3 = H) pygmol
(R^1 = H, R^2 = OH, R^3 = H) dihydroxyeudesmane
(R^1 = OH, R^2 = OH, R^3 = OH) eudesmantetraol



142

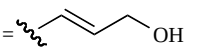
Fostriecin: R^1 = H, R^2 = Me, R^3 = 
Phoslactomycin B: R^1 = Et, R^2 = $CH_2CH_2NH_2$, R^3 = cyclohexyl

Fig. (5). Other selected Natural products from 2009.

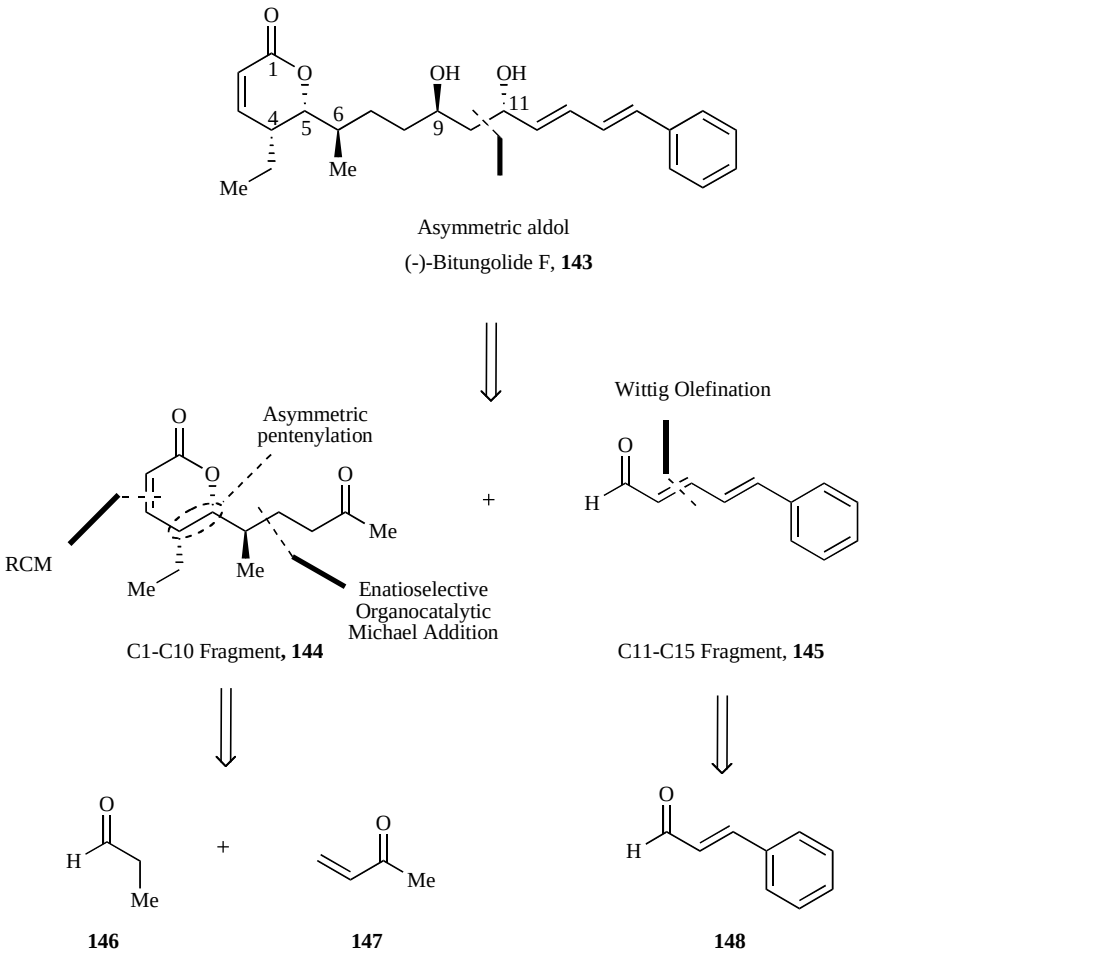
Baylis-Hillman reaction catalyzed by β-isocupreidine (β-ICD) and with hexafluoroisopropyl acrylate (HFIPA) as an activated ester (β-ICD-HFIPA method) [62]. By this method, formal syntheses of (+)-fostriecin and (+)-phoslactomycin B have been successfully accomplished.

3. 2010

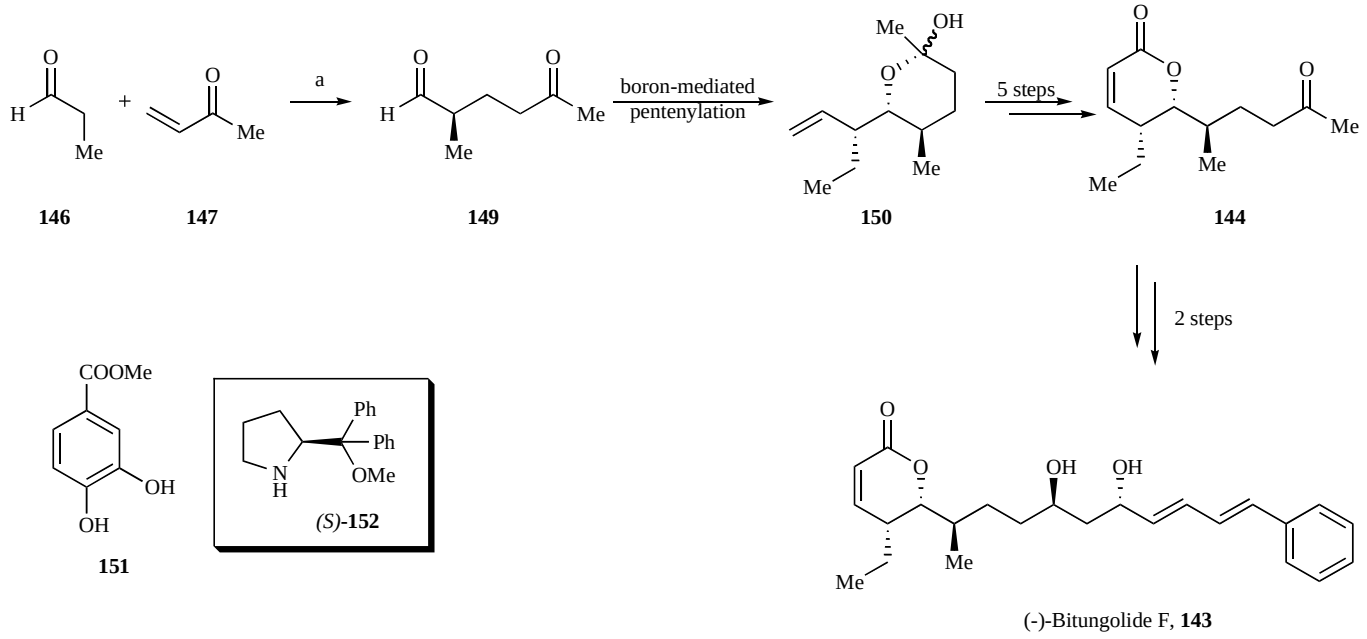
3.1. (-)-Bitungolide F

(+)-Bitungolide A-F are pharmacologically interesting polyketides recently isolated from the Indonesian sponge *Theonella cf. swinhoei* by Tanaka *et al.* [63]. These compounds exhibited cytotoxic effects against 3Y1 rat normal fibroblast cells and inhibition toward VH1-related (VHR) dual-specificity phosphatase [64]. Cossy *et al*. planned an asymmetric convergent route to the synthesis of unnatural (-)-Bitungolide F in nine steps and 11.4% overall yield. Between the two concise total syntheses proposed by the French group, the organocatalytic route involved an enantioselective Michael addition, which affords to the C5- C10 aldehyde in one step, followed by a boron-mediated asymmetric pentenylation/acylation/RCM sequence. A final chiral boron-mediated aldolization generates the C10-C11 bond with the concomitantly setting of C11 stereogenic center in the desired product (Scheme **18**).

In particular, the preparation of the most synthetically challenging fragment **144** of (-)-Bitungolide F, containing 3 stereogenic centers, starts with an enamine promoted Michael reaction between

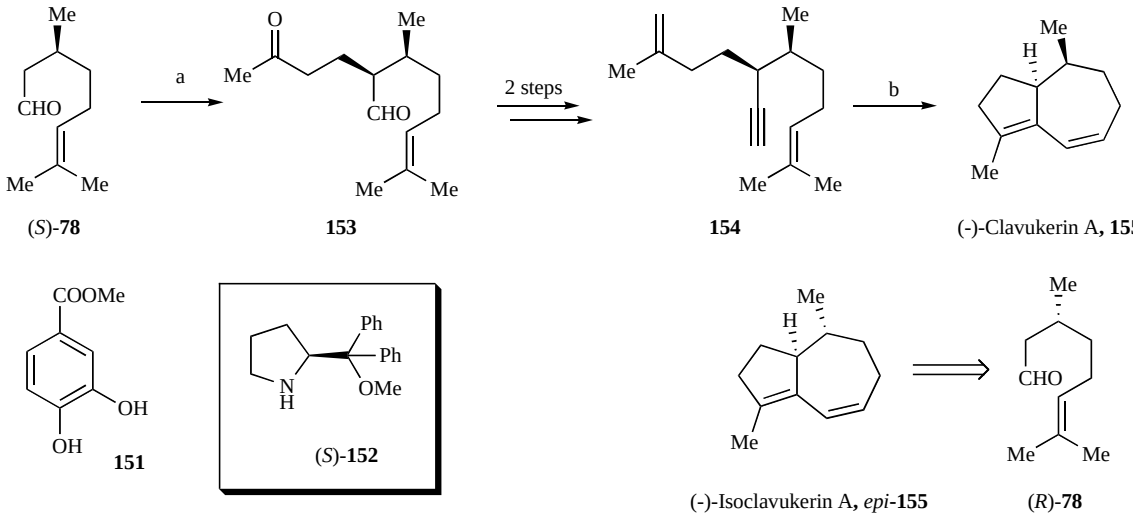


Scheme 18. Retrosynthetic approach to the synthesis of (-)-Bitungolide F.

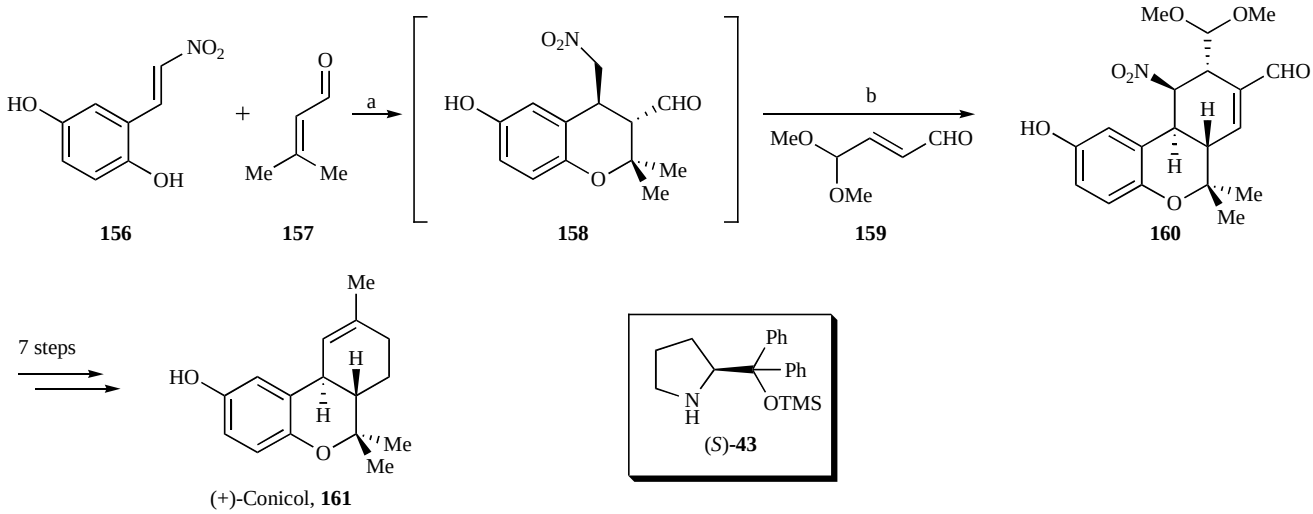


Scheme 19. Synthesis of (-)-Bitungolide F. Reagents and conditions of the organocatalytic step: (a) (*S*)-**152** (5 mol%), **151** (20 mol%), neat, 58%, 90% *ee.*

propanal (**146**, donor) and MVK (**147**, acceptor). Employing catalytic amounts of diphenyl prolinol (*S*)-**152** (5 mol%) and catechol **151** (20 mol%) the desired aldol adduct **149** was obtained in moderate yield (58%) but excellent enantioselectivity (90% *ee*) (Scheme **19**).



Scheme 20. Synthesis of (-)-Clavukerin A and (-)-Isoclavukerin A: (a) (*S*)-**152** (20 mol%), **151** (20 mol%), 3°C, (90%, d.r. = 18:1); (b) Hoveyda–Blechert catalyst (4 mol%), CH_2=CH_2 (1 atm), toluene, reflux, (53%)



Scheme 21. Synthesis of (+)-Conicol. Reagents and conditions: (a) (*S*)-**43**•AcOH (20 mol %), CH_2Cl_2, 25°C, 1h, 79% >99% *ee*; (b) (*S*)-**43** •AcOH (20 mol %), CH_2Cl_2, 25°C, 35h, (69% >99% *ee).*

The subsequent boron-mediated asymmetric pentenylation followed by a spontaneously hemiketalization, furnishes the key intermediate **150**, straightforwardly transformed in the desired ketone **144** in five further steps and 13.9% yield. The end game involved the envisaged boron-mediated aldol reaction/1,3-anti reduction sequence toward the (-)-Bitungolide F (**143**).

3.2. (-)-Clavukerin A and (-)-Isoclavukerin A

(-)-Clavukerin A (**155**) and (-)-Isoclavukerin A (*epi*-**155**) are epimers isolated from coral *Clavularia koellikeri* [65, 66] hydroazulene skeleton. Peter Metz suggests the synthesis of these two compounds starting from optically active citronellal [67]. (*S*)-Citronellal [(*S*)-**78**)] reacts with MVK (**147**) in presence of catalyst (*S*)-**152** (20 mol%) to give the Michael addition product with a d.r. of 18:1 and in 90% of yield.

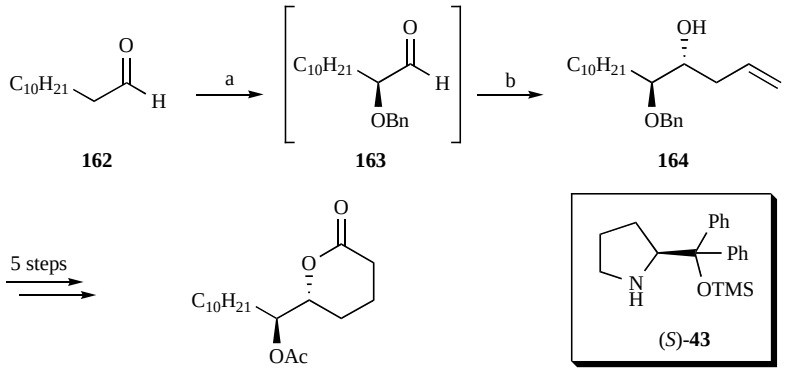
The keto aldehyde is simply converted into polyene **154** that undergoes a cascade ene-ine-ene Metathesis affording to the closure of bicycles. The overall process takes place in 35% of yield. The authors also used the same procedure to synthesize Isoclavukerin A starting from (*R*)-citronellal [(*S*)-**78**].

3.3. (+)-Conicol

Cascade reactions are very important for the formation of multiple stereogenic centers, especially when the closure of cycles is needed. This approach allows the formation of a large number of carbon-carbon or carbon-heteroatom bonds with a high level of stereocontrol. The synthesis of (+)-conicol (**161**) by Hong and coworkers [68] is a very representative example of this strategy. (+)-Conicol is a meroterpenoid isolated from marine invertebrate *Aplidium conicum* [69] containing a hexahydro-6H-benzo[c]chromene system. This same scaffold has been also found in many bioactive molecules such as (+)-Epiconicol [70, 71], (-)-heterophylol, a naturally occurring phenolic compound isolated from root bark of *Artocarpus heterophyllus*, [72], (-)-nabilone, also known as cesamet, a synthetic cannabinoid with both antiemetic and analgesic activity for neuropathic pain [73], and so on.

Hong planned a double sequential cascade reaction occurring in a one-pot step and affording the large substituted product **160** (Scheme **21**).

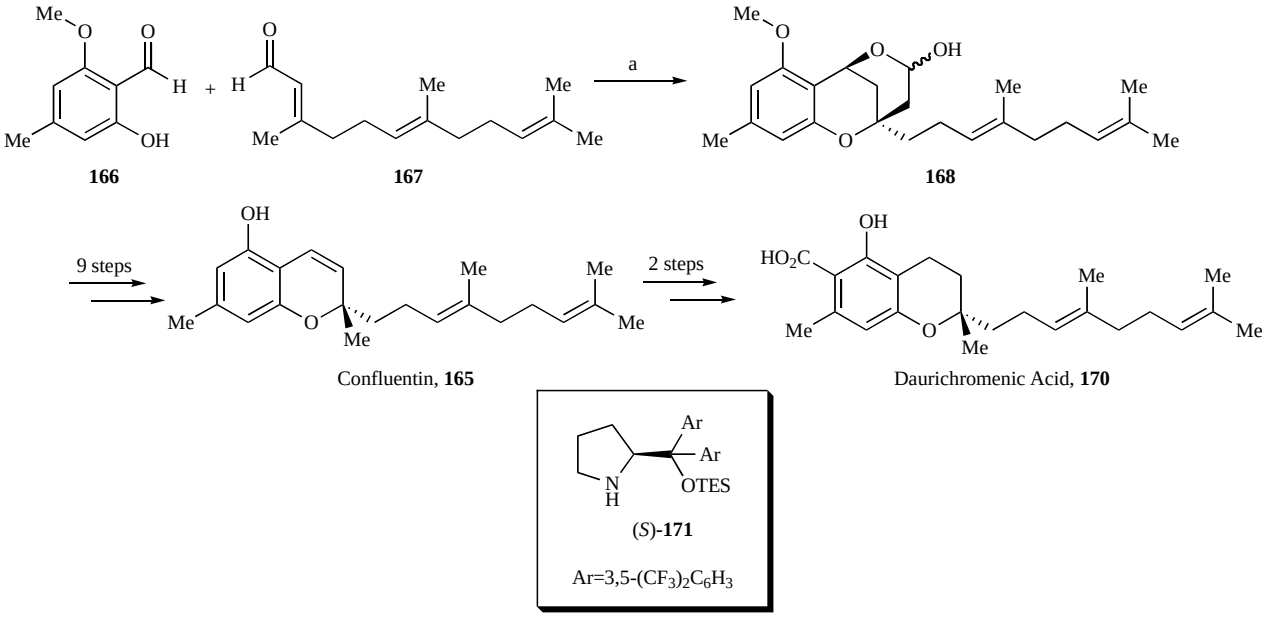
The first step of this sequence is an iminium catalysed oxa-Michael reaction of phenol **156** on conjugated aldehyde **157** and a



162 **163** **164**

(-)-acetoxy-5-hexadecanolide, **165**

Scheme 22. Synthesis of mosquito pheromone **165**. Reagents and conditions for the organocatalytic step: (a) (*S*)-**43** (5 mol%), hydroquinone (10 mol%), BzOOBz (2 eq.), THF, -20°C, 8h (95% *ee*, d.r. = 84:14); (b) CH_2=$CHCH_2Br$ (2 eq.), In (2 eq.), THF/H_2O (5/1), rt, 12h (34% yield over 2 steps).



166 **167** **168**

Confluentin, **165** Daurichromenic Acid, **170**

Scheme 23. Synthesis of Confluentin and Daurichromenic Acid. Reagents and conditions of the organocatalytic step: (a) (*S*)-**171** (30 mol %), $PhCO_2H$, toluene, 76h, rt (63%, 97% *ee*).

sequential intramolecular Michael cyclization on nitroolefin moiety. The high regioselectivity of this passage is noteworthy. Indeed, the aldehyde **157** could react as nucleophile with its γ carbon under secondary amine catalysis but it does not happen. The intermediate **158** undergoes another Michael-aldol reaction followed by the addition of aldehyde **159**. This one pot sequence gives product **160** in 55% yield and 99% *ee*. Further seven steps are necessary to get to (+)-conicol (**161**) in an approximate overall yield of 5%. Moreover, X–ray studies of different derivatives of intermediate **119** disclosed the absolute stereochemistry of (+)-conicol.

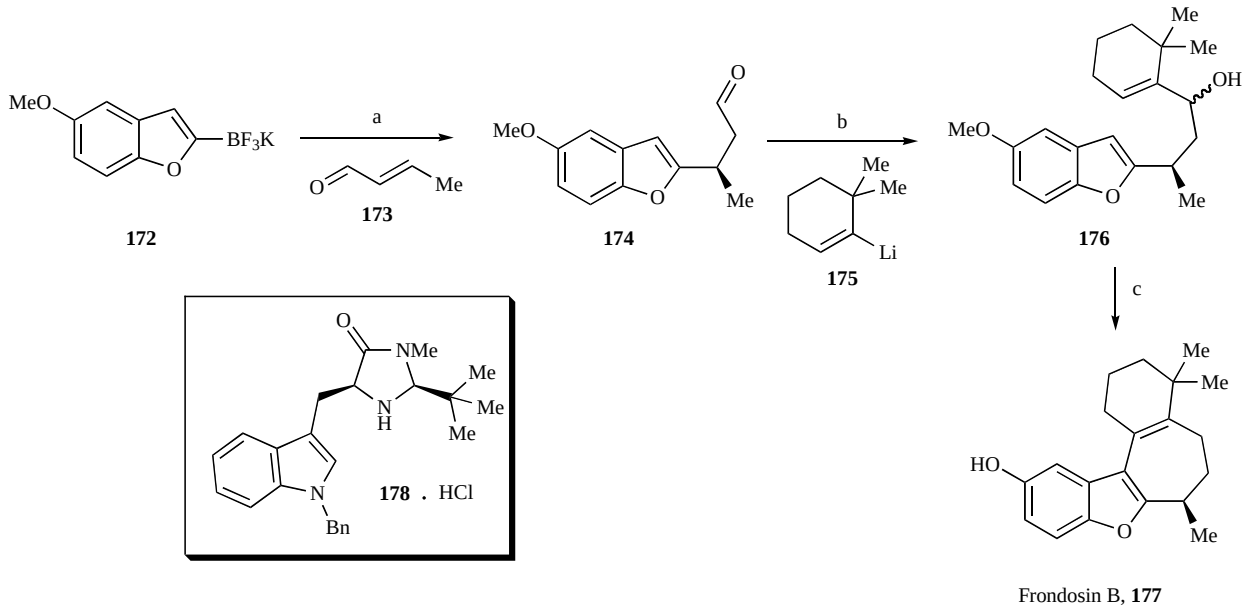
3.4. (-)-6-acetoxy-5-hexadecanolide

(-)-6-acetoxy-5-hexadecanolide **165** is a mosquitoes pheromone which has been an attractive target for the organic synthesis in the last years [74, 75]. Tae and Park developed a stereoselective, organocatalytic synthesis of 6-acetoxy-5-hexadecanolide in seven steps [76]. In order to obtain the 1,2 diols moiety, the authors proposed a one-pot benzoyloxylation followed by an Indium mediated allylation step starting from dodecanal **162**.

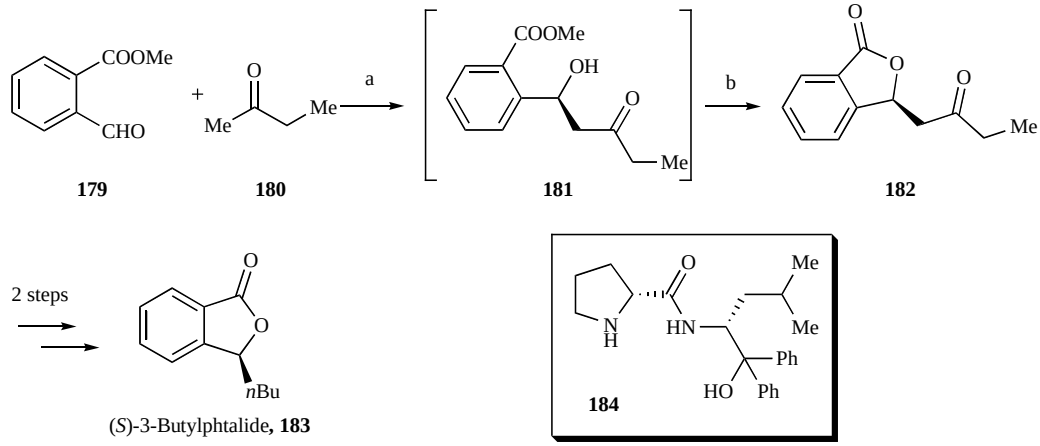
The organocatalytic benzoyloxylation already independently reported by Hayashi's [77] and Maruoka's group [78], was used here for the formation of the first stereogenic centre. The use of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (*S*)-**43** (5 mol%) and hydrochinon, in presence of benzoyl peroxide in THF ensures the product formation with a 95% of *ee*. The subsequent Indium mediated allylation of α-oxy aldehyde in THF/H_2O afforded the *anti* adduct with good diasteroselectivity (*anti:syn* = 86:14), which could be easily explained according to the Felkin-Anh transition state theory [55]. The reaction furnished the monoprotected alcohol **164** in 44% yield after the reported one-pot sequence. Compound 164 was straightforwardly converted into the desired mosquito pheromone **165** in further 5 steps.

3.5. Confluentin and Daurichromenic Acid

Daurichromenic Acid (**170**) is the main component of the methanol extract of leaves and twigs of the Asian plant *Rhododendron dauricum*. This substance showed potent anti-HIV effect in acutely infected H9 cells with a EC_{50}= 5.6ng/mL [79]. Woggon proposed the first enantioselective and organocatalytic synthesis of Daurichromenic Acid and its synthetic precursor Confluentin [80]. Proline derivative silyl ether (*S*)-**171** can mediate the domino aldol/oxa-Michael reaction *via* enamine-iminium catalysis to afford



Scheme 24. Synthesis of (+)-Frondosin B. Reagent and conditions: (a) **178**•HCl (20 mol %), HF (1.0 eq.), DME, -20°C, 24h (94% 92% *ee*); (b) **175** (generated *in situ*) THF, -78°C (86%); (c) BBr_3, CH_2Cl_2, -78°C to 0°C (88%).



Scheme 25. Synthesis of (S)-3-Butylphtalide. Reagents and conditions: (a) **184** (2.5 mol%), $PhCO_2H$ (2.5 mol%), neat, -40°C; (b) K_2CO_3, MeOH, (72%, 96% *ee*).

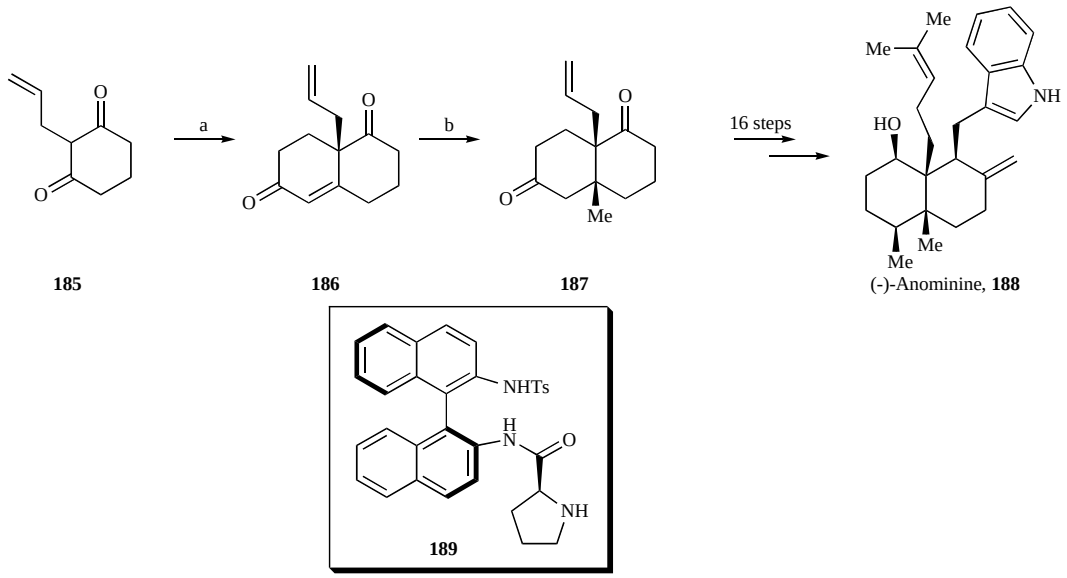
the lactol **168** in good enantiomeric excess (97% *ee*) and 63% of yield [81, 82].

A series of nine steps including a Rh mediated decarbonylation gives rise to Confluentin (**169**) with 6% yield. This compound differs from Daurichromenic Acid in the carboxyl group in position 6 and it is well-known as weak antagonist of human vanilloid receptor VR1, first isolated as racemate from the fruitbodies of the fungi of the genus *Albatrellus spp* [83]. The insertion of carboxyl group occurs in a two-step sequence that affords the final product **170** (39% yield from **169**) which shows the same optical rotation of the naturally occurring product.

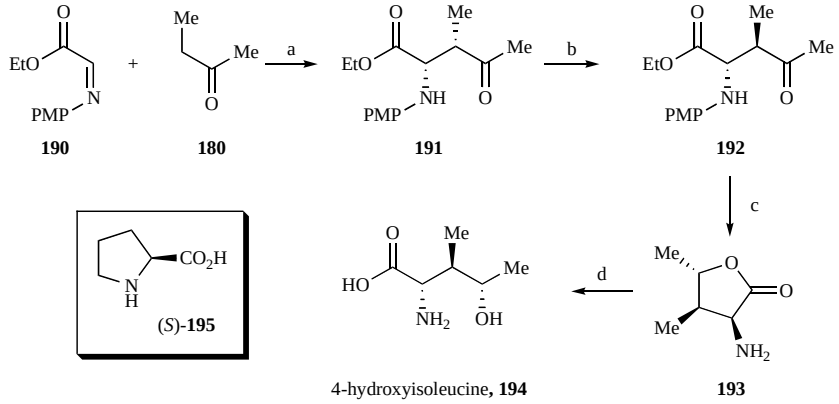
3.6. (+)-Frondosin B

MacMillan's research group developed a very concise and straightforward route to obtain (+)-frondosin B (**177**) in excellent yield (50% for the overall process) [84]. Compared to the previous ones [85, 86], the strategy here gave the natural product in only three steps (e.g. Ovaska and co-workers' approach afforded the product in ten steps and 13% yield [87]). (+)-Frondosin B, isolated from the marine sponge *Dysidea frondosa* [88], showed property as inhibitor of interleukin-8 (IL-8) receptors and protein kinase C, and have been proposed as therapeutic leads for treatment of inflammatory diseases [89]. This sesquiterterpene contains a benzofuran ring fused with cycloeptadiene ring carrying a single stereogenic center. The formation of this stereocenter was seen as an addition of the nucleophilic aryltrifluoroborate salt **172** to crotonaldehyde unsaturated system (**173**) that allows the alkylation of C-2 position of the benzofuran ring instead of the normally activated C-3 position (Scheme **24**).

As investigated by the authors [90], oxazolidinone **178** is able to activate the substrate crotonaldehyde **173** through the formation of the iminium ion intermediate, and affords the aldehyde **174** in 94% yield and 92% *ee*. The intermediate **174** reacts with **175**, obtained *in situ* from the corresponding ketone through a Shapiro reaction [91], furnishing a mixture of diastereoisomers (**176**). The next step implies a tandem reaction promoted by BBr_3, which involves a Lewis acid-mediated conjugate closure of the cycloeptadiene ring, a double bond isomerization, and a final deprotection of the methyl ether intermediate.



Scheme 26. Synthesis of (-)-Anominine. Reagents and conditions: (a) (*i*) MVK, Et_3N (1 mol%); (*ii*) **189** (1 mol%), solvent free (91%, 94% *ee*). (b) Me_2CuLi, Et_2O (79%).



Scheme 27. Synthesis of 4-Hydroxyisoleucine. Reagents and conditions: (a) DMF, (*S*)-**195** (0.35 eq.), rt; (b) MTBE, DBN (0.04 eq.), rt, then crystallization in EtOH, (50% from *p*-anisidine, 99% *de*, 99% *ee*); (c) $(NH_4)_2S_2O_8$ (2 eq.), CAN (0.1 eq.), 0–35 °C, then 2N Na_2CO_3 and $CeCl_3 \cdot 7H_2O$ (0.4 eq.), KBH_4 (1.5 eq.), –10 °C to 10 °C, 1.5 h, (70%, d.r. = 80:20); (d) LiOH (1.5 eq.), H_2O, then AcOH (65% overall yield).

3.7. (S)-3-Butylphtalide

Wang *et al*. [92] developed the first organocatalytic route for the synthesis of (*S*)-3-Butylphtalide **IV**, a molecule isolated from celery seed oil, with multiple biological activities [93].

This is a three-step synthesis based on an asymmetric aldol reaction between butanone **180** and aldehyde **179**. It was observed that this reaction is best catalyzed by pyrrolidine **184** and benzoic acid as co-catalyst. After exclusion of catalyst by filtration on a short silica pad, the intermediate undergoes a lactonization under basic conditions (K_2CO_3 in Methanol) affording the product **182** in 72% yield and 96% *ee*. The rest of the process implies the cleavage of ketone group through thioketalization and reductive desulfurization.

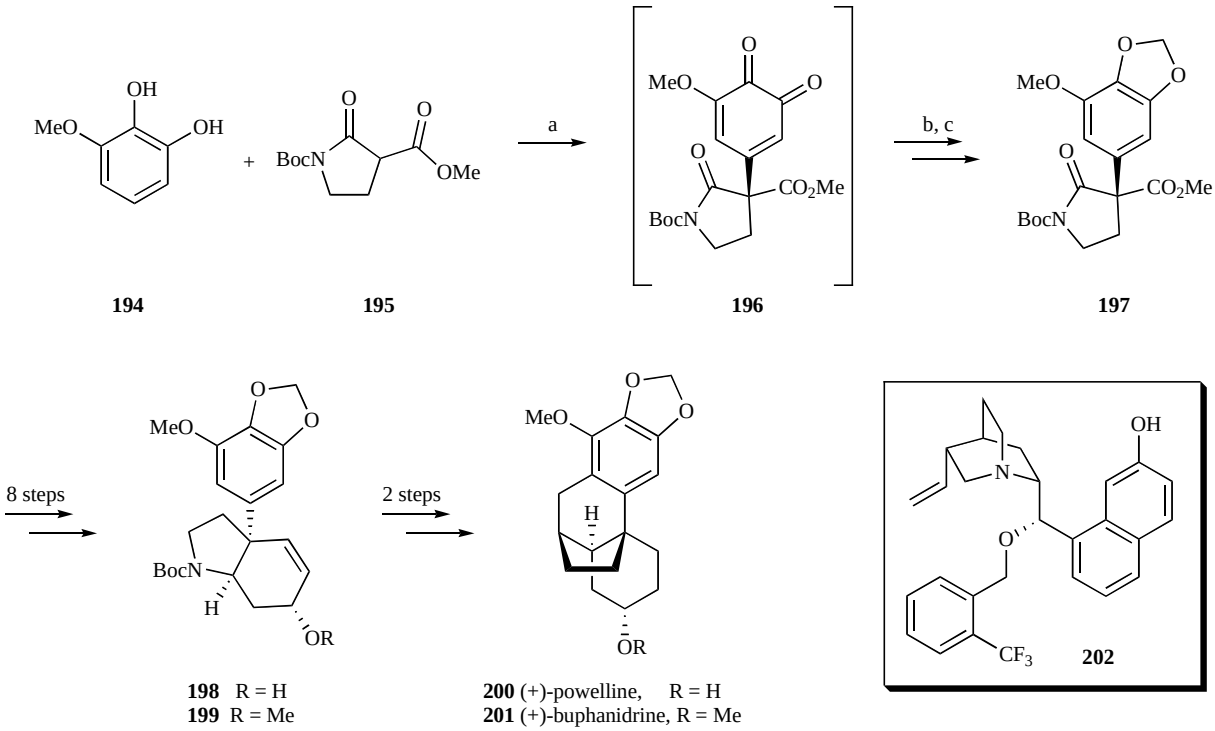
3.8. (-)-Anominine

(-)-Anominine is a diterpenoid isolated by Gloer's in 1995 [94] from the sclerotia of *Aspergillus spp*. Recently Bradshaw and Bonjoch have proposed a synthesis for (-)-Anominine, the unnatural enantiomer of the corresponding isolated substance (Scheme **26**).

The main challenge of this synthesis was to build the five contiguous stereocenters in the right configuration (*cis*), taking into account that two of them are quaternary. The first one was formed *via* Robinson annulation of diketone **185** and methyl-vinyl ketone (MVK) affording the Wieland-Miescher-like ketone **186**. Prolinamide **189** was used to promote, *via* iminium catalysis, the subsequent Michael addition reaction, ensuring 91% of yield and 94% of enantiomeric excess [95]. It has to be highlighted that once set the first stereogenic center, it influences and drives the formation of the other four. In particular, the synthesis proceeds with the C15 methylation affording the intermediate **187**, where the *cis*-junction makes one side of the double bond less hindered inducing the control on the formation of the remaining stereogenic centres. The synthesis ends in further sixteen steps affording (-)-Anominine (**188**) which differs from the natural product because of an inverse value of $[\alpha]_D$.

3.9. 4-Hydroxyisoleucine

4-Hydroxyisoleucine is a natural compound isolated for the first time from γ-aminitin hydrolysate as well as the corresponding lactone, and then in the seeds of *Trigonella foenum-graecum* as free hydroxy acid. This substance showed activity on insulin secretion and insulin resistance [96] and it has the chance to be marketed as a new antidiabetic lead. For this reason Alain Wagner *et al.* developed an asymmetric organocatalytic route to the synthesis of



Scheme 28. Synthesis of (+)-powelline and (+)-buphanidrine. Reagents and conditions: (a) PS-IO_4^-, 202 (20 mol%), DCM, -20 °C, (b) $Na_2S_2O_{4aq}$, (c) CH_2ClBr, Cs_2CO_3, DMF, 85°C (57%, 3 steps; 70% *ee*).

(2*S*,3*R*,4*S*)-4-hydroxyisoleucine (**194**), containing three contiguous stereogenic centres [97].

The 1,3 amino alcohol moiety suggests an organocatalytic Mannich-type condensation catalysed by (*S*)-proline [(*S*)-**195**], already reported by Barbas *et al.* [98]. The reaction is performed in DMF and the catalyst can be recovered by filtration up to 70%. The reaction gave the condensation product with a good regiocontrol. The nucleophylic attack of the most substituted carbon furnished the thermodynamic product, which is favoured over the kinetic one (86:14). Unfortunately the major product is the *sin* diastereoisomers, although in excellent enantioselectivity (99% *ee*). To have the right *anti*-isomer **192**, the initial product had to undergo the epimerization at C3 carbon, which was accomplished using a catalytic amount of DBN. The corresponding lactone **193** was isolated after the basic treatment in a very good diastereoselectivity (d.r. >95:5 after crystallization). In the next step the third stereogenic centre is formed. After oxidative deprotection of the amino group, the ketone is reduced to alcohol using potassium borohydride and cerium chloride in a one-pot passage. The overall synthesis affords the product in a 22% of yield on a 50g scale.

3.10. (+)-powelline and (+)-buphanidrine

The stereoselective construction of all-carbon arylated stereogenic centers is a very challenging issue [99]. Despite this, a lot of natural compounds like Amaryllidaceae alkaloids (+)-powelline and (+)-buphanidrine contain this kind of motif. In addition, two more contiguous stereocenters and a complex polycyclic structure have made this total synthesis very attractive and challenging. The titled natural products were isolated from several Amaryllidaceae species and both of them have shown affinity for the serotonin transporter in [H3]-citalopram binding assays [100-102]. Dixon *et al*. [103] proposed an organocatalytic synthesis based on an oxidative coupling of catechol **194**, oxidized to quinone from polymer supported IO_4^-, and malonate derivative **195**. The initial *in situ* oxidation converted the nucleophilic substrate **194** in a good Michael acceptor, very susceptive to the attack of the stable enolate of **195** promoted by the chiral base **202**. This sequence is followed by the reduction of quinone to free catechol subsequently protected as acetal (**197**) (Scheme **28**).

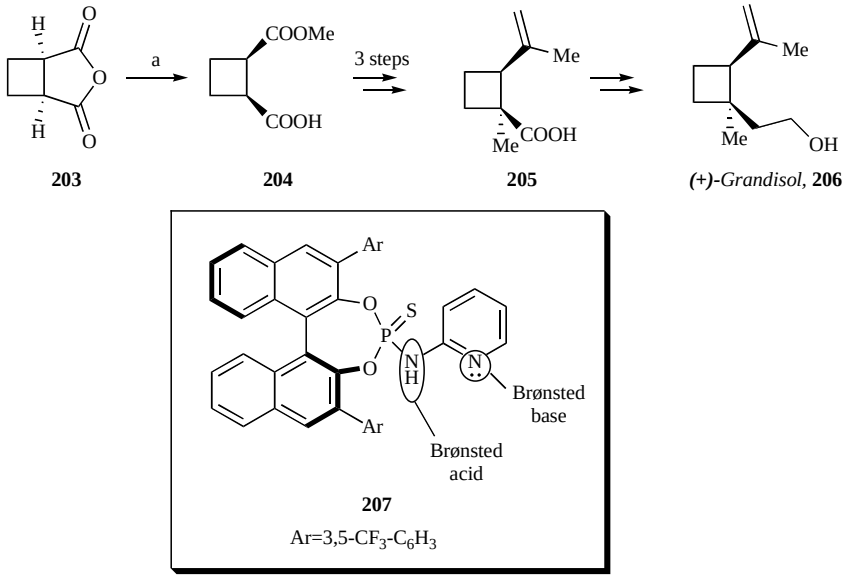
This path affords product **197** in moderate enantioselectivity (70% *ee*) and considering the three steps of this sequence an acceptable yield of 57%. Further eight steps led to the common intermediate **198** that was alkylated or not in order to obtain the two different alkaloids (+)-powelline **200** and (+)-buphanidrine **201** respectively.

3.11. (+)-Grandisol

Bifunctional organocatalysts are in many cases a valid approach to mediate a lot of organic reactions. For example catalysts containing basic and acid groups, either Brønsted or Lewis as well, can promote reactions of protic nucleophiles with electrophiles (*vide introduction*). List's group developed a new kind of bifunctional catalyst containing an acid phosphoramide group coupled with a basic pyridine moiety (Scheme **29**). It was found that this BINOL derivative (**207**) is able to catalyse the methanolysis of symmetric anhydride **203** providing substituted cyclobutane **204** containing two well defined stereogenic centres [104]. The reaction shows an excellent enantioselectivity and yield (98%*ee*, 97% respectively) and this fact allowed the development of **205**, already known as precursor of (+)-Grandisol (**206**) [105]. So it has been proved that desymmetrization is an interesting route for obtaining optically active molecules.

3.12. Other Synthesis of Natural Products

(-)-Pancracine (**208**) belongs to the montonine-type Amaryllidaceae alkaloids, whose structure is characterized by an octahy-



Scheme 29. Synthesis of (+)-Grandisol. Reagents and conditions: (a) **207** (10 mol%), MeOH (10 eq.), toluene, -35°C (97%, 98% *ee*).

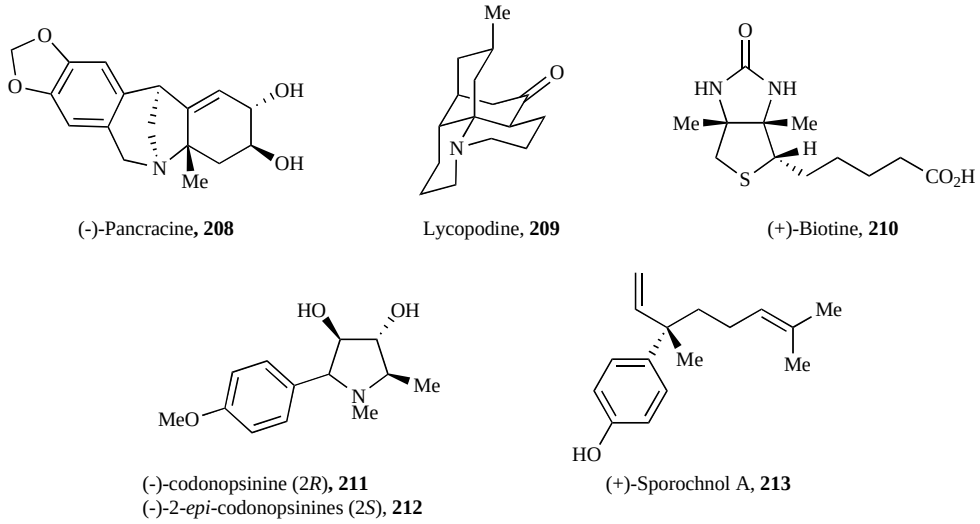
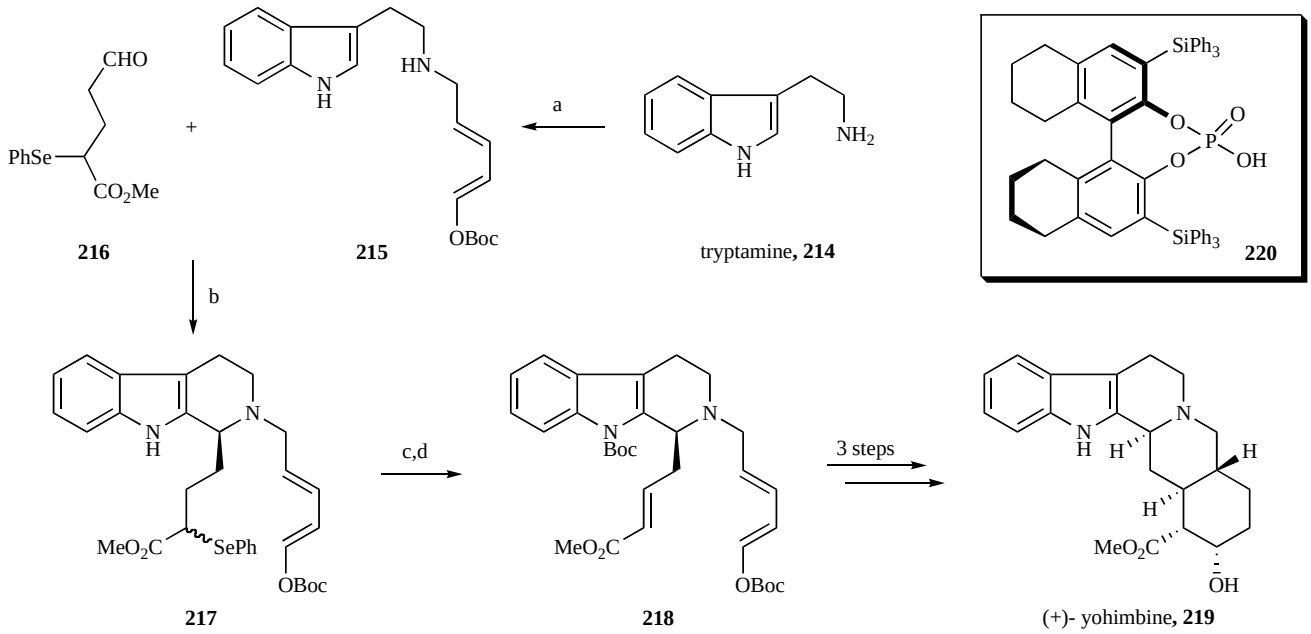


Fig. (6). Selected other natural products synthesised in 2010.

droindole motif. Pansare *et al.* developed a high valuable approach to the total synthesis of such a natural product. Particularly, the Canadian group devised a simple and stereoselective preparation of *cis*- and *trans*-3-aryloctahydroindoles by means of an enamine-based organocatalytic Michael addition of cyclic ketones (Michael donor) and suitable 2-nitrovinylarene (Michael acceptor) (up to 90% yield, up to 99% *ee*). syn/anti ≥ 19/1) [106]. Likewise, an organocatalytic intramolecular Michael addition was the first key step in the total synthesis of Lycopodine (**209**), one of the major subclass of *Lycopodium* alkaloids, well-known for their wide-ranging biological active and structural complexity. After having synthesised a novel sulphonamide proline derivative, Yang and Carter validated the potential of their organocatalyst by achieving the desired precursor of Lycopodine and a series of six-membered ring in high yield (up to 80%) and excellent stereoselectivity (up to 95% *ee*, up to d.r. > 20:1) [107]. A slight different kind of sulfonamide resulted the most suitable organocatalyst toward the total synthesis of (+)-biotine (**210**) [109]. Chen *et al*. employed a cinchona alkaloid base-mediated alcoholysis strategy for the construction of the two contiguous stereogenic centres of the biotin skeleton. The use of extremely mild conditions appeared to be high compatible with industrial scale and a valid alternative to the previous existing syntheses. An organocatalytic asymmetric direct Henry reaction was the key point toward the short total synthesis of (-)-codonopsinine (2*R*, **211**) and its epimer (-)-2-*epi*-codonopsinine (2*S*, **212**). Particularly, Ooi *et al.* efficiently mediated the acyl addition reaction by means of a chiral tetraaminophosphonium salt, obtaining the first common intermediate of either four or five steps syntheses with excellent *anti*-selectivity (94% yield, *anti*/*syn* = 20/1) and enantioselectivity (99% *ee*) [108]. Finally, it has to be mentioned the short synthesis of (+)-sporochnol A (**213**), whose interest relies in the construction of a cyclohexanone derivative bearing a quaternary carbon stereogenic center [110]. Such a challenging target was elegantly reached by Kotsuki *et al*. developing a new method for a Robinson-type annulation mediated by the combined use of (1*R*,2*R*)-1,2-cyclohexanediamine with (1*R*,2*R*)-1,2-cyclohexanedicarboxylic acid. The desired enantioenriched intermediates were obtained in moderate yield (up to 65%) and good enantioselectivity (up to 94%*ee*), one of which was straightforwardly transformed in the natural product **213** with further four steps.



Scheme 30. Synthesis of (+)-Yohimbine. Reagents and conditions: (a) Boc-protected glutaconaldehyde, MeOH, -20°C, 2h, then $NaBH_4$, 1h and quenched with acetone (45%); (b) **220** (10 mol%), MS 4 Å, toluene, 50°C; (c) $(Boc)_2O$, DMAP, 40°C (82%); (d) mCPBA, -78°C, then Et_3N -78°C-> 20°C (88%, 84% *ee*).

4. 2011

4.1. (+)-Yohimbine

Over the years, organocatalysis provides equally efficient access not only to new and efficient methodologies, but also to a wide range of natural products. The total synthesis of (-)-Yohimbine (**219**), one of the well-known alkaloids [111], represents a clear example of such eclectic behaviour and broad applicability of organocatalytic strategies. Since its first total synthesis as racemic compounds more than 50 years ago [112], several asymmetric approaches have been published by famous research groups [113, 114]. Recently, as compromise between Jacobsen methodology [115] and their on-going research on Pictet-Spengler cyclization of *N*-monosubstituted tryptamines [33], Hiemstra *et al.* [116] have illustrated the general synthetic utility of their strategy by developing the total synthesis of (-)-Yohimbine (**219**) (Scheme **30**). After having prepared the rather unstable tryptamine derivative (**215**), its enantioselective reaction with the phenyl seleno aldehyde partner (**216**) was performed overnight in presence of catalytic amount of enantiopure binolphosphoric acid (**220**) (20 mol%) producing the adduct (**217**) as a mixture of diastereomers. The subsequent two steps, in which the protection of NH group and the removal of the phenylselenio moiety have carried out, gave the optically active **218** in good yield (88%) and enantioselectivity (84% *ee*). Further 3 steps including a key IMDA furnished the wanted natural product (**219**) in excellent enantiomeric excess (98% *ee*).

It is noteworthy that the optimized conditions for the Pictet-Spengler reaction were the results of an elaborate screening. Indeed, the aldehyde amount resulted to be crucial for the reaction, which either did not proceed without an excess of **216**, or gave lower enatioselectivity if it is present a too large amount of **216**.

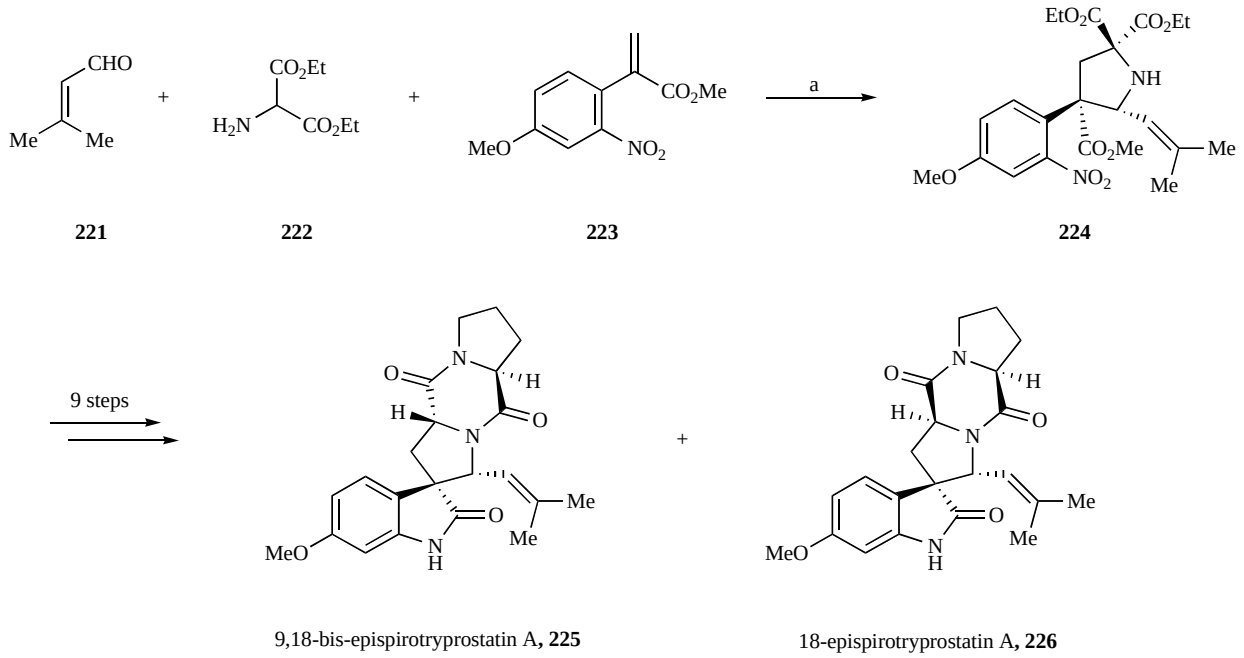
4.2. Spirotryprostatins A and B

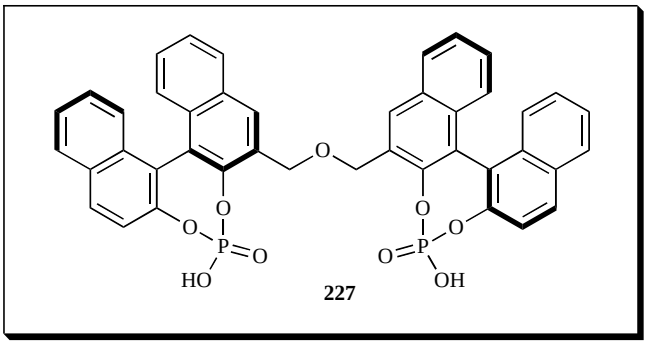
The spiro[pyrrolidin-3,3'-oxindole] unit is a common structural feature for a large family alkaloid natural products exhibiting important biocidal activity [117]. For example, Spirotryprostatins A and B isolated from the fermentation broth of *Aspergillus fumigates*, inhibit the G2/M progression of cell division in mammalian tsFT210 cells. Due to such intriguing activity and to the challenging structural core, several efforts have been made towards the enantiocontrolled synthesis of the natural products themselves and their analogues [118, 119]. Within this context, Gong and co-workers applied their enantioselective 1,3 dipolar cycloaddition to the total synthesis of 9,18-bis-epispirotryprostatin A (**225**) and 18-epispirotryprostatin A (**226**) [120]. Particularly, they envisioned that the prenyl aldehyde (**221**) and diethyl-2-aminomalonate (**222**) in the presence of a suitable chiral Brønsted acid (2**27**), react with methyl-(2-nitrophenyl)-acrylate (**223**) to furnish the key intermediate **224** (Scheme **31**).

Conducting the reaction with 10 mol% of catalyst **227** under argon atmosphere at 40°C, an excess of acrylate **223** gave the expected product **224** in 94% yield and amazing stereocontrol (d.r. > 99%, *ee* >99%). Further nine steps straightforwardly led to the target spiro[pyrrolidine] derivatives.

4.3. (-)-Zampanolide

Since the discovery of paclitaxel inhibition action mode, the search for analogues anticancer drugs has become a subject of immense interest in chemical, biological and medicinal fields [121]. Besides few antitumor therapeutics, which have exhibited intriguing synergic effect with taxol, quite recently, (-)-zampanolide (**228**), a 20 membered macrolide, have revealed potent microtubule-stabilising properties [122]. Indeed, isolated from marine sponge *Fasciospongia rimosa* in Okinawa and from *Cacospongia mycofijiensis*, a Tongan marine sponge, (-)-zampanolide (**228**) showed potent cytotoxic activity against SKM-1 and U937 cell lines, quite resistant to paclitaxel. Although from structural point of view, the unique unsaturated macrocycle contains only three stereogenic centres and a chiral *N*-acylaminal side chain, the chemistry and biology of this therapeutic have attracted much synthetic attention over the years. Amongst the total syntheses, which have been reported from its isolation in 1996, Ghosh and Cheng have recently accomplished the enantioselective synthesis of (-)-zampanolide





Scheme 31. Synthesis of Spirotryprostatin A analogues. Reagents and condition for the organocatalytic reaction: (a) **227** (10 mol%), toluene, 3 Å MS, 40°C, 72h (94%, *ee* > 99%, d.r. >99:1).

(**228**) [123], relying on a convergent approach, which allowed them to prepare a wide range of analogues (Scheme **32**).

Besides the several steps featured by a novel intramolecular oxidative cyclization, a cross-metathesis reaction to construct a trisubstituted olefin, and a ring-closing metathesis to form a highly functionalized precursor, the strategic bond disconnection resulted to be the cleavage of the sensitive *N*-acylaminal side chain at C20, which provide the macrolactone **229** in the retrosynthetic scheme.

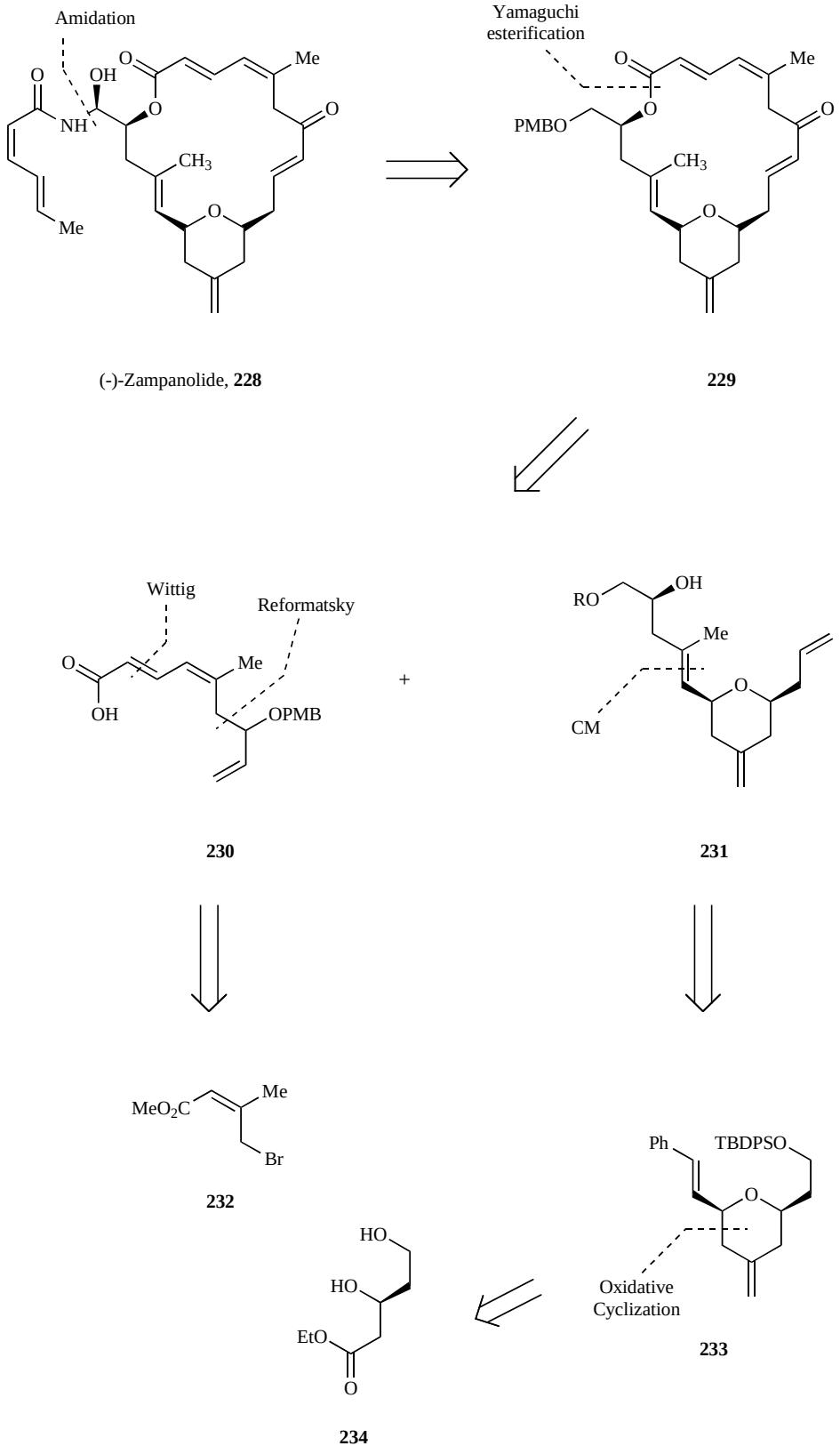
Particularly, once prepared the lactone **229**, the conversion of (-)-**235**, the unnatural antipod of dactylolide, to the desired (-)-zampanolide (**228**) included the reaction between a carboxamide **236** and the aldehydic moiety with the consequent formation of the desired *N*-acylaminal **228**. Such a direct addition was accomplished in excellent chemoselectivity toward the monoaddition performing the reaction in presence of matched chiral phosphoric acid (*S*)-TRIP (**237**), at 23°C for 12h. (-)-Zampanolide **228** and its epimer *epi*-Zampanolide (*epi*-**228**) were isolated respectively in 51% and 18% yield after separation/purification by HPLC.

Conversely, the employment of the corresponding mismatched (*R*)-TRIP afforded a 1:1 mixture of the two epimers.

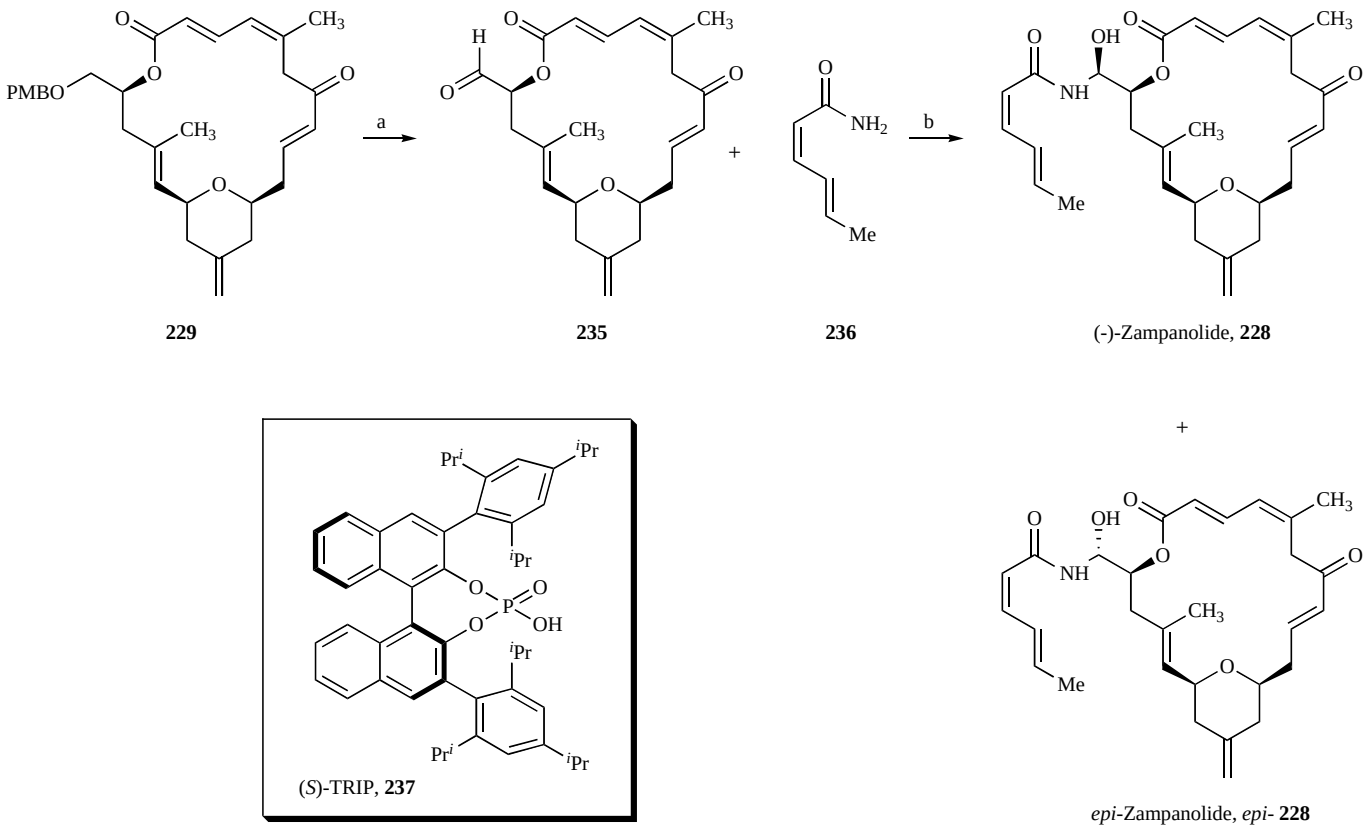
4.4. Baclofen

Due to their readily availability, efficiency and versatile catalytic action, chincona alkaloids with their pseudoenantiomers forms, are among the most privileged and useful catalysts or ligands in asymmetric organocatalysis [124-127]. Likewise, the second generation dimeric ligand, such as $(DHQ)_2PHAL$ [Bis(dihydroquinidine)phthalizine], showed superior activity and selectivity as consequence of their enzyme-like binding pocket [128]. Prompted by the successful achievement of such compounds in Sharpless AD (Asymmetric Dihydroxylation) reactions, Lin *et al*. [129] envisaged the possibility to design a new type of biscinchona alkaloids, which should have been used in various and different asymmetric fields. After having developed and fully characterized the novel dimeric ligand, and its pseudoenantiomer, the Chinese group validates its efficiency and effectiveness by exploiting QD-**244** in the first step toward the synthesis of Baclofen (**243**) (Scheme **34**).

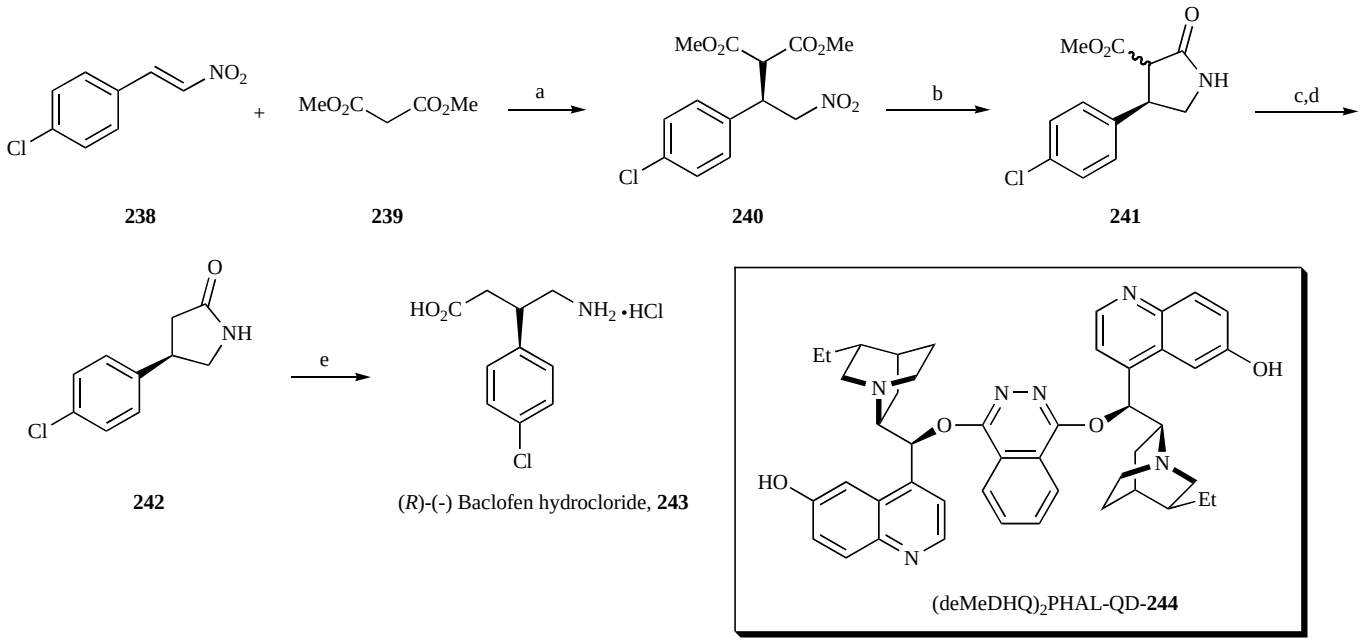
Indeed, the conjugate addition of dimethylmalonate **239** to a suitable nitroalkene **238**, was perfomed at rt in the presence of just 1 mol% of QD-**244** affording the desired product **240** in good yield



Scheme 32. Retrosynthetic approach to the total synthesis of (-)-zampanolide (**228**).



Scheme 33. Synthesis of (-)-zampanolide. Reagents and Conditions: (a) DDQ, H_2O, then Dess-Martin, CH_2Cl_2, rt (52%); (b) (*S*)-TRIP (**237,** 20 mol%), 23°C, 12h (**228** 51% yield, *epi*-**228** 18% yield).

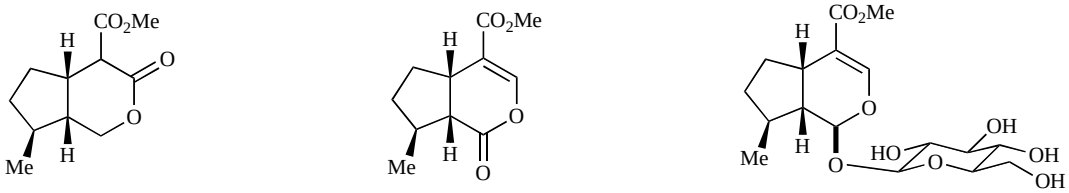


Scheme 34. Synthesis of (*R*)-(-)-Baclofen Hydrochloride. Reagents and conditions: (a) QD-**244** (1 mol%), THF (1 M), rt, [98% (87% after recrystallization), 92% *ee* (>99.9% *ee* after a single recrystallization)]. ; (b) $NiCl_2$•$6H_2O$, $NaBH_4$, MeOH, 0°C (93%); (c) NaOH (1 M), EtOH; (d) toluene, reflux [95% (after 2 steps)]; (e) HCl (6M), reflux (94%).

(87%) and excellent enantioselectivity (>99% *ee*) after only a single recrystallization. Further five steps nicely converted the first intermediate to (*R*)-4-(4-chlorophenyl)-2-pyrrolidinone hydrochloride (**243**).

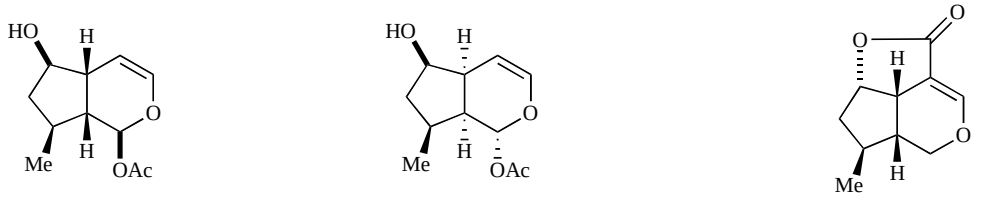
4.5. (-)-7-Deoxylonganin

Cyclopentapyrane core of type I and II with a *cis* relationship between H9 and H5 is the common main scaffold of Iridoids, a diverse family of natural products which shows a pivotal involve-



Type I, **245** Type II, **246** 7-deoxyganin, **247**

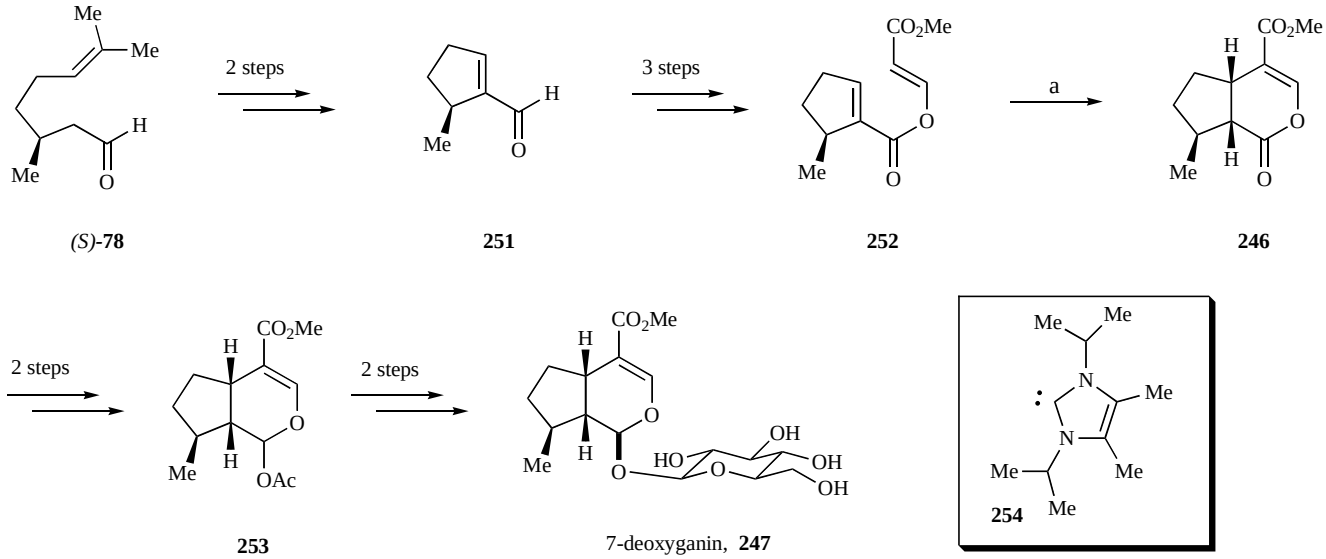
cyclipentapyran



248 **249** 9-deoxygelsemide, **250**

antiproliferative catalpol derivatives

Fig. (7). Iridoid natural products.



(S)-**78** **251** **252** **246**

253 7-deoxyganin, **247**

Scheme 35. Synthesis of (-)-7-deoxyloganin. Reagents and conditions for the organocatalytic reaction: (a) **254** (20mol%), THF, -78°C to rt, 14h (63%, 97% *ee*).

ment in the non-nitrogenous component in alkaloids biosynthesis (Fig. **7**) [130].

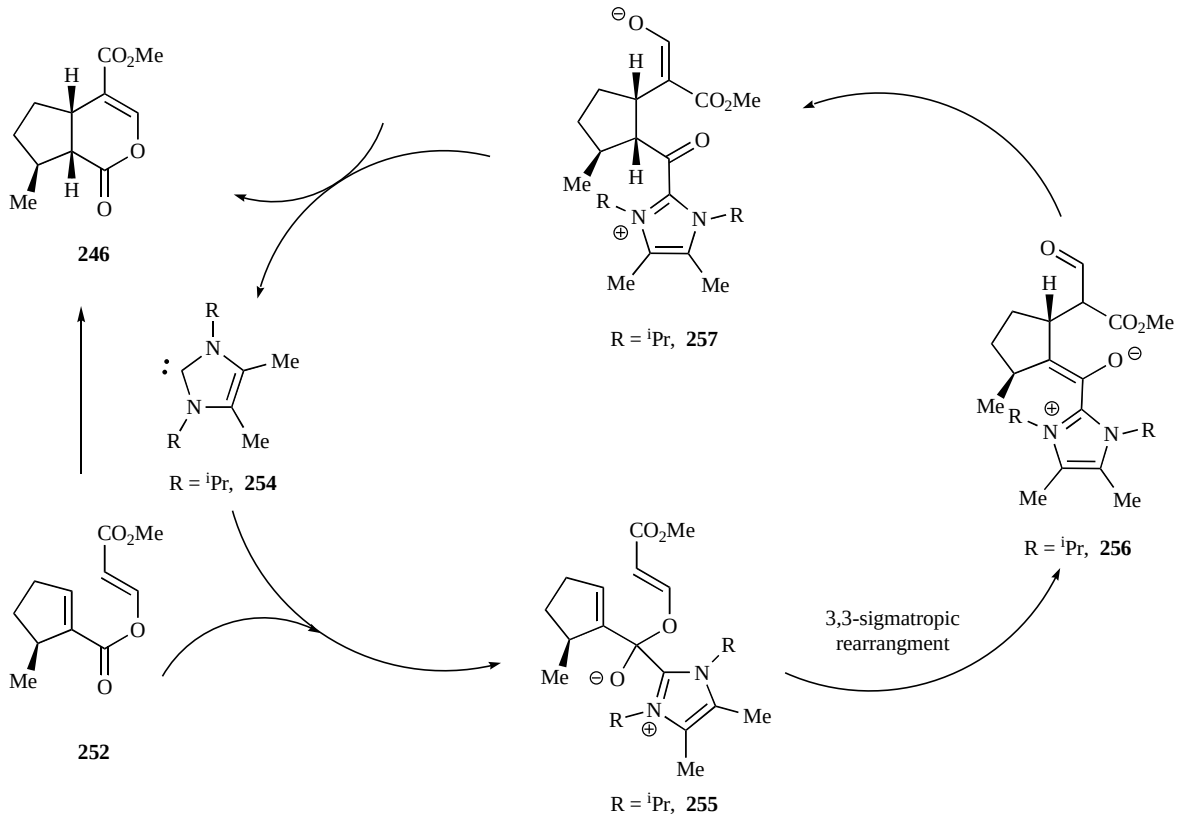
Pursuing their research in the use of *N*-heterocyclic carbene (NHC) catalysts [131], Candish and Lupton provide a nice access to the cyclopentanpyrane core of (-)-7-deoxylonganin **247**, and ultimately the natural product itself (Scheme **35**) [132]. After having optimised the reaction conditions on the pilot substrate, the Australian group accomplished the stereocontrolled formation of the lactone **247** (78%, 97% *ee*) upon the rearrangement of the optically active α,β-unsaturated ester **252** (prepared in 5 steps from citronellal (*S*)-**78**) employing the diisopropyl dimethyl NHC **254** (20 mol%) as catalyst in THF.

In order to explain the observed stereochemical outcome, the authors postulated and demonstrated the formation of a hemiacetal **255**, which *via* the key 3,3-sigmatropic rearrangement (Claisen rearrangement) furnishes the intermediate **256**, on which the second stereogenic centre is installed before the catalyst elimination (Scheme **36**).

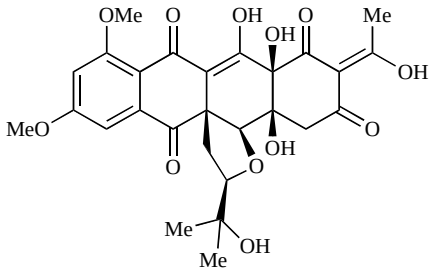
The multistep synthesis toward the desired natural product (-)-7-deoxyloganin (**247**) was successfully ultimated in further four steps.

4.6. Seragakinone A

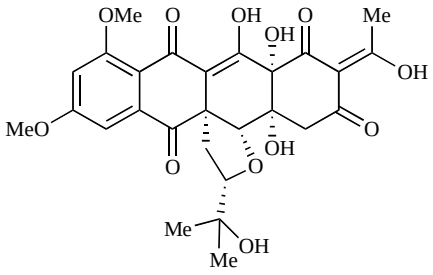
Sometimes, extensive spectroscopic studies and single-crystal X-ray analysis are not able to unambiguously assign the absolute configuration to new and biologically active molecules. As consequence, the total synthesis of such compounds is the only reliable tool in order to defined the stereochemistry. This is the case of (+)-Seragakinone A (**258**, Fig. **8**), an antifungal and antibacterial compound produced by a marine fungus, and its enantiomer (-)-Seragakinone A (*ent*-**258**, Fig. **8**) [133], which has been recently synthesised by Takada *et al*. [134].



Scheme 36. A possible reaction mechanism.

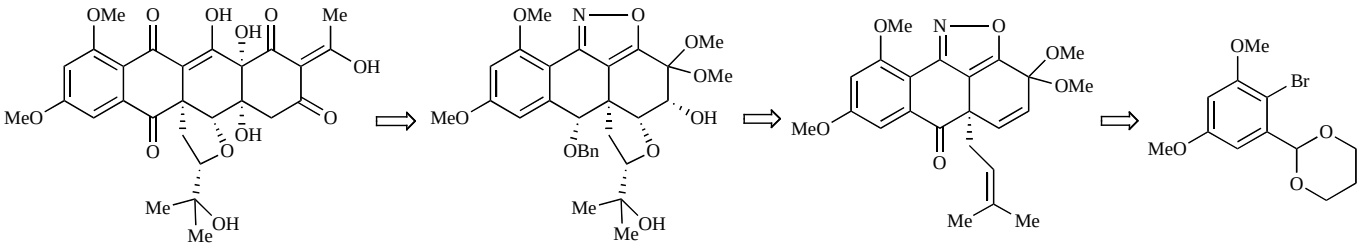


(+)-Seragakinone A**, 258**



(-)-Seragakinone A**,** *ent*-**258**

Fig. (8). Structure of (+)-Seragakinone A (**258**) and its enantiomer *ent*-**258**.

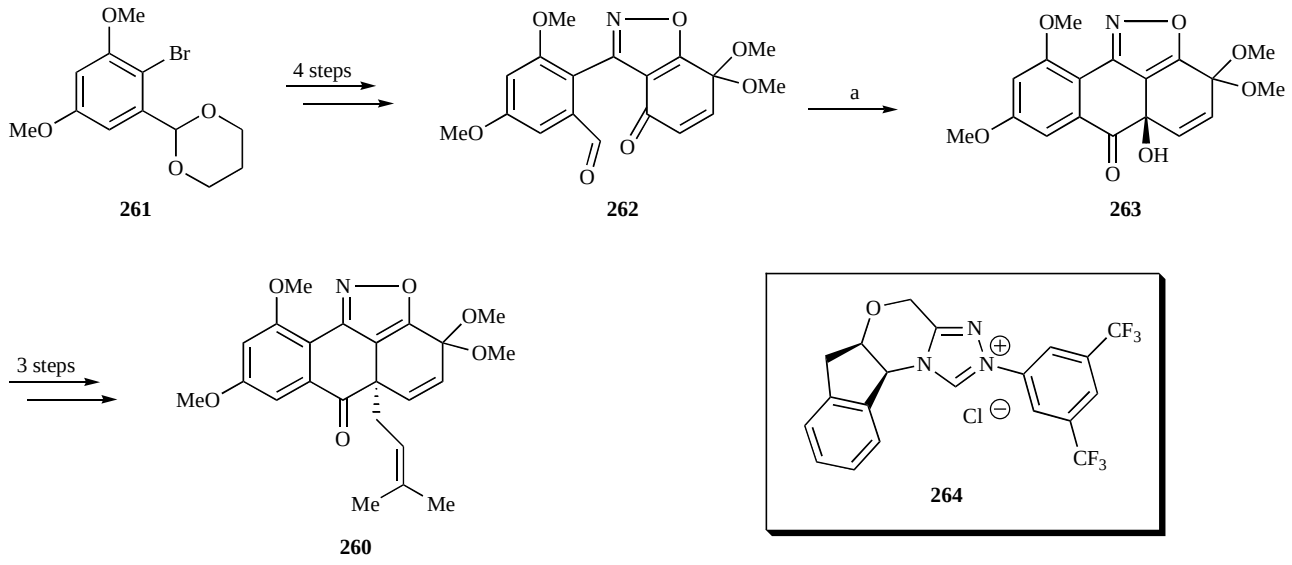


(-)-Seragakinone A**,** *ent*-**258** **259** **260** **261**

Scheme 37. Retrosynthetic approach to (-)-Seragakinone A.

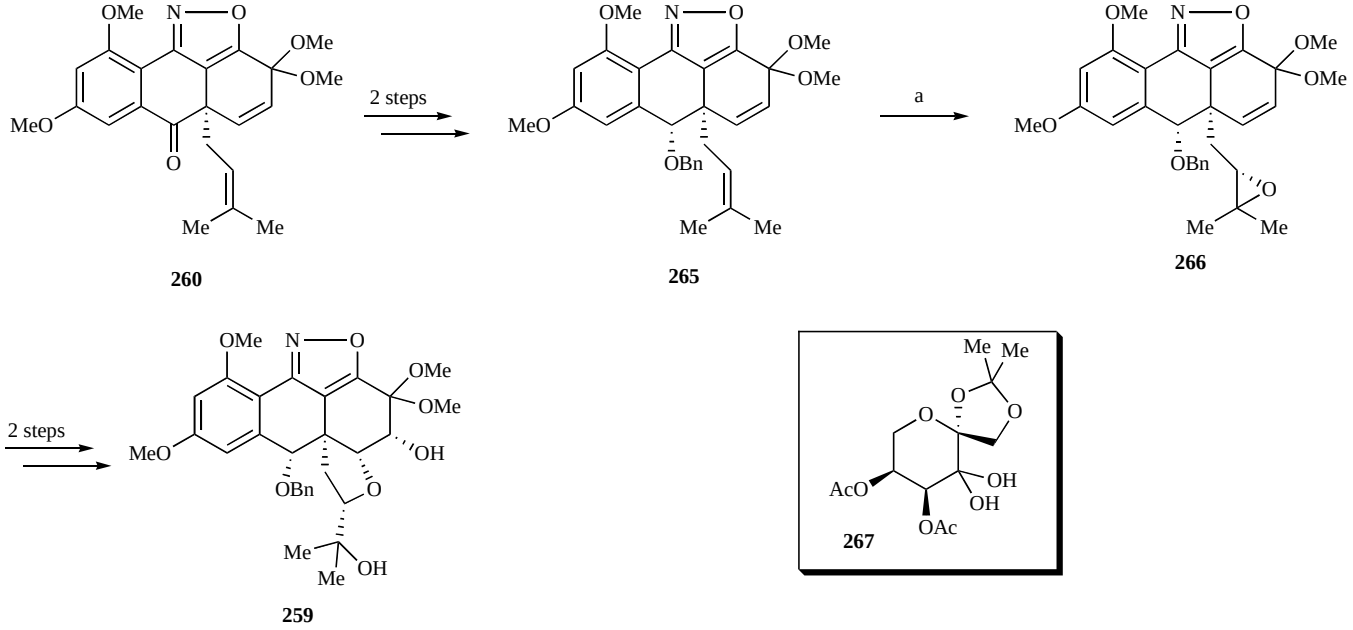
Despite the molecular complexity, the authors have bravely chosen a linear synthetic approach, which could be divided in three main blocks (see above) starting from the well-known bromide **261** (Scheme **37**). Each of them involves a pivotal organocatalytic reaction, which allows the stereocontrolled installation of key stereogenic centres.

Concerning the achievement of the first intermediate (**260**), the benzoin cyclization of ketoaldehyde **262** is worthy to be noted. Employing the modified Rovis triazolinium salt **264** (10 mol%) in the presence of Et_3N (10 mol%) at rt, [135] the desired cyclic ketol (*R*)-**263** was successfully obtained in high yield (86%) and excellent enantiocontrol (99% *ee*) (Scheme **38**).



261 **262** **263** **260** **264**

Scheme 38. Synthesis of prenyl ketone **260.** Reagents and conditions of the organocatalytic step: (a) **264** (10 mol%), Et_3N (10%), THF, rt (86%, 99% *ee*).



260 **265** **266** **259** **267**

Scheme 39. Reagent and conditions of the organocatalytic reaction: (a) **267** (20 mol%), Oxone, K_2CO_3, nBu$_4$NHSO$_4$, $(CH_3O)_2CH_2$, CH_3CN, H_2O, (pH 6), 0°C, 24h (92%, d.r. = 8.2:1).

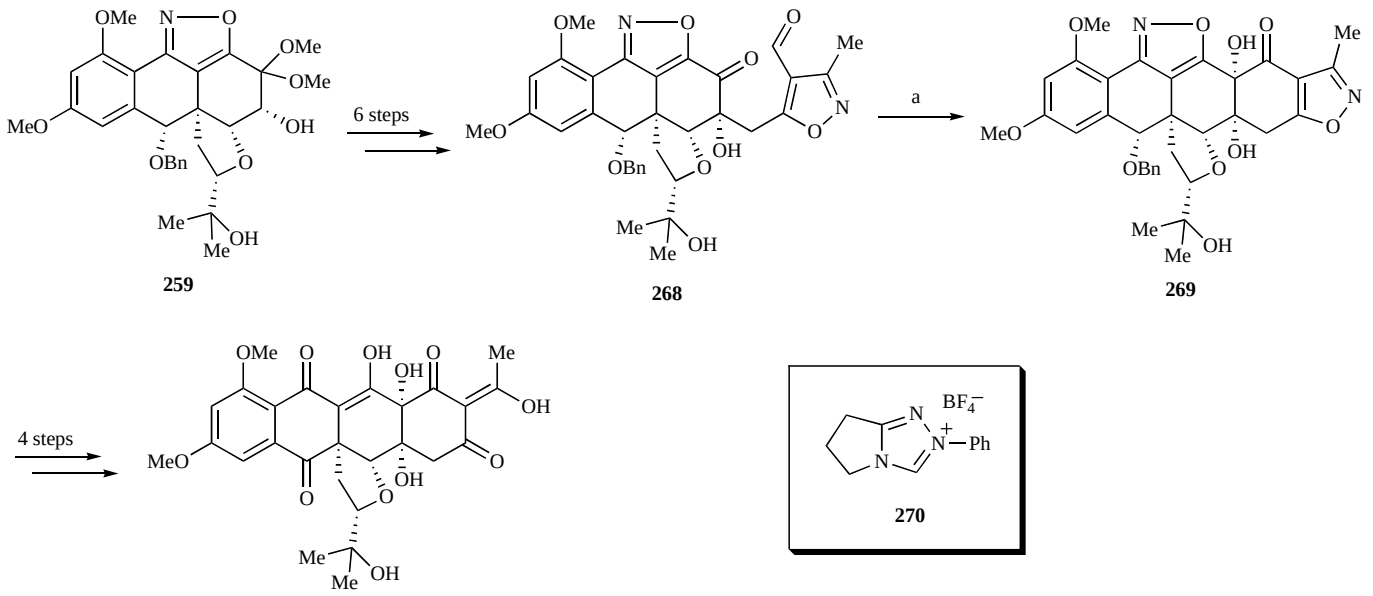
Three further steps involving a final cross-methatesis furnished the key prenyl ketone **260**, which was subsequently transformed in the intermediate **265**, a suitable substrate for the electrophilic Shi epoxidation [136]. The ketone hydrate **267** (20 mol%) proved to be the most effective catalyst, furnishing the desired epoxide **266** in high stereoselectivity (d.r. = 8.2:1, Scheme **39**). Although, in this context the organocatalyst activated the oxidizing agent and not the substrate, it was the electron-rich methylene that performs a nucleophilic attack toward the electron-poor reagent.

A second benzoin cyclization was required to achieve the formation of the densely oxygenate pentacyclic core. The reaction of **268** preceded nicely employing the triazolinium salt **270** (20 mol%) [137] and DBU (20 mol%) in methanol to give ketol **269** in 90% yield and excellent diastereoselectivity (d.r = 15:1, Scheme **40**). The first asymmetric total synthesis of (-)-Seragakinone A (*ent*-**258** was than straightforwardly achieved by further four steps.

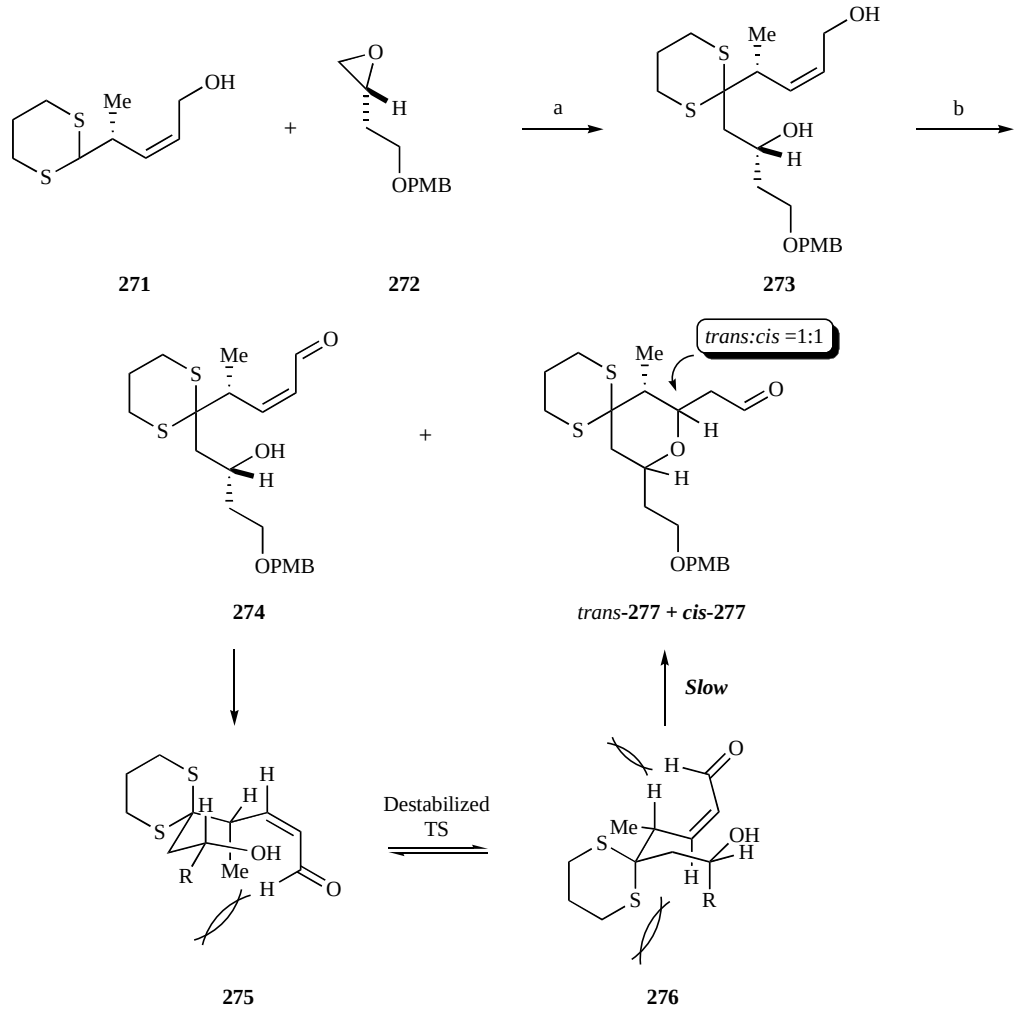
4.7. Leucascandrolide A

The stereoselective formal synthesis of Leucascandrolide A represents a successful employment of organocatalysis to the preparation of macrolide. In particular, Hong and co-workers assembled the 2,6-*cis* and 2,3-*trans*-2,6-*trans*-tetrahydropyran moieties implanted in the natural product, through an organocatalytic oxa-Michael reaction [138]. The coupling between epoxide **272** and allylic alcohol **271** followed by an allylic oxidation, provided the aldehyde **274** as the major product, which initially did not afford only the desired Michael adduct *trans*-**277**, but to a 1:1 mixture of the possible *trans:cis* isomers (Scheme **41**). Such an unexpected behaviour was probably due to the stereochemical mismatch between the C3 methyl group and the C6 alkyl group in **275** and **276**.

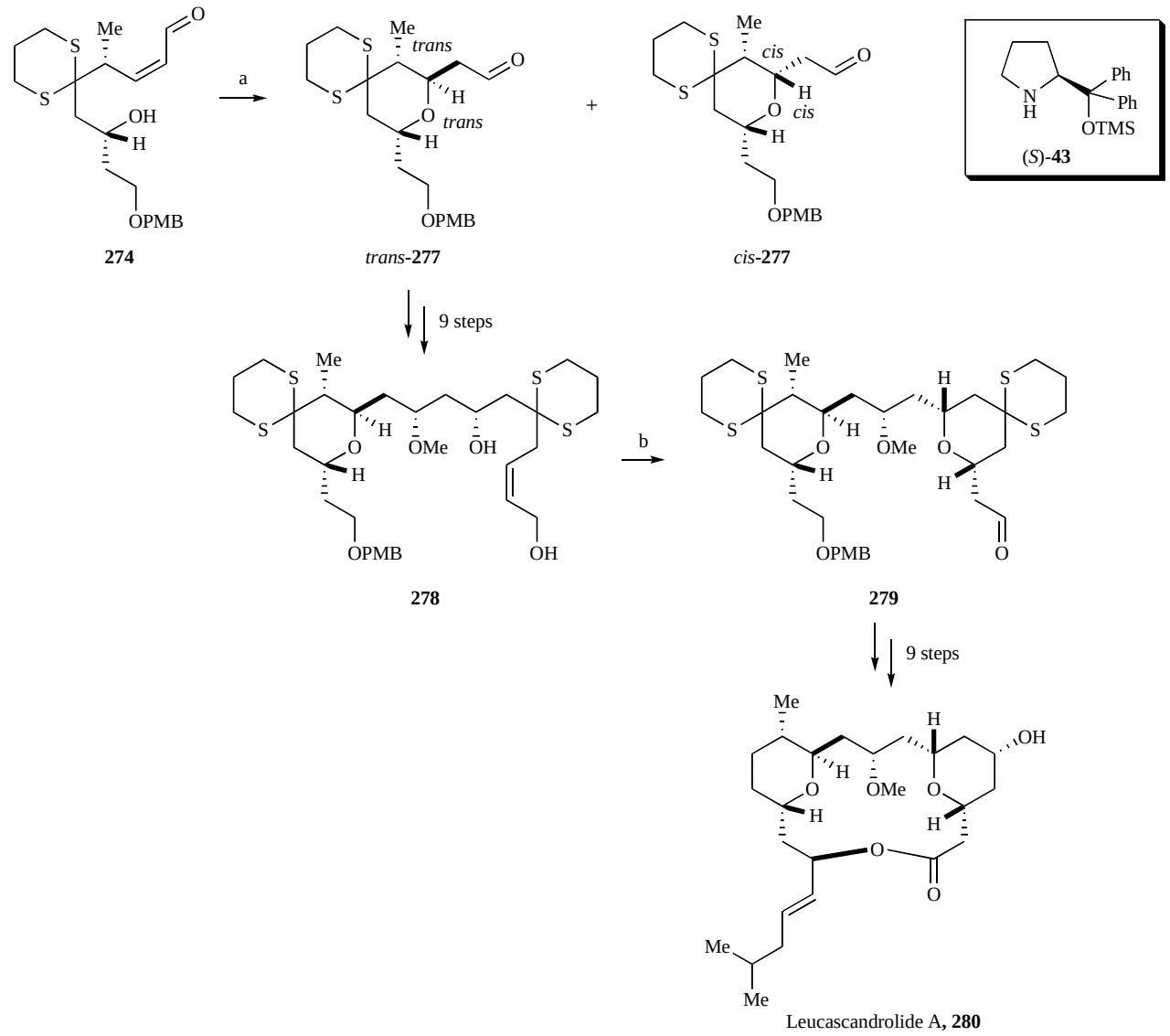
Conversely, the intramolecular 1,4-addition smoothly proceeded by treating the aldehyde **274** with Hayashi catalyst (*S*)-**43** at -40°C, so that the requested intermediate *trans*-**277** was achieved in



Scheme 40. Synthesis of (-)-Seragakinone A. Reagents and conditions for the organocatalytic reaction: (a) **270** (20 mol%), DBU (20 mol%), MeOH, rt, 30 min (90%, d.r = 15:1).



Scheme 41. Reagents and conditions: (a) ^{t}BuLi, HMPA/THF (1/10), -78°C, 10 min, then **272** -78°C, 1h (81%); (b) MnO_2, CH_2Cl_2, 0°C, 4h (70% of **274**, 12% of *trans*-**277** and *cis*-**277** as 1:1 mixture).



Scheme 42. Ending game for the total synthesis of Leucascandrolide A. Reagents and conditions: (a) (*S*)-**43** (20 mol%), BzOH (20 mol %), CH_2Cl_2 at -40°C (d.r. > 20:1, 98%); (b) MnO_2, CH_2Cl_2, 0°C, 4h (d.r. > 20:1, 86%).

excellent stereoselectivity (d.r. > 20:1) and yield (98%). Further seven steps allowed the stereoselective preparation of a second key allylic alcohol **278** which this time successfully underwent to the key tandem allylic oxidation/oxa-Michael reaction without the use of an organocatalytic support and stereoselectively providing the desired 2,6-cis-tetrahydropyran aldehyde **279** (d.r. >20:1, 86%). The completion of the total formal synthesis was subsequently accomplished in no more than 9 steps.

Although the proposed synthetic route resulted to be quite long and complex, it clearly demonstrated the potential of the tandem and organocatalytic oxa-Michael reaction in conjunction with the dithiane coupling as valuable alternative to the classical transformation, which could be extended to the synthesis of other and related macrolactones.

4.8. Bromopyrrole Alkaloids

The pyrrolopiperazine moiety is one of the key scaffolds found in a great number of bromopyrrole alkaloids, a critical class of natural products featured by interesting and various biological properties [139, 140]. Among others, noteworthy examples are: Longamide B (**281**), isolated from the Caribbean sponge *Agelas dispar*, exhibits antibiotic activity against the Gram-positive bacteria *Bacillus subtilis* and *Staphilococcus aureus* [141]; (-)-Cycloroidin (**282**) [142], obtained from the Mediterranean sponge *Agelas oroides* and the epimeric mixture of Agesamide A (**283**) and B (*epi*-**283**), found in the Okinawan sponge *Agelas sp*. (Fig. **9**).

Despite the interest due to the presence of a relatively rare nitrogen-substituted stereogenic carbon center, only few asymmetric total syntheses have been reported [143-147], among which the organocatalytic approach represents the most unexplored field. Nevertheless, Cho and co-workers, pursuing their research on enantio- and diastereoselective organocascade reaction [148], have devised a concise asymmetric formal synthesis of several bromopyrrole alkaloids *via* aza-Michael addition followed by lactamization [149]. The first key organocatalyzed step employed the 4,5-dibromo-1*H*-2-carbonitrile (**284**) as Michael donor and the TBDPS-protected (*E*)-4-hydroxybut-2-enal (**285**) as Michael acceptor, exploiting the exceptional action mode of the Jørgensen catalyst (20 mol%) (Scheme **43**). Adding a substoichiometric amount of benzoic

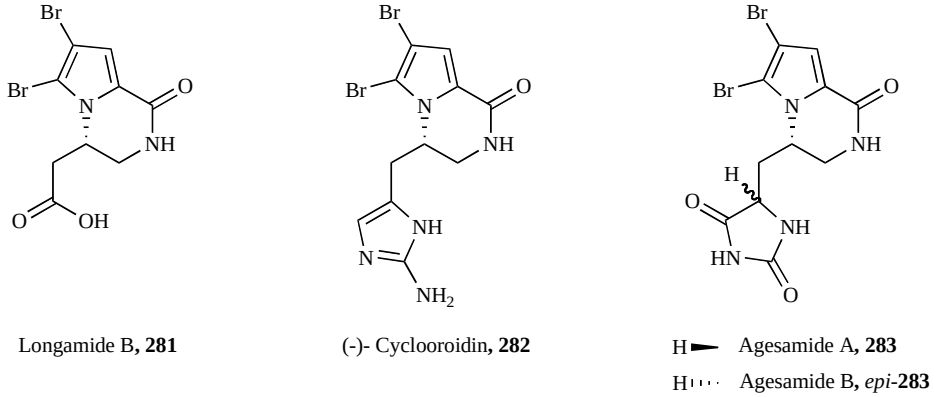
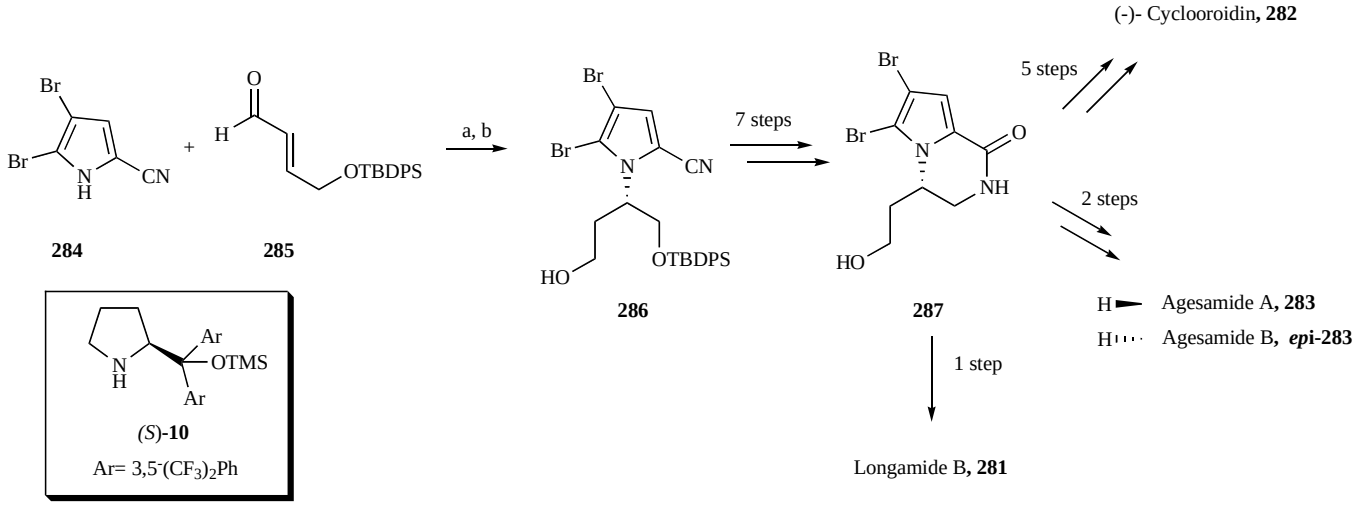


Fig. (9). Bromopyrrole alkaloids with the pyrrolopiperazinone skeleton.



Scheme 43. Reagents and conditions for the organocatalytic step: (a) (*S*)-**10** (20 mol%), $PhCO_2H$ (40 mol%), toluene (0.1M) -40°C 18h; (b) $NaBH_4$ (110 mol%), EtOH (0.1M), -40°C (76%, 93% *ee* over 2 steps).

acid (40 mol%) and lowering the reaction temperature at -40°C, the enantioselectivity reached the 93% *ee* and the desired intermediate **286** was isolated in 76% yield after the *in situ* reduction of the parent aldehyde.

Further 7 steps including a Staudinger-type reductive cyclization, provided the common key bromopyrrole **287**, which upon the already well-known procedures could be easily and directly converted in the previous named natural products [144, 145].

4.9. Psymberin

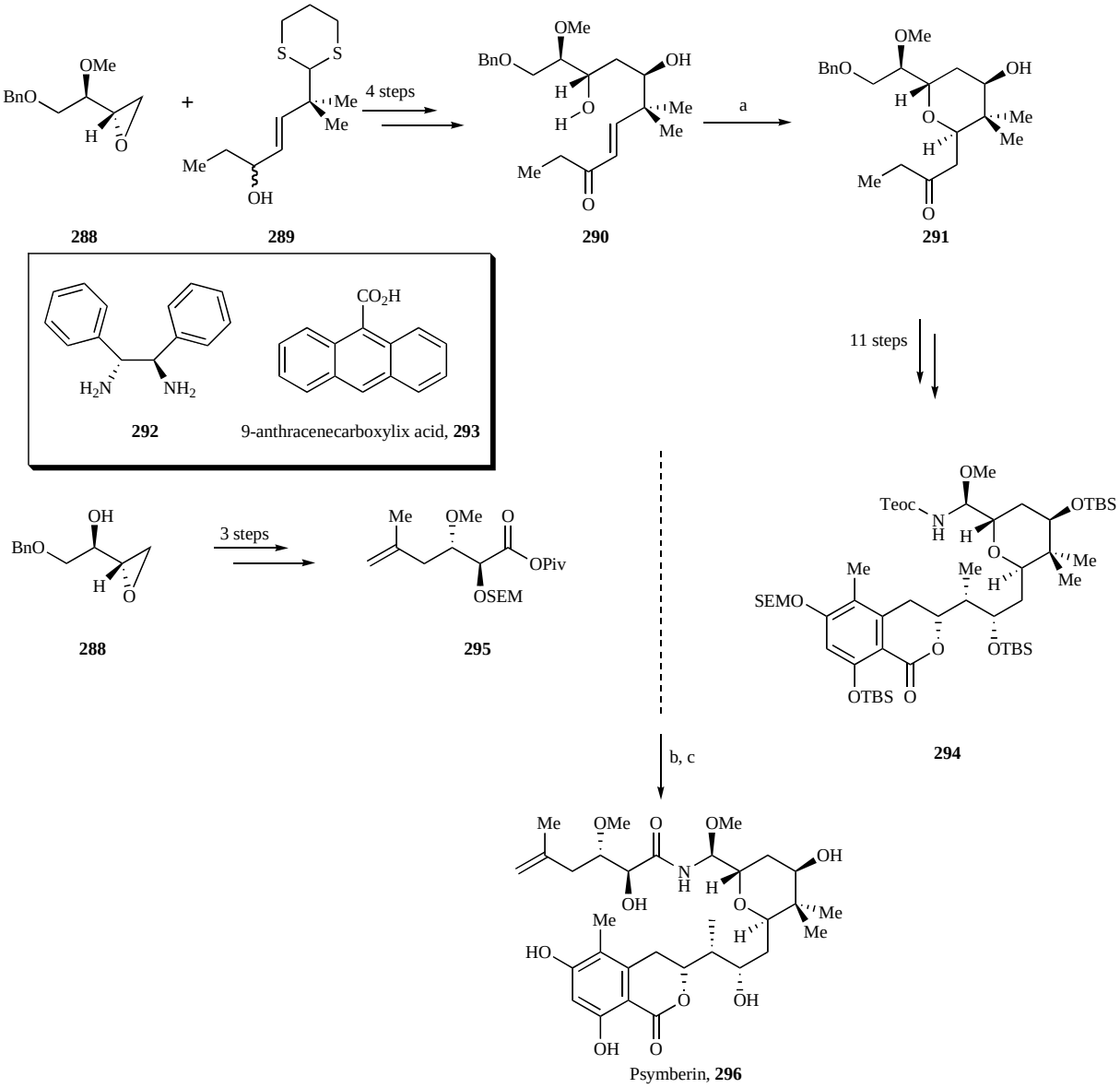
Another example of hetero-conjugate addition has been reported in 2011 by Hong's group [150] toward the total synthesis of Psymberin, a potent inhibitor of cancer cell proliferation mainly characterized by a 2,6-trans-3,3-dimethyl tetrahydropyran-4-ol and a dihydrocumarin [151, 152]. Due to their poor thermodynamically stability, the stereoselective formation of 2,6-*trans*-tetrahydropyran motif represents one of the most interesting synthetic challenges [153-156]. Within this context, Hong *et al.* developed a simple and elegant approach to such a high-demanding target, which relies on an organocatalytic oxa-conjugate addition to prepare the critical intermediate **291** in a reagent-controlled manner (Scheme **44**). After several attempts, the freshly prepared hydroxyl ketone **290** was successfully converted into the desired compound **291** by employing a combination of the (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (**292**, 0.4 eq.) and 9-anthracenecarboxylic acid (**293**, 1 eq).

The observed high stereoselectivity (d.r. =10:1) and the yield (92%) seems dramatically depend not only on the employed diamine, but also on the used acid additive. Such outcome was rationalized as a function of the steric bulkiness of the acid, which enhances the steric repulsions in the less favourable dimeric conformer **297** and increases the population of conformer **298** (Scheme **45**).

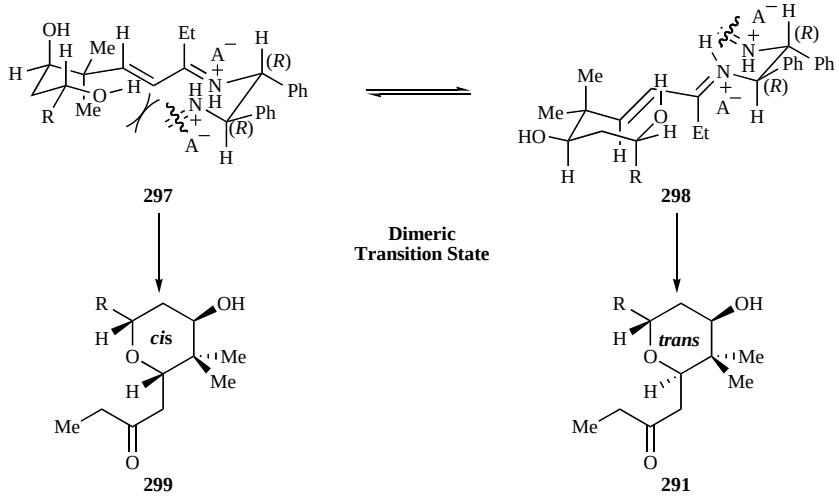
Further 11 steps and a last coupling reaction with a pyvalate mixed anhydride **295** to insert the side chain, led to the completion of the synthesis of Psymberin (**296**).

4.10. Collective Synthesis

Resembling the "biochemical assembling line" performed by the Nature [157], MacMillan and co-workers addressed their efforts to the construction of a crucial scaffold which resulted to be a common intermediate for the total synthesis of natural product collections, an approach named "collective total synthesis" [54]. As last and undoubtedly one of the most outstanding examples of 2011, we cannot avoid reporting the marvellous collective synthesis of natural products by means of organocascade catalysis reported by the famous American group [158]. A deep study of six well-known, structurally complex alkaloids belonging to the *Strychnos*, *Aspidosperma* and *Kopsia* families, revealed a potential common intermediate, the tetracycle **30**, which incorporates all the requisite functionality to be converted into the target natural products (Fig. **10**).



Scheme 44. Total synthesis of psymberin. reactions and conditions: (a) **292** (0.4 eq.), **293** (1 eq.), EtOAc, 0°C, 48h, 92%, d.r. 10:1; (b) LHMDS, THF,-78°C, 0.5h, then **295**, -78°C, 2h, -60°C, 0.5h, 82%; (c) TASF, DMF, 50°C, 48h, 64%.



Scheme 45. Proposed Transistion State (TS) for the oxa-conjugate addition reaction catalysed by (*1R,2R*)-1,2-diphenylethane-1,2-diamine **292**.

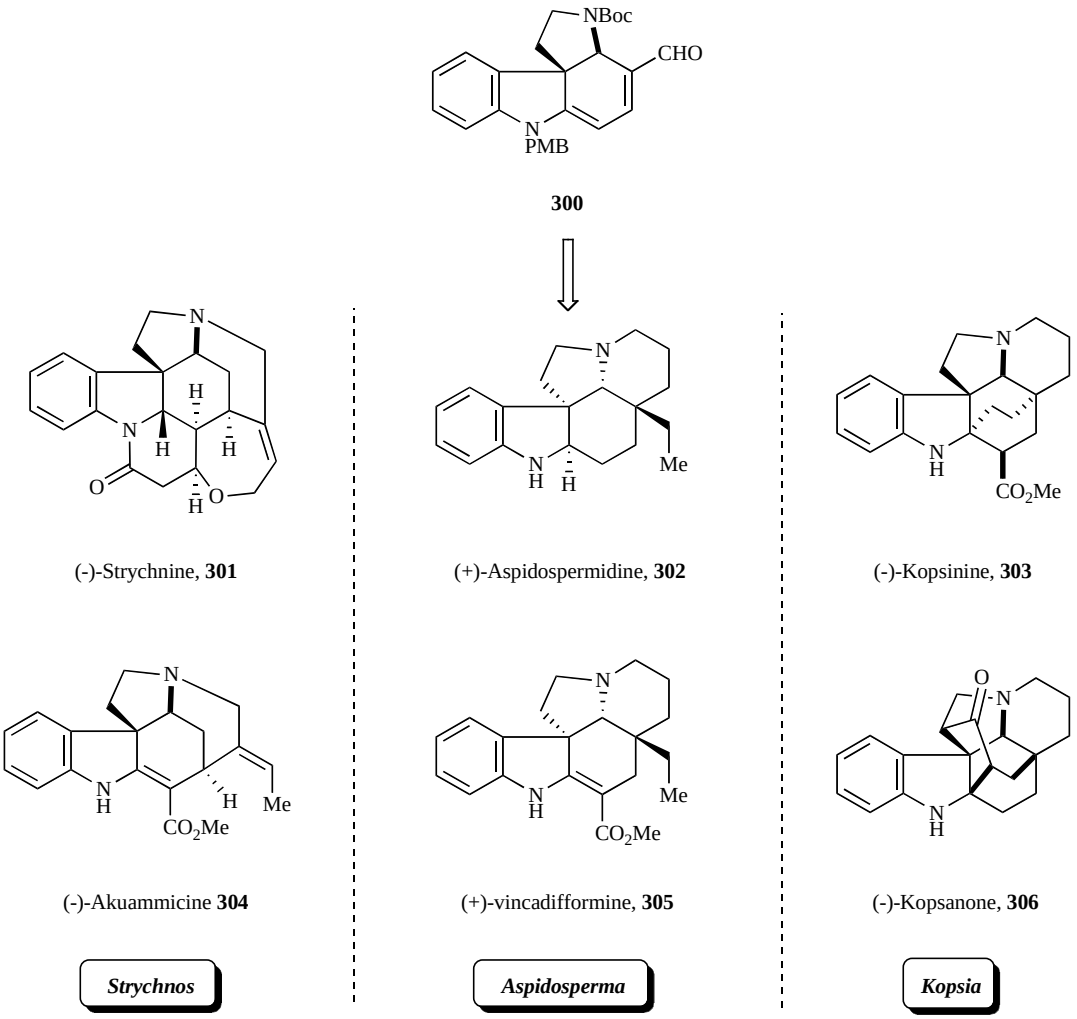
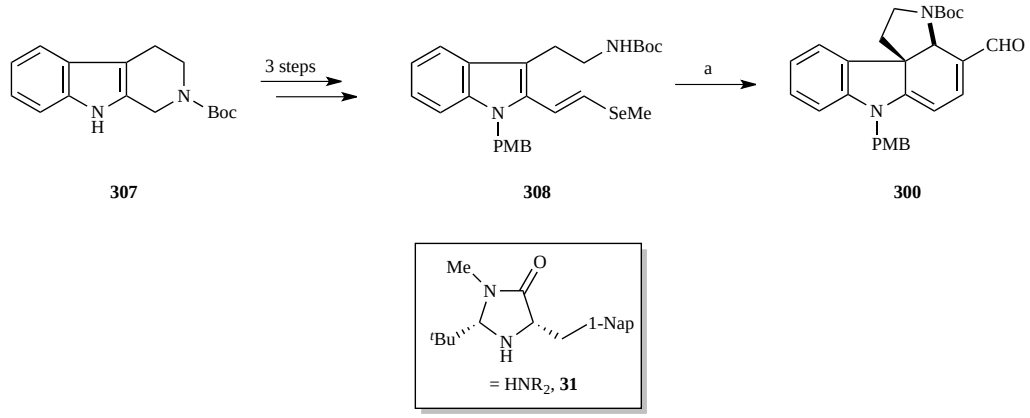


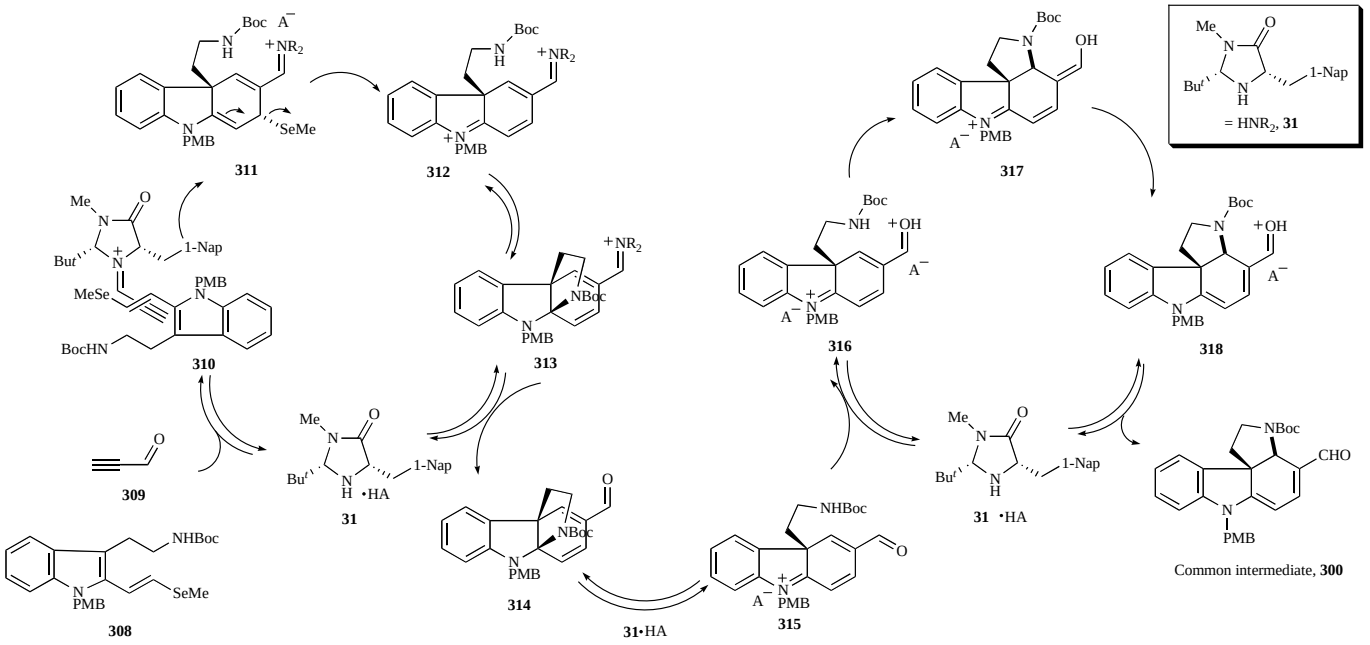
Fig. (10). The six structurally diverse *Strychnos*, *Aspidosperma* and *Kopsia* alkaloids, which have a common precursor **300**.



Scheme 46. Synthesis of the common spiroindoline intermediate **300**. Reagents and conditions for the organocatalytic step: (a) Propynal, **31**•TBA (20 mol%), -40°C to rt, toluene, (82%, 97% *ee*).

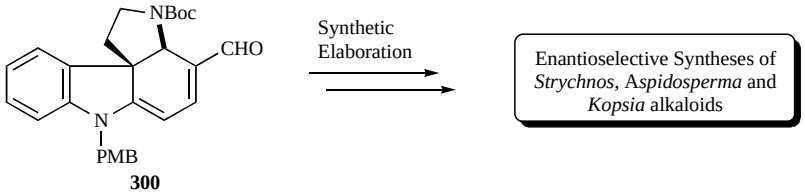
According to their previous and very precious experience [159], the key intermediate **300** was accessed through a one-flask, asymmetric Diels-Alder/elimination/conjugate addition organocascade sequence, starting from the simple triptamine substrate **308** (Scheme **46**). Performing the reaction in the presence of imidazolidinone catalyst (20 mol%) and tribromoacetic acid (TBA, 20 mol%) as co-catalyst, the spiroindoline **300** was achieved in 82% yield and with excellent levels of enantioinduction (97% *ee*).

The proposed organocascade reaction involves two catalytic cycles which should be connected along with Brønsted acid catalysis as demonstrated by further additional experimental work (Scheme **47**). In detail, according to the author statements, the ace-



Scheme 47. Proposed mechanism of organocascade cycles for the generation of a common spiroindoline intermediate (**300**).

Table 1. Enantioselective Synthesis of the Six Well-known Indole Alkaloids



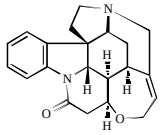
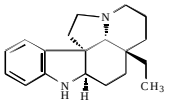
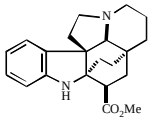
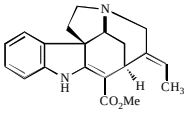
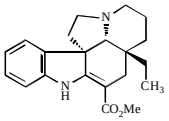
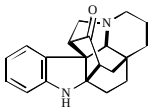
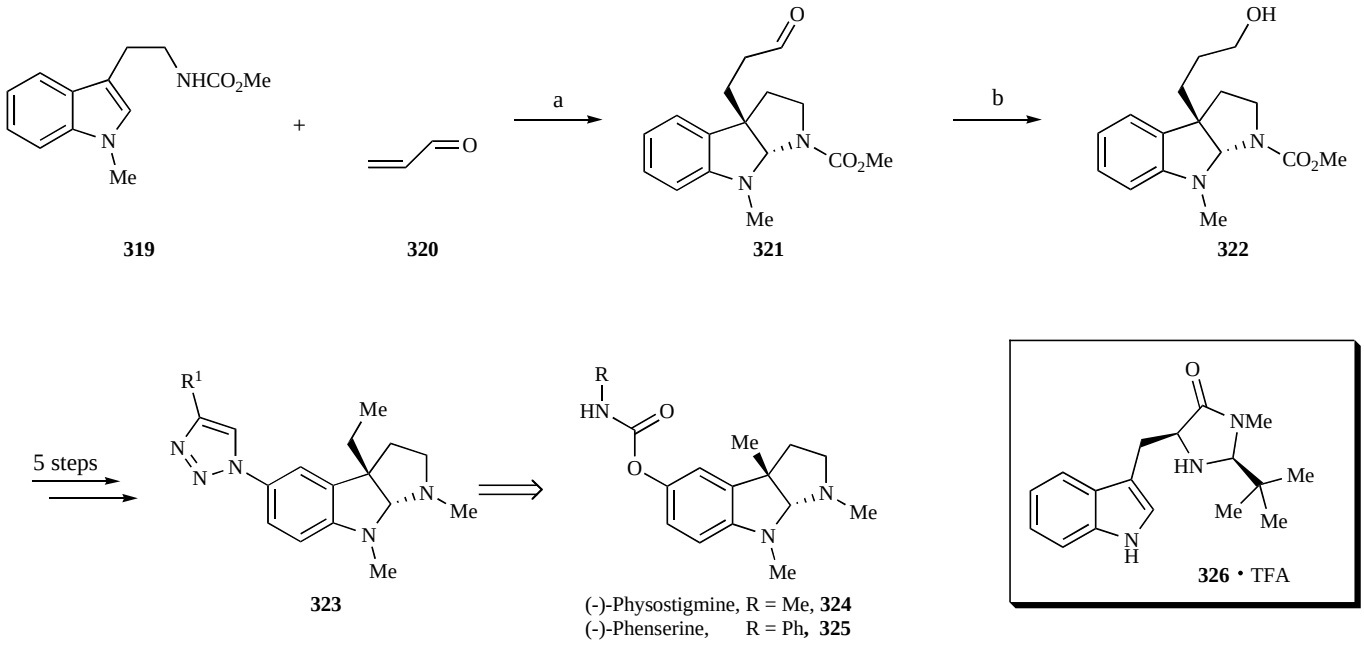
Natural Product	Steps by MacMillan	Overall Yield	PSAC Steps	Ref.	PSCA Steps	Ref.
 (-)-Strychnine, **301**	12	6.4 %	25	[160, 161]	16	[162]
 (+)-Aspidospermidine, **302**	9	24%	13	[163]	11	[164]
 (-)-Kopsinine, **303**	9	14%	Not Applicable		19	[165]
 (-)-Akuammicine, **304**	10	10%	Not Applicable		Not Applicable	
 (+)-Vincadifformine, **305**	11	8.9%	Not Applicable		10	[166]

Table 1. contd….

Natural Product	Steps by MacMillan	Overall Yield	PSAC Steps	Ref.	PSCA Steps	Ref.
 (-)-Kopsanone, **306**	11	10%	Not Applicable		Not Applicable	

PSAC = previous shortest asymmetric catalytic synthesis; PSCA= previous shortest chiral auxiliary or chiral pool synthesis.



Scheme 48. Synthesis of (-)-Physostigmine analogues. Reagents and reaction conditions: (a) **326** ·TFA (10 mol%), CH_2Cl_2/H_2O 85:15, -78°C (87%, 88% *ee*); (b) $LiAlH_4$, THF, reflux (86% 99 % *ee*).

tylenic functionality of the *in situ* formed catalyst-bound propynal partitions away from the bulky *tert*-butyl (*t*-Bu) group, so that the naphtyl group could shield the bottom face of the reacting alkyne (**310** in Scheme **47**). The activated dienophile undergoes to *endo*-selective Diels-Alder cycloaddition with the the 2-(vinyl-1-selenomethyl)triptamine system **308**. As consequence of the selenide propensity to undergo β-elimination, the cycloadduct **311** easily furnishes the unsaturated iminium ion **312**, which in turn undergoes facile cyclization at the indoline carbon to give the pyrrolindoline **314**. Thereafter, the Brønsted acid catalyst induces the necessary 5-*exo*-heterocyclization of the pendant carbamate to provide **317** and than the tetracyclic spiroindoline **300**.

Once isolated the common intermediate **300**, the author's initial hypothesis was further and fully validated by accomplishing the total synthesis of the six studied natural products in the step number and overall yield reported below (Table **1**).

The just depicted methodology, a hybrid form between the strategies of collective natural product synthesis and enantioselective organocascade catalysis, opens the door to single enantiomer natural products with unprecedented level of efficiency, which was clearly demonstrated by comparing the outcome from MacMillan's approach to the other previous asymmetric total synthesis (Table **1**).

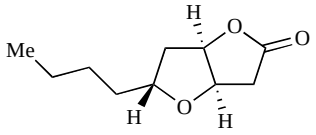
4.11. (-)-Physostigmine Analogs

(-)-Physostigmine, isolated from the African Calabar bean seed *Physostigma venenosum*, is one of the earliest compounds to be used as an inhibitor of acetylcholinesterase and a therapeutic agent against *Alzheimer*'s disease [167]. Due to its low bioavailability and narrow therapeutic window, several efforts have been made in order to develop valuable analogues with potent anti-*Alzheimer* activity [168, 169]. Among others, Qin *et al*. have reported an efficient synthesis of (-)-Phisostigmine's library, which could be screened as selective inhibitors of acetylcholinesterase [170]. Applying a slight modification of MacMillan's procedure to the preparation of 3a-substituted hexahydroxypyrrolo[2.3-*b*]indole core [171], the Chinese group stereoselectively built the tetracyclic scaffold **323** (87%, 88% *ee*) from tryptamine derivative **319** and acrolein **320** in the presence of 10 mol% of imidazolidinone trifluoroacetic acid salts **326** ·TFA (Scheme **48**).

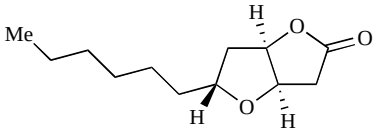
The subsequent reduction with $LiAlH_4$ surprisingly improved the enantiomeric excess (99% *ee*), which was preserved during the further five steps obtaining the desired physostigmine's analogues **323**.

4.12. (+)-Hagen's Gland Lactones

Certain species of parasitic wasps belonging to the Braconidae family, act as biological control agents for fruit fly population in Hawaii and Queensland, addressing a considerable interest in their morphology and taxonomy. Particularly, Hagen's gland of few Braconid wasps and fopius contains fragrant volatile biological control agents, rich in lactones such as the furanosides depicted in Fig. (**11**) [172]. Due to such a peculiar balance keeper activity, these natural products were addressed as challenging targets by several research groups [173-175].

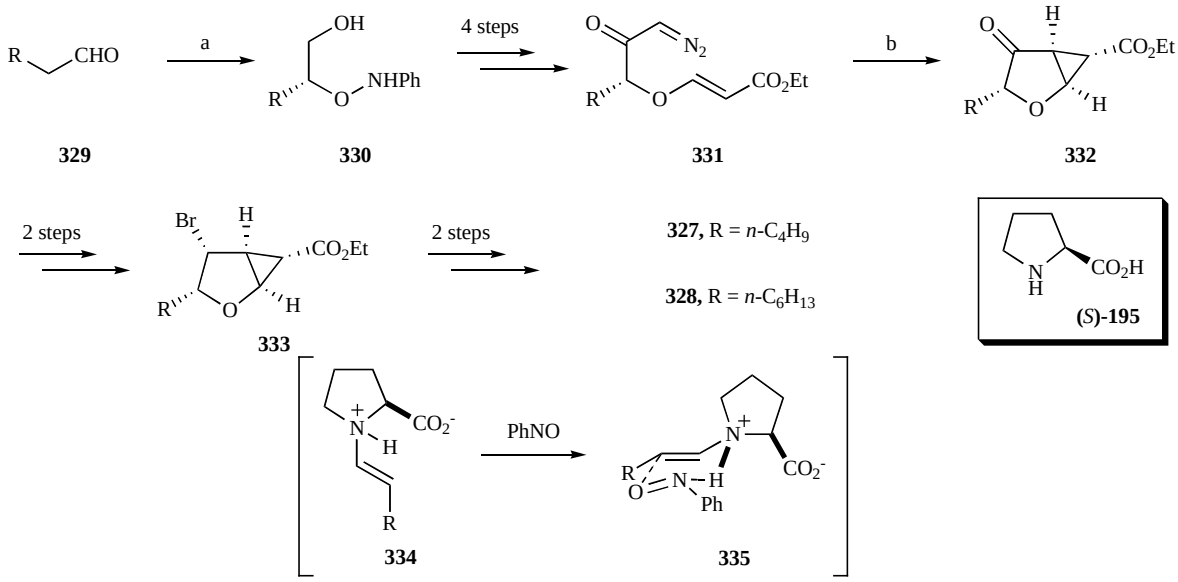


(3aα,5β,6aα)-5-*n*-butyltetrahydrofuro-[3,2-*b*]furan-2(3H)-one**, 327**



(3aα,5β,6aα)-5-*n*-hexyltetrahydrofuro-[3,2-*b*]furan-2(3H)-one, **328**

Fig. (11). Hagen's gland lactones.



Scheme 49. Synthesis of Hagen's Lactones. Reagents and conditions of stereoselective steps: (a) PhNO, (*S*)-proline [(*S*)-**195**, 10 mol%], $CHCl_3$, 4°C, 2h; then $NaBH_4$, EtOH, 0°C, 0.5h; (b) $Cu(acac)_2$, CH_2Cl_2, reflux, 2h (80% for R = *n*-C_4H_9, 60% for R = *n*-C_6H_{13}).

Among others, Gharpure *et al*. have reported the diastereoselective total synthesis of the *cis* isomer of (+)-Hagen's gland lactones (**327, 328**) in twelve-step procedure [176]. The key stereoselective transformation involves the enantioselective, organocatalytic direct α-oxyamination of the starting aldehyde **329**. The use of (*S*)-proline [(*S*)-**195**, 10 mol%] as catalyst allowed the aldehyde activation *via* enamine (**334**) avoiding the preformation of the corresponding enol derivative, while the enhanced Brønsted basicity of the nitrogen atom (PhNO) drove the nucleophile towards the desired *O*-addition manifold (Scheme **49**).

The installed stereogenic centre ensured the further highly regio- and stereoselective intramolecular cyclopropanation (80% and ≥ 99% *ee* for R = *n*-C_4H_9; 60% and 97% *ee* for R = *n*-C_6H_{13}) of vinylogous carbonates, and facile regioselective radical ring of the Donor-Acceptor Cyclopropane (DAC).

4.13. Streptorubin B

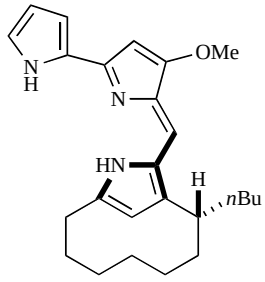
Since protein phosphorylation and dephosphorilation reactions are ubiquitous in biological processes, the development of powerful protein kinase antagonists moved into the focus of a plethora of research projects [177]. This is the particulary case of prodigiosin alkaloids (Fig. **12**), which, have been addressed by both outstanding chemists and biologists as challenging targets also due to their unique molecular architecture [178, 179]. From a structural point of view, streptorubin B (**336**) [180] and metacycloprodigiosin (**338**) [181] are quite peculiar because of their highly strained pyrrolphane cores, easily formed from the common precursor undecylprodigiosin (**337**) [182]. Additionally, prodigiosin R1 (**339**) [183] represents a fascinating link between these molecules and roseophilin (**340**), deeply investigated by Füstner *et al*. [177, 178].

In the wake of their successful achievement with prodigiosin R1 (**339**) and metacycloprodigiosin (**338**) [184], Thomson *et al*. envisaged the possibility to easily accomplished the total synthesis of Streptorubin B (**336**), confirming its relative and absolute configuration [185]. The planned total synthesis relied upon a proline-catalyzed enantioselective *exo*-enol-6-*exo*-trig aldol reaction developed by List and co-workers in 2003 as an effective means for deasymmetrizing acyclic aldehydes (Scheme **50**) [186]. According to the reported protocol, the dialdehyde **342** was treated with 10 mol% of (*S*)-proline [(*S*)-**195**, 10 mol%] and the intermediate α-hydroxy-aldehyde underwent to an *in situ* Wittig reaction, which afforded the homoallylic alcohol **344** as major diastereomer in 69% yield and impressive stereoselectivity (d.r. = 10:1, 96%*ee*).

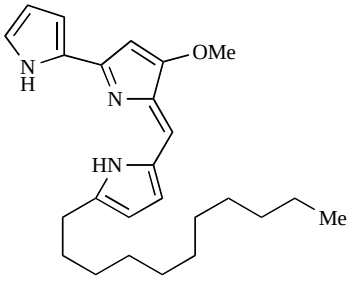
The subsequent seven steps, involving a successful stereochemical transfer during the anionic oxy-Cope rearrangement, led to the desired Steptorubin B in 20% of overall yield.

4.14. (+)-Przewalskin B

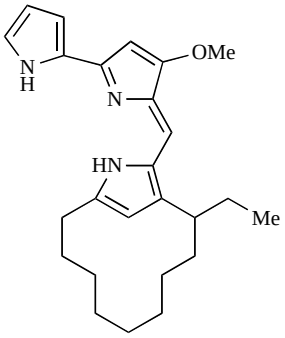
Przewalskin B, isolated by Zhao *et al*. from a Chinese medicinal plant *Salvia przewalskii*, possesses an unprecedented tetracyclic framework with two spiro rings, a α-hydroxy-γ-lactone moiety and an all-carbon quaternary centre (Fig **13**) [188]. Due to its intriguing architectural features and the potential biological activities, Przewalskin B represents a challenging synthetic target, which attracted the interest of several synthetic chemists. After the outstanding She's work to determine the absolute configuration of the natu-



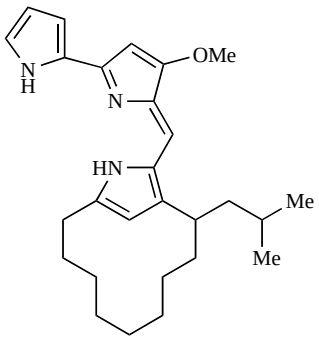
anti-Streptorubin B, **336**



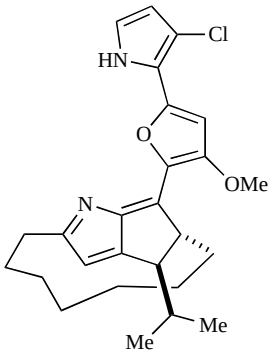
undecylprodigiosin, **337**



metacycloprodigiosin, **338**

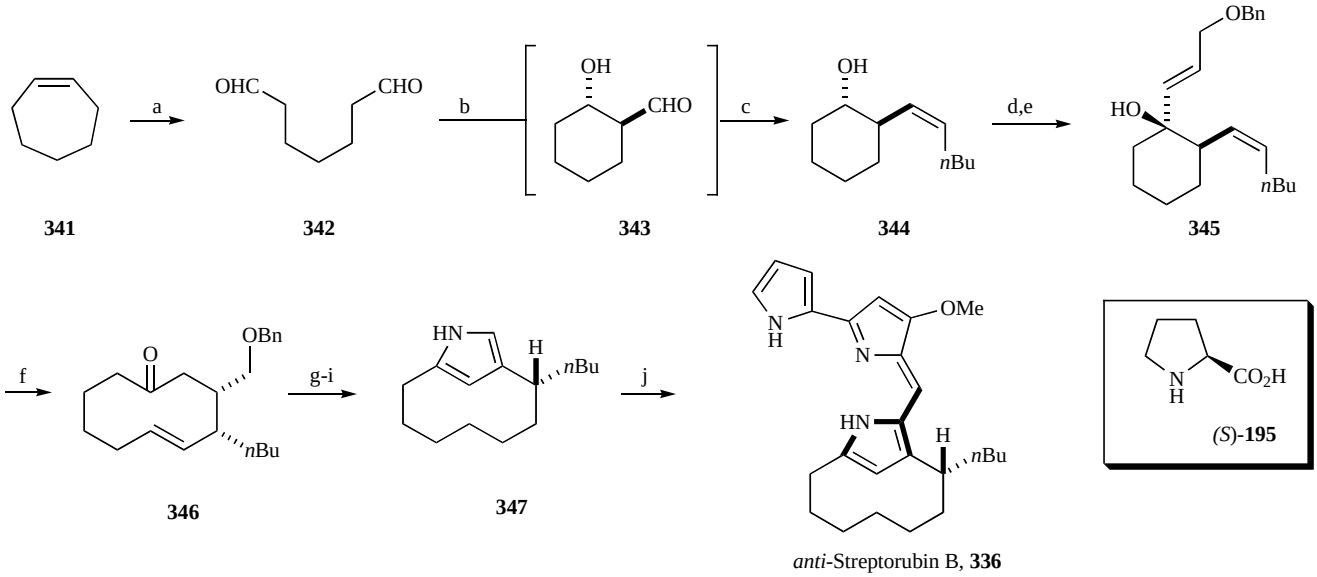


prodigiosin R1, **339**



roseophilin, **340**

Fig. (12). Some prodigiosin alkaloids and roseophilin.

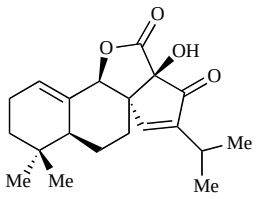


Scheme 50. Enantioselective total synthesis of Steptorubin B. Reagents and conditions: (a) $RuCl_3$, $NaIO_4$, (85%) [187]; (b) (*S*)-Proline [(*S*)-**195**, 10 mol%]; (c) pentylidenetriphenylphosphorane, (69%, 96%*ee* over one-pot enantioselective aldol/Wittig reaction); (d) $(COCl)_2$, DMSO, *i*Pr_2EtN, -40° to rt; (e) (*E*)-(3-(benzyloxy)prop-1-en-1-yl)lithium (83%, 94% *ee*, over 2 steps); (f) KHMDS, 18-C-6 (85%); (g) Pd/C, H_2; (h) Dess-Martin oxidation; (i) NH_4OAc (67% over 3 steps); (j) *tert*-butyl 5'-formyl-4'-methoxy-1*H*,1'*H*-[2,2'-bipyrrole]-1-carboxylate, then NaOMe, (72%.).

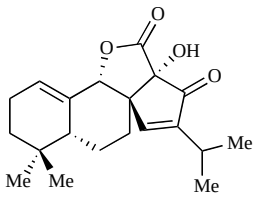
ral product **348** [189], Tu and co-workers have recently disclosed the total synthesis of the corresponding (+) enantiomer (*ent*-**348**) (Fig. **13**) [190].

Although authors' efforts were initially devoted to the Rhodium-mediated intramolecular C-H insertion reaction to build the C- and D- rings (Scheme **51**), they exploited the high efficiency of organocatalysis, to enantioselectively accomplish the formation of the A/B spirofused rings. In particular the exposure of dialdehyde **350** to the aldol condensation catalysed by 0.1 equiv. of L-prolinammide in NMP, resulted in the formation of **351** as the sole product.

Based on the relative configuration of the subsequent intermediate **351**, the authors suggested the intermediacy of the transition state **353A**, which also represents the lower energy conformation than the state **353B** (Scheme **52**). Indeed in the transition state **353A**, the *Re* face of the carbonyl of α,β-unsaturated aldehyde is

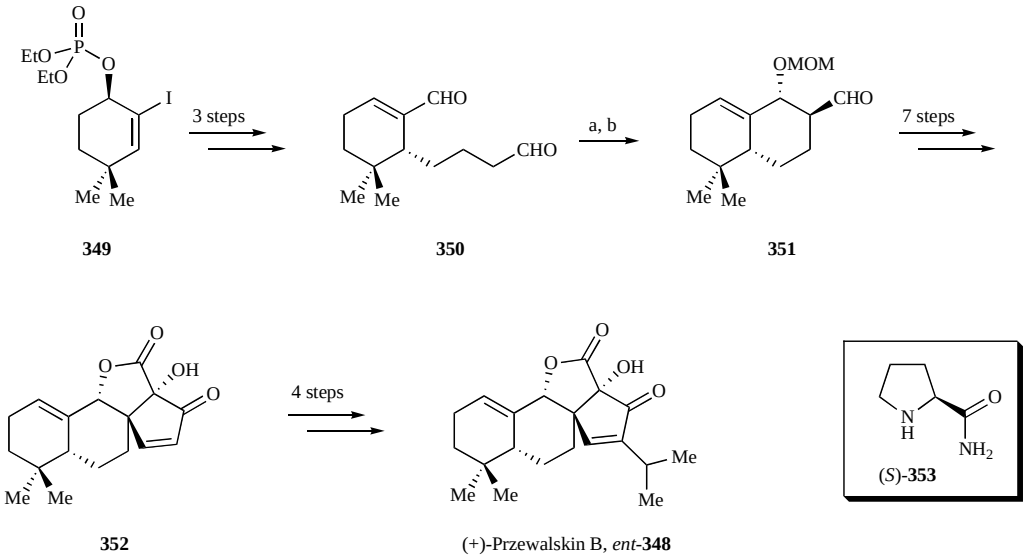


(-)-Przewalskin B, **348**



(+)-Przewalskin B, *ent*-**348**

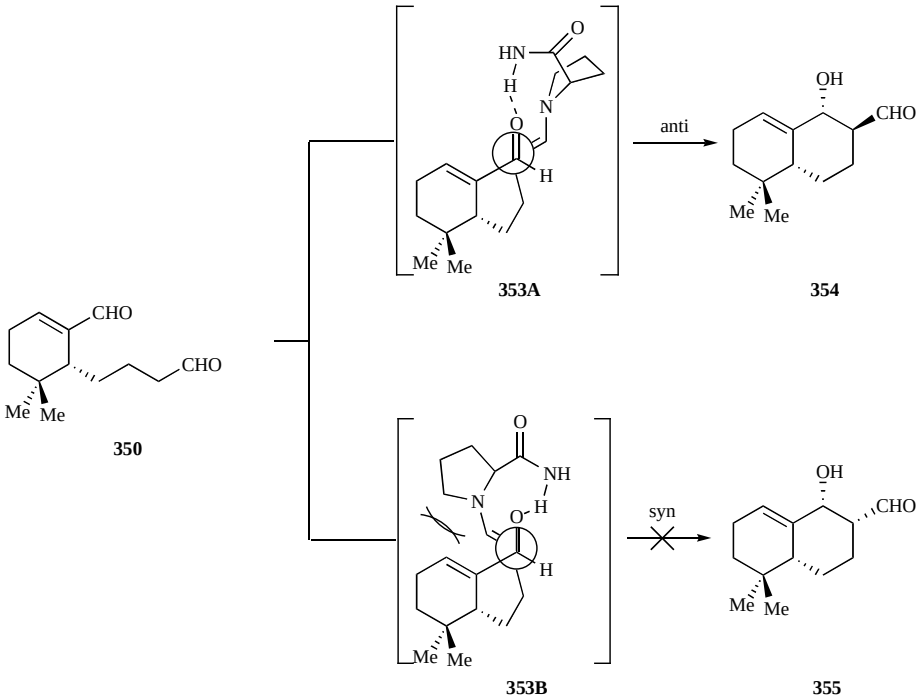
Fig. (13). Przewalskin B and its enantiomer**.**



349 **350** **351**

352 (+)-Przewalskin B, *ent*-**348**

Scheme 51. Synthesis of (+)-Przewalskin B. Reagents and conditions: (a) (*S*)-**353** (10 mol%), NMP, rt; (b) MOMCl, *i*Pr_2Net, CH_2Cl_2, 0°C to rt, (64% over 2 steps, **351** as sole product).

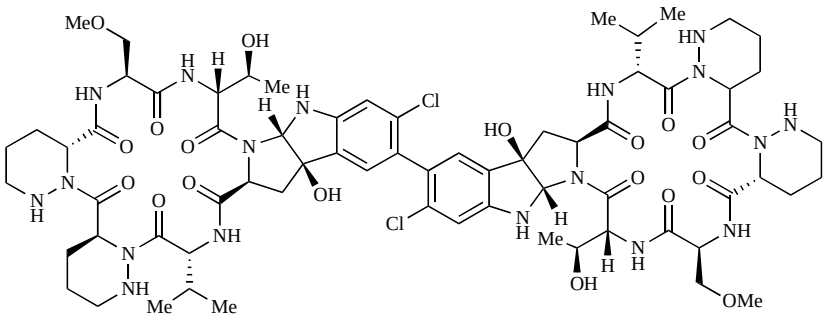


350 **353A** **354** **353B** **355**

Scheme 52. Proposed explanation of aldol reaction outcome.

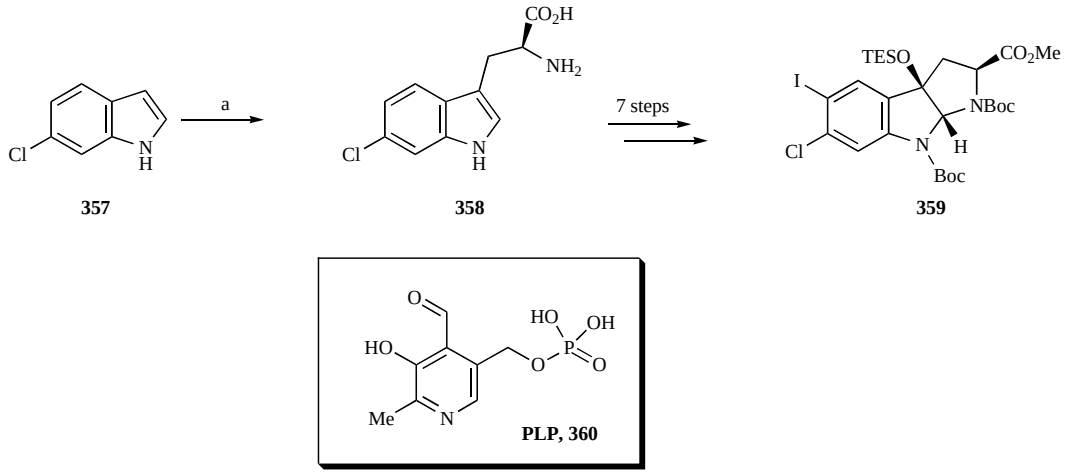
much more accessible to *Re* face of enamine and the *anti* product **354** was formed. Conversely, in the state **353B** the repulsion between pyrrolidine and cyclohexane moiety of substrate **350** would not let form the *syn* adduct **355**.

Further several steps firstly furnished the key tetracyclic intermediate **352**, which X-ray have been reported to define the absolute configuration, and subsequently the desired final product *ent*-**348**, which is currently under biological investigation.



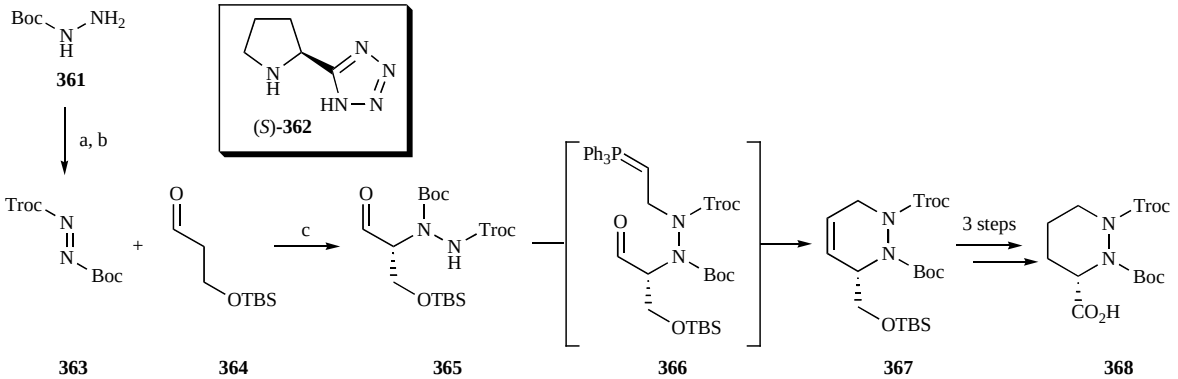
Chloptosin, **356**

Fig. (14). Chloptosin**, 356.**



357 **358** **359** **PLP, 360**

Scheme 53. Preparation of 6-chlorotryptophan. Reagents and conditions of the biotransformation: (a) cell lysate containing tryptophan synthase, L-serine, Pyridoxal phosphate (PLP), KH_2PO_4, H_2O, rt, 35%.



361 (*S*)-**362** **363** **364** **365** **366** **367** **368**

Scheme 54. Organocatalytic preparation of the piperazic acid building block **368**. Reagents and conditions: (a) TrocCl, NMM, THF, 0°C to rt; (b) NBS, pyridine, toluene, rt, quant. (2 steps); (c) **362** (10 mol%), CH_2Cl_2, -5°C, then vinyltriphenylphosphonium bromide, NaH, THF, -5°C to rt, (90%, 84% *ee*).

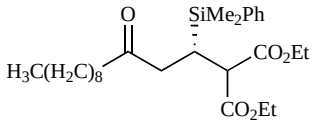
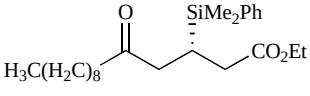
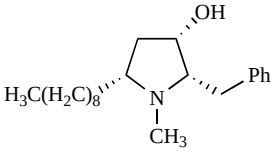
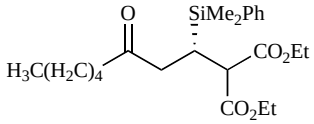
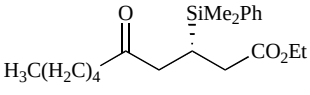
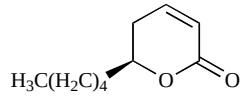
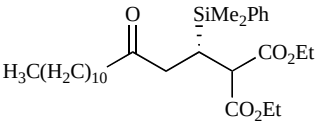
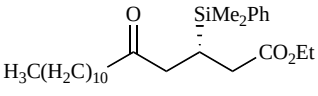
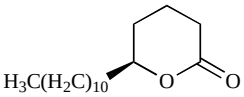
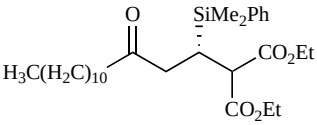
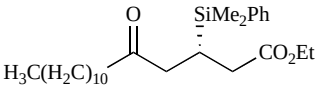
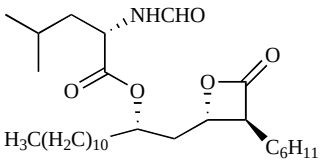
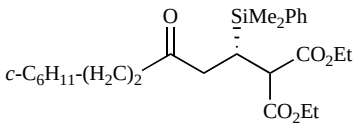
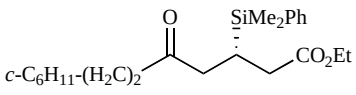
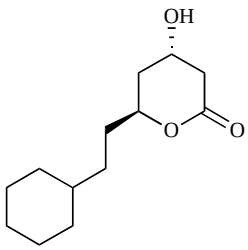
4.15. Chloptosin

Chloptosin is a dimeric cyclohexapeptide produced by Streptomyces strain MK498-98F14, which exhibits both apoptotic activity in the apoptosis-resistant human pancreatic adenocarcinoma cells and antimicrobial activity against Gram-positive bacteria [191]. In term of structure, the two identical cyclic hexapeptide subunits are connected with a biaryl linkage (Fig. **14**). Each monomer contains, in alternating enantiomeric forms, only non–proteinogenic amino acid including 6-chloropyrroloindole residue as well as (*R*)- and (*S*)-piperazic acid, which represents a significant synthetic challenge [192-194].

The overall convergent synthesis realized by Ley *et al.* [195] resulted to be a synergic collaboration among enantioselective biotransformations, organocatalytic processes, and classic organic chemistry. Indeed, the preparation of the pyrroloindole core was accomplished in just 8 steps mainly relying on the treatment of the 6-chloroindol **357** with cell lysate containing tryptophane synthase, L-serine, and Pirydoxal-Phosphate (PLP, **360**) as cofactor, which acts *via* iminium catalysis. (Scheme **53**) [196, 197]. Such biotransformation provided a rapid access to multigram quantities of **358**, with a 75% yield. The subsequent seven steps, involving a diastereoselective *syn-cis* pyrroloindole formation, transformed the just obtained compound in the first key intermediate **359**.

Contemporarily, the organocatalytic strategies resulted to be the successful approach to the differentially protected piperazic acid. Actually, the α-amination reaction between the TBS-protected al-

Table 2. Regio- and Stereoselective Addition of Alkyl Methyl Ketones to (Silylmethylene)malonate 370, and Subsequent Transformation into Natural Products (381-385)

Entry	First Adduct	Y (%)	*ee* (%)	Second Adduct	Y(%)	Natural Product	Ref.
1	 **371**	88	91	 **375**	85	 **381**	[199]
2	 **372**	94	99	 **376**	90	 **382**	[200]
3	 **373**	80	87	 **377**	80	 **383**	[201]
4	 **373**	80	87	 **377**	80	 **384**	[202]
5	 **374**	76	90	 **378**	80	 **385**	[198]

[a] Reagents and conditions: (a) **379** (30 mol%), TFA (10 mol%) NMP, -10°C, 3-7 days; (b) NaCl, DMSO-H_2O, 165-180°C.

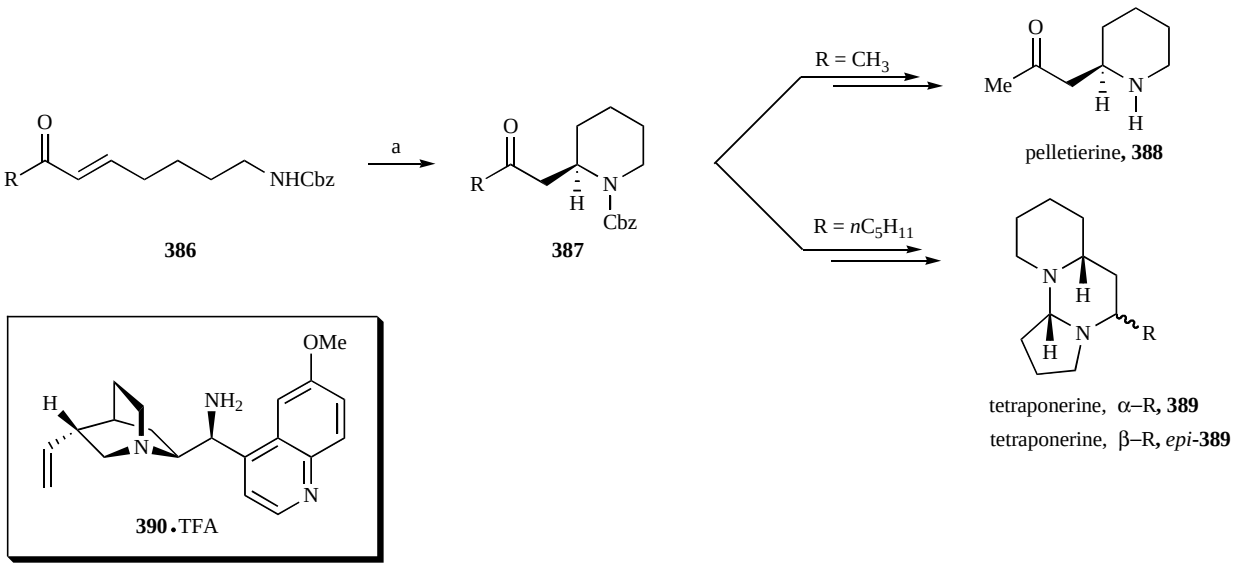
dehyde **364** and the azadicarboxylate **363** furnished the hydrazino aldehyde **365**, which was directly cyclised to the 3,6-dihydropyridazine product **367**, by adding NaH and vinyltriphenylphosphonium bromide (Scheme **54**). The use of low temperature (-5°C) and of two different protecting groups (Boc, Troc) created such a different electronic environment to achieve a high regioselective attack of the nucleophilic enamine, enhancing, at the same time, the asymmetric organocatalytic action of the employed tetrazole **362** (84% *ee*).

Further quite hard efforts and various strategies changes led the authors to the final Chloptosin **356** in a total of 30 steps and a 4% overall yield. This successfully synthesis represents not only a very elegant approach to a complex dimeric structure, but also a reliable access to a wide range of novel chloptosin analogues for biological testing and studies on their mechanistic action in human cells.

4.16. (+)-Preussin, (+)-Massoialactone, (+)-5-hexadecanolide, (-)-tetrahydrolipstatin, (+)-mervinolin Analogue

Ghosh *et al.* [198] combined the simplicity of organocatalysis with the versatile nature of carbonyl compounds having a silyl group at the β-position. The direct Michael addition of an alkyl methyl ketone **369** to the silylmethylene malonate (**370**) furnished a straightforward access to optically active β-silyl-δ-ketoesters. In particular, the catalytic system diamine **379** (30 mol%)/TFA (10 mol%) together with quite mild reaction conditions (-10°C, NMP, as solvent) afforded the ketoesters **371-374** in good yields (76-94%) and very interesting enentioselectivity (87-99%*ee*) (Table **2**).

According to the enamine mechanism suggested by Barbas [203, 204] and taking into consideration the stereochemical outcome, the author hypothesized the transition-state assembly (**TS-380**) depicted above (Scheme of Table **2**). The (silylmethylene)malonate **370** is driven to the less hindered *Si* face of the *in situ* formed enamine. The hydrogen bond network among the catalyst tertiary nitrogen, one of the carbonyl group of (silylmethylene)malonate and the trifluoroacetic acid activated both substrates by bringing them to proximity, clarifying how the TFA catalytic amount speeds up the reaction. The obtained synthones were easily and smoothly transformed in *O*- and *N*-heterocyclic natural products, highlighting the effectiveness and the extreme synthetic usefulness of the investigated methodology (Table **2**).



386 **387**

Scheme 55. Organocatalytic asymmetric synthesis of functionalized piperidines. Reagents and Conditions of the organocatalytic step: (a) **390** (0.2 eq.), TFA (0.4 eq.) THF, 25°C (95%, 98% *ee* for R = CH_3 and 96% *ee* for R = nC_5H_{11}).

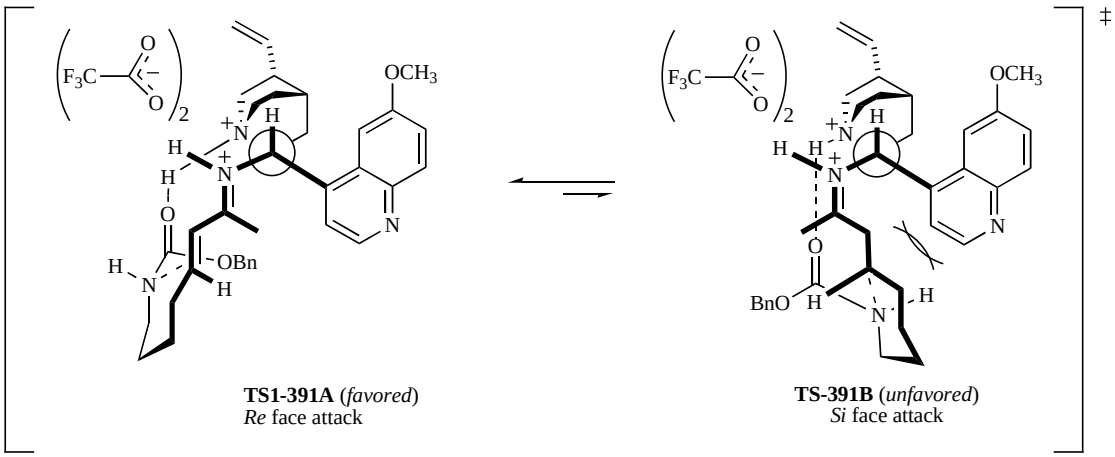


Fig. (15). Proposed mechanistic model for the observed enantioselectivity under the catalysis of **390**.

4.17. Functionalized 2-Substituted Piperidines: Pelletierine, Tetraponerine

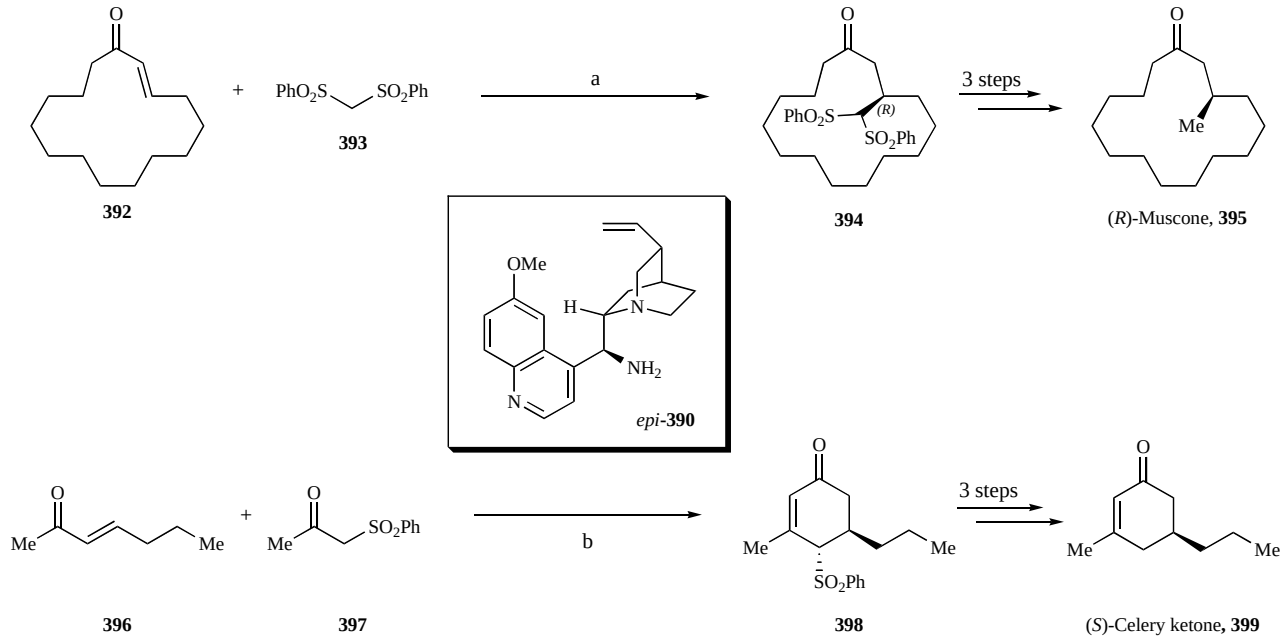
The functionalized 2-substitued piperidine fragment characterized by the critical chiral nitrogen-containing carbon centre is a widespread feature in many biologically active natural products and pharmaceuticals [205]. Consequently, a number of alternative synthetic routes have been developed to asymmetrically construct such a key building block [13, 206-208]. Among others, Fan *et al*. have recently developed an effective and efficient approach to various alkaloids having a piperidine core [209]. Specifically, an organocatalytic conjugate addition strategy furnished a direct enantioselective access to the key synthon **387**, a 2-substituted piperidine bearing a β-amino ketone moiety. The asymmetric intramolecular aza-Michael reaction between an α,β-unsaturated ketone moiety (Michael acceptor) and the carbamate unit (Michael donor) was performed in the presence of an *in situ* formed chiral catalyst salt (**390**·TFA). The quinine-derived primary-tertiary diamine **390** and CF_3CO_2H (TFA) as Brønsted acid additive resulted to be the best catalytic system, which smoothly afforded the functionalized 2-piperidine **387**, easily convertible into the corresponding natural products **388** and **389** (Scheme **55**) [13, 210, 211].

Moreover, the Chinese group suggested a hypothetical Transition State in order to explain the observed enantioselectivity. According to the assigned absolute configuration, the favoured (*E*)-*s-trans* conformer of α,β-unsaturated iminium ion was favourably formed *in situ*, simultaneously followed by the critical H-bond interaction between the protonated tertiary amine and the carbamate carbonyl oxygen, resembling the proposed acid-base catalysis action mode.

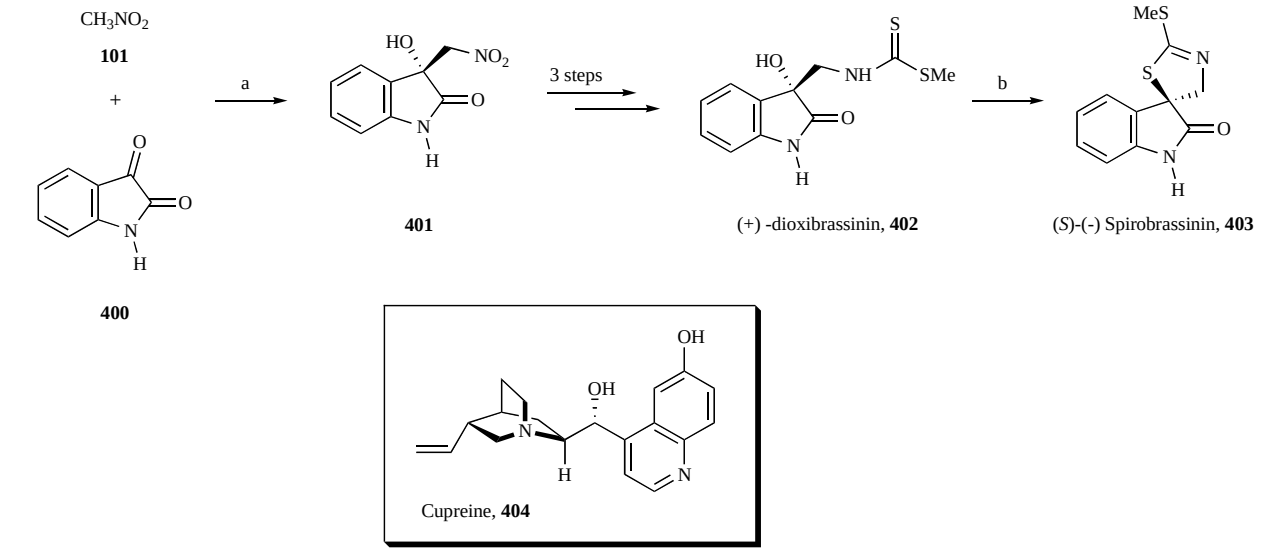
Due to an unfavourable steric hindrance in **TS-391B**, the carbamate nitrogen (the nucleophilic centre) preferentially attacks onto the *Re* face of the unsaturated iminium moiety (the electrophilic centre) *via* the energetically favoured **TS-391A**, delivering the (*R*)-aza-Michael adduct **387**.

4.18. (R)-Muscone

The chemistry of sulfonyl group was elegantly exploited by Ye and co-workers toward the chiral synthesis of macrocyclic natural products. In particular, following the example recently reported by Ruano and Alemán [212], Rios [213], and Palomo [214] on the asymmetric Michael reaction of enals with bis(phenylsulfonyl)



Scheme 56. Asymmetric synthesis of (*R*)-Muscone and (*S*)-celery ketone. Reagents and conditions for the organocatalytic reaction: (a) *epi*-**390** (20 mol%), benzoic acid (40 mol%), dioxane, 4d, 35°C (74%, 98% *ee*); (b) *epi*-**390** (20 mol%), benzoic acid (40 mol%), dioxane, 5d, 35°C (56%, d.r. = 96:4, 95% *ee*).



Scheme 57. Synthesis of (-)-Spirobrassinin. Reagents and conditions: (a) **404** (10 mol%), $PhCO_2H$ (10 mol%), DMA, -15°C, 3h [99%, 91% *ee* (99% *ee* after having washed with CH_2Cl_2)]; (b) MsCl, 45%.

methane (BSM), the Chinese group nicely developed a highly enantioselective conjugate addition of α,β-unsaturated ketones with BSM as Michael donor, catalysed by a chiral primary amine salt. The notable synthetic value of such a transformation was successfully corroborated by its employment in the chiral synthesis of (*R*)-Muscone **395** and (*S*)-Celery ketone **399** (Scheme **56**) [215]. Performing the reaction with 9-amino(9-deoxy)epiquinine (*epi*-**390**, 20 mol%) as organocatalyst and benzoic acid (40 mol%) as additive at 35°C in dioxane, the cyclopentadec-2-enone enantioselectively provided the adduct **394** (74%, 98% *ee*), which was easily transformed in the desired (*R*)-Muscone upon a protection/reduction/deprotection reaction sequence.

Likewise, the disclosed catalytic system delivered the optically active intermediate **398** *via* tandem Michael/aldol reaction of 4-substituted 3-buten-2-ones **396** with 1-(phenylsulfonyl)propan-2-one **397**. Further three steps straightforwardly furnish the (*S*)-Celery ketone **399**, amply used by Givaudan as modifier of aldehydic chypres and fougères.

4.19. (S)-(-)-Spirobrassinin

3-Substituted 3-hydrxyoxyindoles emerged as a privileged scaffold in drug discovery due to their presence as core structural motif in a broad spectrum of fascinating natural products [117]. Within this context, Wang *et al*. developed a simple, cuprein (**404**) catalysed enantioselective Henry reaction of readily available nitroalkanes with isatins to make the valuable 3-substituted 3-hydrxyoxyndoles [216]. Performing the reaction with 10 mol% of catalyst at -15°C in dimethylacetamide (DMA) as solvent and benzoic acid (10 mol%) as additive, the key intermediate **401** was quantitatively obtained as pure product in excellent enantiocontrol (99% *ee*) after the usual workup and a treatment with CH_2Cl_2 (Scheme **57**).

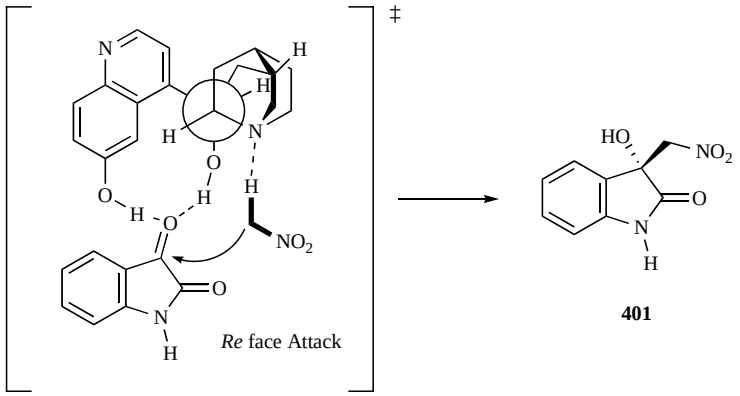
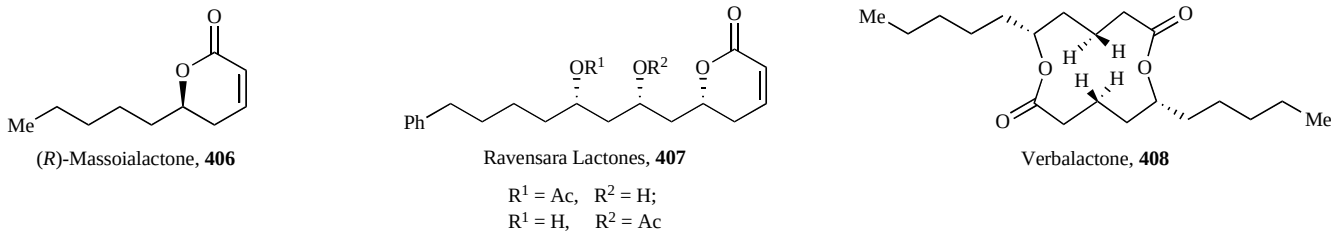


Fig. (16). A proposed transition state for the reaction.



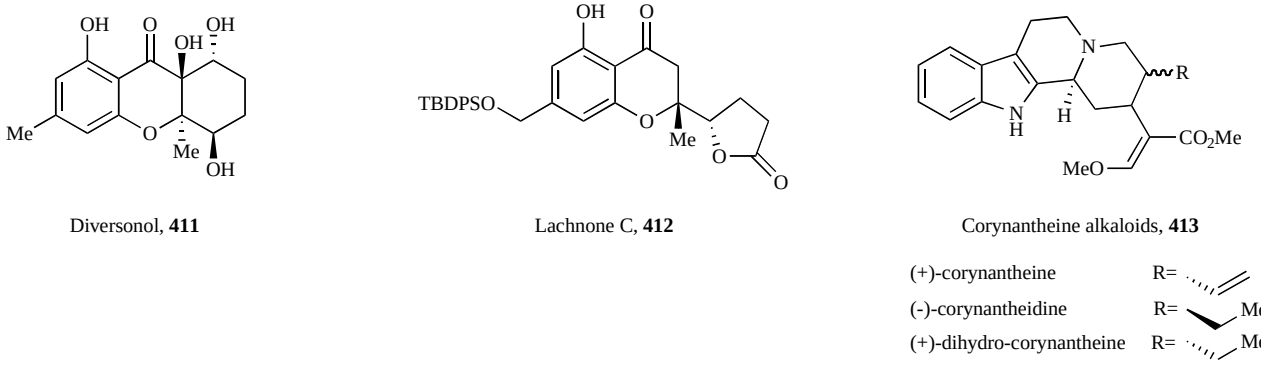


Fig. (17). Other selected natural product devised in 2011.

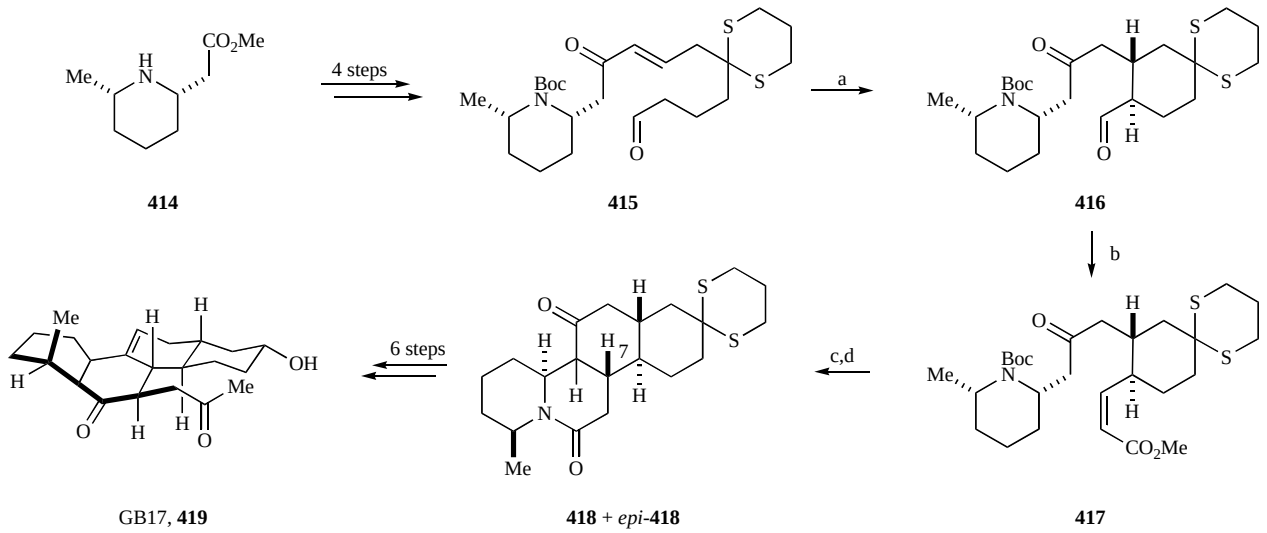
Such high enantioselectivity and the observed absolute configuration (*R*) was supposed to be a consequence of the transition model **405**, where the bifunctional catalyst **404**, simultaneously activates the nucleophile **101** through a base-acid interaction and the electrophile **400** *via* the stronger double-hydrogen-bond interaction of the 6' and 9-OH group (Fig. **16**). Additionally, the amino group directs the nitromethane attack to the *Re*-face of isatin evolving to the adduct **401**.

The synthetic utility of the just disclosed methodology was easily demonstrated by accomplishing in only four further steps the total synthesis of (*S*)-(-)-Spirobrassinin (**403**), avoiding the time- and yield-consuming use of several protecting groups.

4.20. Other Natural Product Syntheses

As well as in 2009 and 2010, it is noteworthy that a very large amount of procedures, which imply active methylene reactions promoted by various and different organocatalysts, were devised in 2011. In addition to the just depicted total syntheses, several other bioactive compounds have been elegantly achieved exploiting different and surprisingly approaches, few of which, we have reported in Fig. (**17**).

Among others, Harbindu and Kumar developed a novel protocol for the preparation of 1,3-polyols based on the iterative use of L-proline-catalysed tandem α-aminoxylation and Horner-Wadsworth-Emmons (HWE) olefination of aldehydes [217, 218].



Scheme 58. Synthesis of *Galbulimina* alkaloid (-)-GB17. Reagents and conditions: (a) (*S*)-**43** •TFA (5 mol%) THF (99%); (b) LiCl (2.0 eq.), *i*Pr$_2$EtN (2.0 eq.), methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl] ethanoate (1.2 eq.) (*cis*-80%, *trans*-20%); (c) TFA; (d) NaOMe (6.0 eq.), MeOH (70% **418** and *epi*-**418**).

The employment of these sequence to the synthesis of natural products, made possible the preparation of several lactones less or more complex such as (*R*)-massiolactone (**406**), ravensara lactones (**407**), and verbalactone (**408**), in a very concise and efficient manner with a quite high selectivity. L-proline resulted to be the best choice also for the synthesis of quinine (**409**) and quinidine (**410**) which, during last decades, have been object of a growing interest not only for their medicinally important activities, but also and above all as consequence of their prolific role in the organocatalysis golden rush. Among the number of reported stereocontrolled syntheses, Hatakeyama *et al.* accomplished the enantiocontrolled total synthesis of quinine (**409**) and quinidine (**410**) starting from the common benzylammine in 10% and 6%overall yield, over 23-steps, respectively [219]. The employed strategy also furnished an efficient route to enantiopure 3,4-cis-disubstituted piperidines, which relies on a novel proline-catalyzed intramolecular aldolization reaction. Using the slightly more complex Jørgensen's catalyst, Bräse *et al.* reported a successfully application of their vinilogous aldol oxa-Michael domino reaction [220], developing a general method for the asymmetric preparation of Diversonol (**411**) and Lachnone C (**412**). Finally, exploiting the broad applicability of the Pictet-Spengler reaction, Hiemstra and co-workers accomplished the total synthesis of few Corynanthe Alkaloids **413** [221] by chiral Brønsted acid improving the synthetic strategy developed in 2009 for (-) Arboricine (vide intra). Independently, Franzen *et al.* devised a stereodivergent strategy for the analogous Corynantheine alkaloids as well as for the Ipecac ones [222]. Alternatively to Hiemstra, the approach reported by the Swedish group relies on an enantioselective and diastereodivergent one-pot cascade sequence promoted by the Hayashi's catalyst *via* covalent iminium activation. Both these routes gave high level of enantio- and diastereoselectivity, highlighting how due to its efficiency, product diversity, operational simplicity and economy, organocatalytic procedures have the potential to find always broader and more important employment in total synthesis of natural and unnatural products.

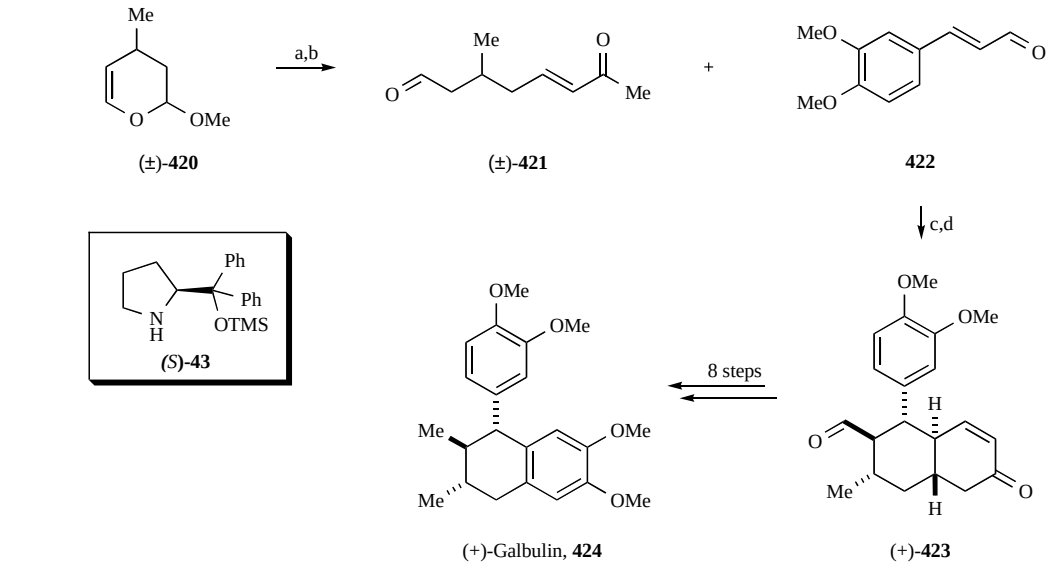
5. 2012

5.1. Galbulimina Alkaloid (–)-GB17

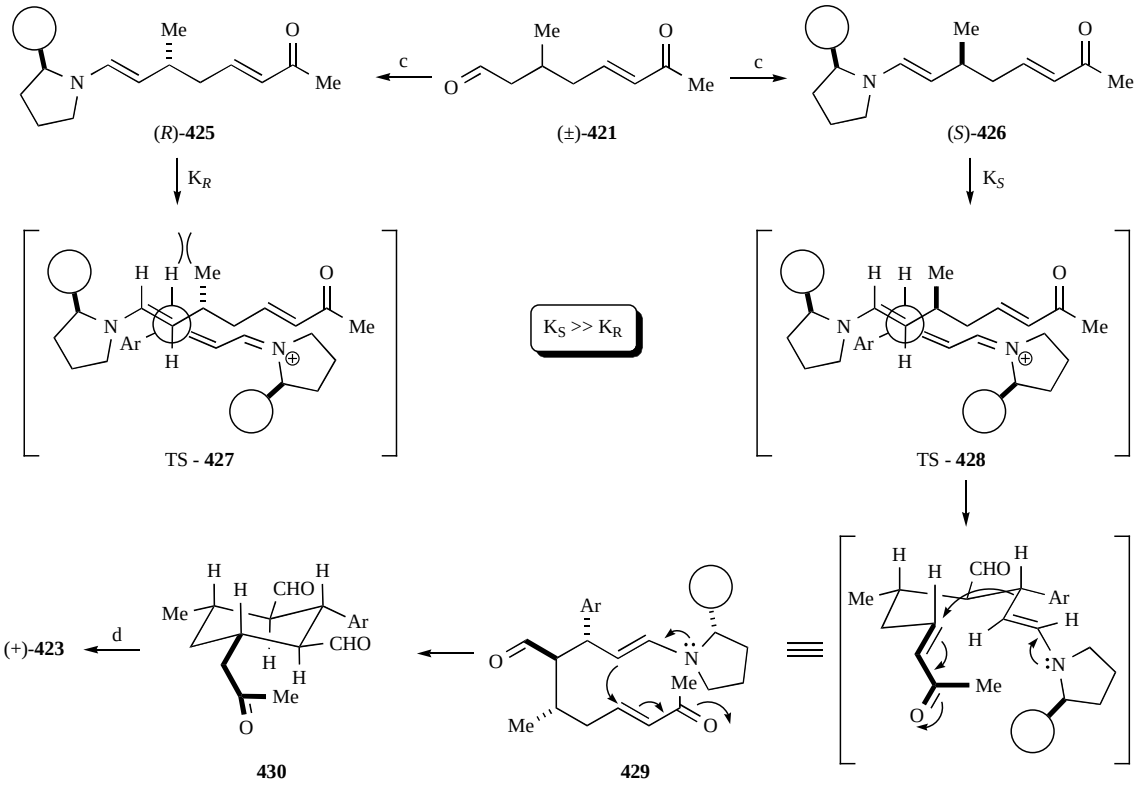
The *Galbulimina* alkaloids are fascinating molecular entities that exhibit high therapeutic potential. All members of this alkaloid family possess a common piperidine ring and a *trans*-decalin carboxylic core. Recently, Thompson and co-workers reported the first total synthesis of the tetracyclic GB17 [223], a novel *Galbulimina* alkaloid which structure has been only recently elucidated by means of X-ray crystal structure [224]. Their strategy relies on the application of two stereoselective intramolecular Michael additions in which the first one was successfully realized by means of diphenylprolinol-catalysis (5 mol%) and the second one was carried out under substrate control in the presence of sodium methoxide in methanol. Accordingly, exposure of aldehyde **415 (**prepared in 4 steps from *cis*-piperidine **414**) to their previously developed reaction conditions smoothly gave rise to the required *trans*-substituted cyclohexane in 99% yield (Scheme **58**). They have observed that in the absence of the dithiane moiety, this intramolecular Michael reaction takes place with very poor results and the authors assumed that these unfavourable outcomes could probably arise from the lack of the Thorpe-Ingold effect that is present in **415**. Thus, a Still-Gennari olefination of **416** provided the desired *cis*-enoate **417** in 80% yield which after Boc deprotection and a second intramolecular Michael addition gave the tetracyclic framework of **418** and its epimer at position 7, *epi*-**418**. Additional 6 steps were than necessary to finally accomplish the first total synthesis of (–)-GB17 (**419**), the naphthoquinolizinone derivative of *Galbulimina* alkaloids.

5.2. (+)-Galbulin

Hong and co-workers have explored the potential of organocatalytic transformations on the enantioselective total synthesis of (+)-galbulin, a natural lignin first isolated from *Himantandra baccata* and *Himantandra belgraveana* [225]. Starting from 3,4-dihydro-2-methoxy-4-methyl-2*H*-pyran (**420**), the intermediate (*E*)-3-methyl-7-oxooct-5-enal (**421**) was obtained in 2 steps and engaged, in the presence of aldehyde **422**, to the key reaction step of the synthesis: the domino organocatalytic double Michael-aldol reactions. The Michael-Michael sequence was mediated by Hayashi catalyst (*S*)-**43** (20 mol%) and in order to reach good reaction outcomes, a ratio of **421**/**422** of 2.4:1 was necessary. Subsequent addition of *p*-TsOH allowed the aldol reaction and afforded adduct (+)-**423** as single stereoisomer in 82% yield (d.r. >20:1, 99% *ee*) (Scheme **59**).

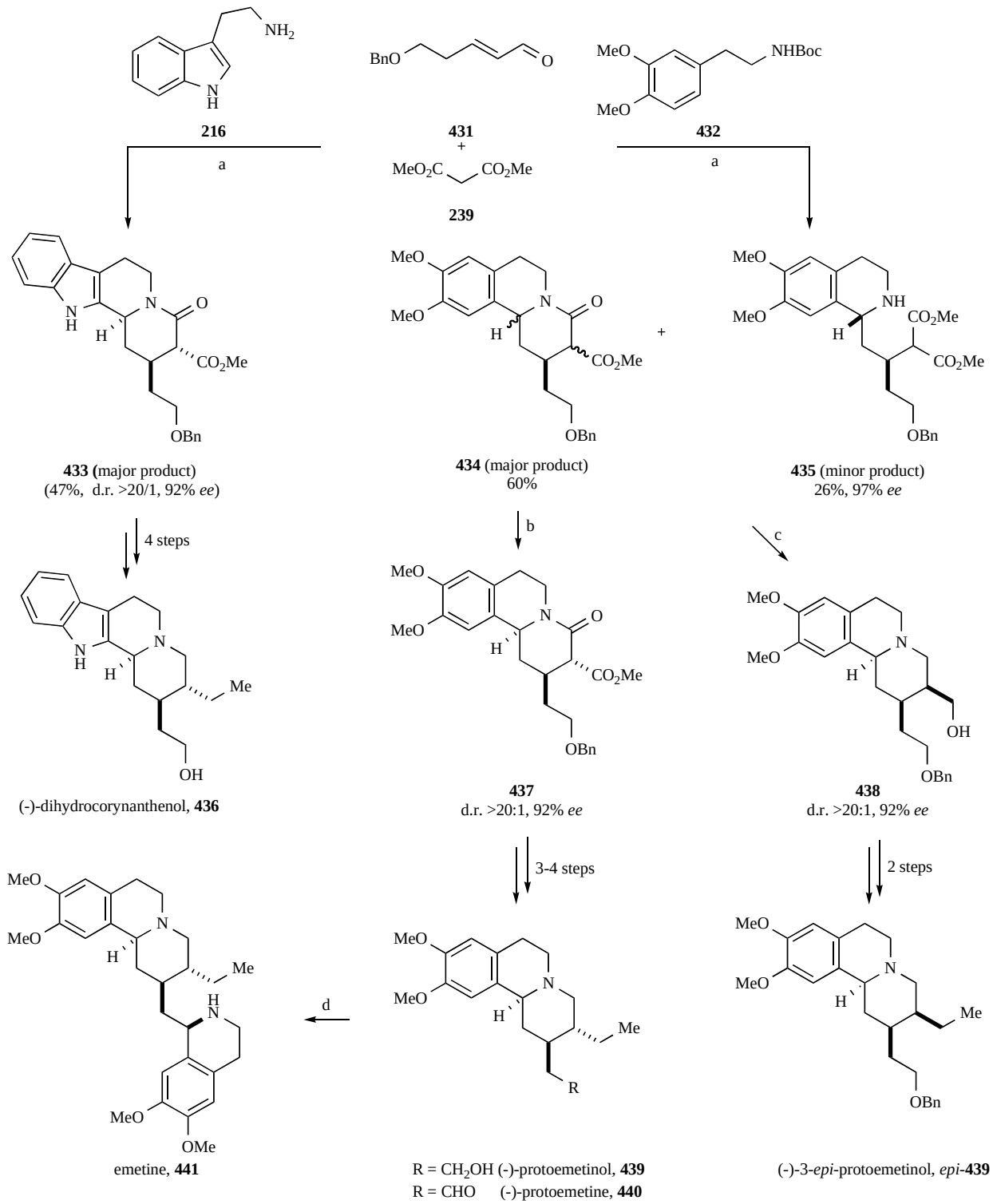


Scheme 59. Synthesis of (+)-Galbulin. Reagents and conditions: (a) aq. HCl, H_2O, 2h; (b) $Ph_3PCH_2COCH_3$, CH_2Cl_2, rt, 14h (54%, 2 steps); (c) (*S*)-**43** (20 mol%), CH_3CN, rt, 72h; (d) *p*-TsOH, CH_3CN, rt, 5h (82%, 2 steps, 99% *ee*).



Scheme 60. Proposed mechanism pathway for the domino organocatalyzed Michael-Michael-aldol condensation *via* kinetic asymmetric transformation (KAT) of (±)-**421**. For reaction conditions see Scheme **59**.

This result supports an unusual kinetic asymmetric transformation (KAT) of (±)-**421** and a mechanistic pathway which is depicted in Scheme **60** has been proposed in order to shed light into the stereoselectivity outcome observed in this transformation. Accordingly, the authors have postulated that the first Michael addition of (*S*)-**428** to the *Re*-face activated iminium-ion, resulted from aldehyde **422** and catalyst (*S*)-**43**, afforded intermediate **429** *via* transition state TS-**428,** which further cyclizes by means of a second Michael reaction giving rise to compound **430**. Addition of *p*-TsOH mediates the subsequent aldol reaction of **430** and, after dehydration, the desired adduct (+)-**423** was created. On the other hand, the Michael addition of (*R*)-**425** to the activated iminium-ion from aldehyde **422** *via* transition state TS-**427** is disfavoured owing to severe steric hindrance, which hampers the subsequent reaction and thus results in a kinetic resolution of (±)-**421**. Therefore, by using an organocatalyzed domino sequence of Michael-Michael-aldol condensations, Hong and co-workers have established a valuable strategy and achieved the first enantioselective synthesis of (+)-galbulin, (**424**) in 11% overall yield (12 steps) (Scheme **59**).

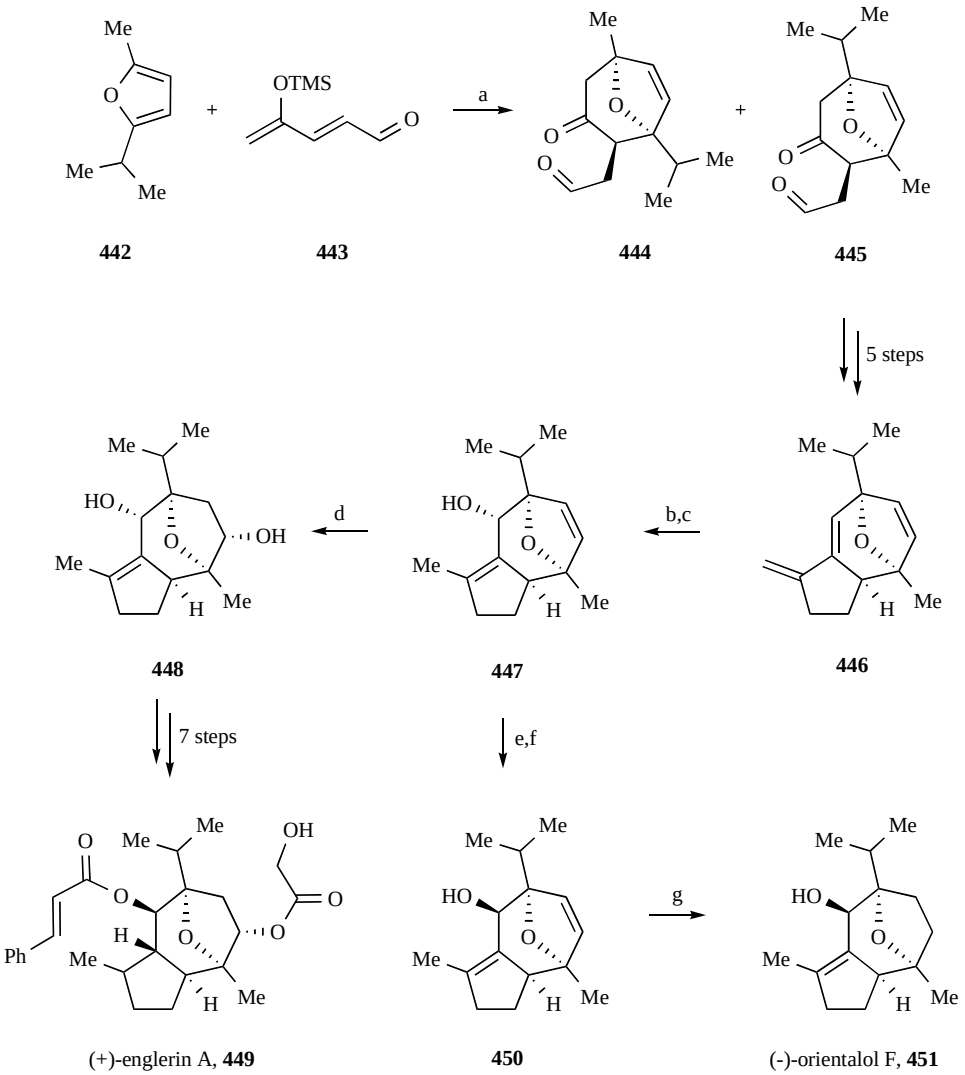


Scheme 61. Synthesis of secologanine dopamine and tryptamine alkaloids. Reagents and conditions: (a) (*i*) (*S*)-**43** (10 mol%), EtOH, rt, 64h, (*ii*) **216**, TFA, CH_2Cl_2, 50 °C or **432**, HCl (4N dioxane), CH_2Cl_2, rt; (b) LDA, THF, -78 °C; (c) $LiAlH_4$, THF, reflux; (d) **432**, HCl (4N dioxane), CH_2Cl_2, rt.

5.3. (−)-Dihydrocorynanthenol, (−)-Protoemetinol, (−)-Protoemetine, (−)-3-epi-Protoemetinol and Emetine

An attractive strategy based on a one-pot, three-component catalytic asymmetric Michael/Pictet-Spengler/lactamization cascade reaction has been developed by Cordova and co-workers during the total synthesis of secologanine tryptamine and dopamine alkaloids [226] that are known for being highly biologically active. By employing aliphatic enal **431**, malonate **239** and either tryptamine **216** or dopamine **432** derivatives as the substrates and chiral amine (*S*)-4**3** (10 mol%) as the catalyst, the synthesis of the valuable quinolizidine precursors **433-435** could be achieved (Scheme **61**).

Further classical structural elaboration, allowed the successful transformation of intermediates **433-435** into secologanin, dopamine, and tryptamine alkaloids as depicted in Scheme **61**.



Scheme 62. Formal Synthesis of (+)-Englerin A and (-)-Orientalol F. Reagents and conditions: (a) **17** •TFA (20 mol%), CH_3NO_2 (**445**/**444** = 2.4:1); (b) MCPBA; (c) Dibal-H; (d) $Hg(OTFA)_2$, $NaBH_4$ (38%); (e) TPAP, NMO (70%); (f) $NaBH_4$ (99%), (g) H_2, Pd/C (85%).

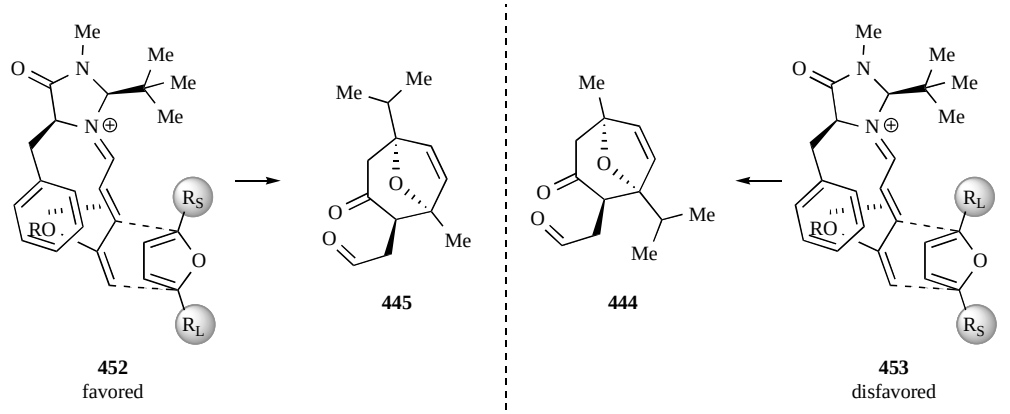
5.4. (+)-Englerin A (formal synthesis) and (–)-Orientalol F

Englerin A (**449**) belongs to the 7,10-epoxy-guaianoids group of exquisite natural products isolated from the root and bark of *Phyllanthus engleri*, a tree indigenous to East Africa. Owing to its intriguing and challenging molecular structure together with its biological activity (potent and selective inhibition of renal cancer cell lines), Englerin A has recently attracted high interest among the synthetic community [227-236]. Due to the similar molecular architecture found in orientalol F (**451**), a Chinese herbal medicine isolated from the rhizome of *Alisma orientalis*, an enantioselective total synthesis of both natural compounds by means of a common precursor was recently devised [237]. The strategy used was based on the Harmata's organocatalyzed [4+3]- cycloaddition reaction between furan **442** and dienal **443** catalyzed by imidazolidinone **17,** that affords **445** and **444** in a 2.4:1 ratio, respectively (Scheme **62**) [238]. Further elaboration of the major product **445** allowed the preparation of the advanced intermediate **446** which is in turn successfully transformed into allylic alcohol **447** *via* a sequence of epoxidation/S_N2'-type reduction. With this key intermediate in hands, the enantioselective formal synthesis of (+)-englerin A (**449**) and the total synthesis of (–)-orientalol F (**451**) was than pursued. Regioselective oxymercuration/reduction of **447** through an *exo-syn* addition (due to steric and electronic factors) gave rise to diol **448,** which can be further advanced to the natural product englerin A as previously shown [232]. The absolute stereochemistry was ascribed by comparison of the optical rotation of **448** with literature data [231].

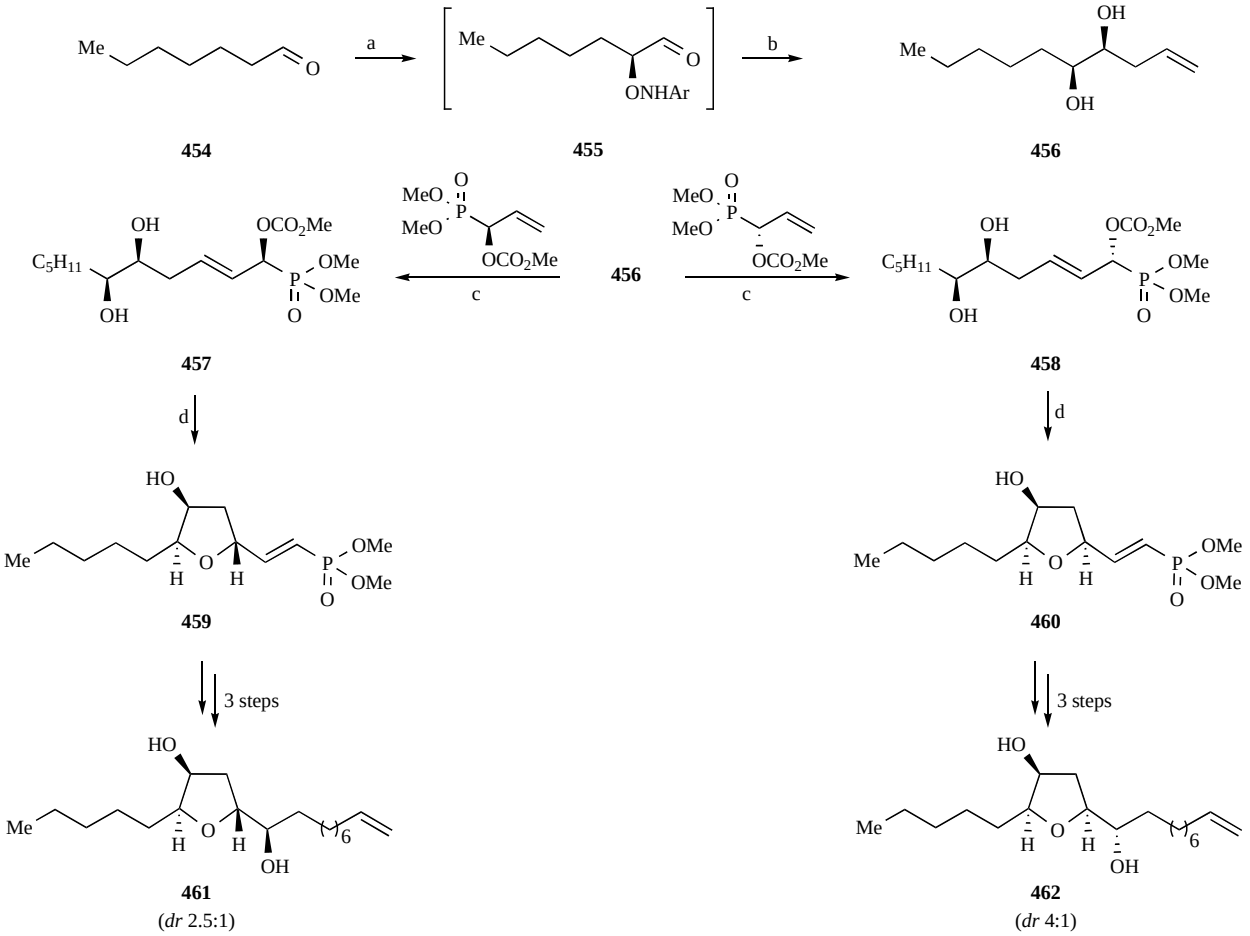
Thus, they have proposed that the stereochemical conclusion of the [4+3]-cycloaddition reaction could be explained by means of intermediates **452** and **453** in which steric factors drive the *endo*-addition reaction outcome between dienal **443** and furan **442** (Scheme **63**). In turn, the total synthesis of (–)-orientalol F was accomplished from **447** in 3 addition steps (oxidation, reduction and hydrogenation).

5.5. Oxylipids

Another example that illustrates the potential of proline-catalyzed nitrosoaldol condensation affording α-hydroxyl aldehydes was reported by Spilling and Roy during the total synthesis of both diastereoisomers of lipid dihydroxytetrahydrofurans **461** and **462** from Australian brown algae *Notheia anomala* [239]. The preparation of a key *syn*-diol intermediate was accomplished in two steps: the first one consists of the α-aminoxylation of heptaldehyde **454** in the presence of D-proline (10 mol%) and, the second one is



Scheme 63. Harmats's [4+3]-cycloaddition reaction stereochemical outcome.



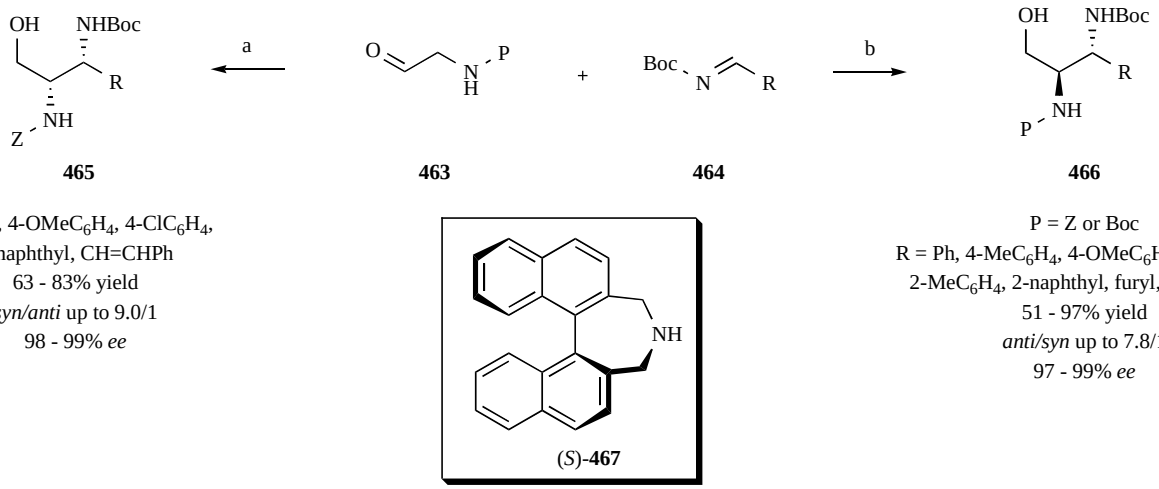
Scheme 64. Synthesis of oxylipids from Australian brown algae *Notheia anomala*. Reagents and conditions: (a) D-proline (10 mol%), $CHCl_3$, *o*-TolNO, 4 °C, 2h; (b) allylMgCl, $CeCl_3{\cdot}2LiCl$, THF, -78 °C to rt, 16h (75%, 2 steps); (c) Grubbs II, CH_2Cl_2, 40 °C, 3h (74%); (d) $Pd(PPh_3)_4$, *i*$PrNEt_2$, THF, 60 °C, 3h (93% and 89%).

the direct allylmagnesium chloride addition to the previously obtained aldehyde for giving rise to the desired *syn*-diol **456** in 75% yield. From this common intermediate and by alkene cross metathesis in the presence of (*S*) and (*R*)-carbonate, both of the diastereomeric phosphono allylic carbonates were isolated and further engaged in a Palladium(0)-catalyzed cyclization affording the 2,5-*trans*-tetrahydrofuranyl-(*E*)-vinyl phosphonate **457** and its *cis*-isomer **458** in 69% and 66% yield respectively. Additional four steps for each diastereoisomer provided a novel entry to the two natural diastereomeric oxylipids in six overall steps.

5.6. (−)-Agelastatin A (Formal Synthesis)

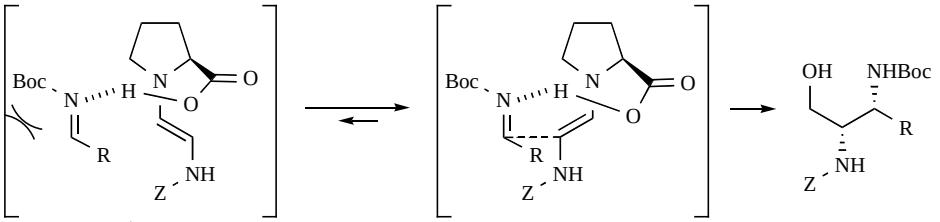
A diastereo- and enantioselective direct Mannich reaction of Z or Boc-protected aminoacetaldehydes with *N*-Boc-protected imines was recently devised by Maruoka and co-workers [240]. The method allowed a straightforward way to prepare a vicinal diamine and both *syn*-and *anti*-adducts can be successfully obtained by using L-proline and the axially chiral amino sulphonamide (*S*)-**467** respectively (Scheme **65**).

When the reaction is carried out on the presence of (*S)*-proline, they have hypothesized a transition stated **TS-468** (*via E-s-cis-*



Scheme 65. Maruoka's organocatalytic asymmetric Mannich reaction of *N*-protected aminoacetaldehydes Used catalysts: (a) (*S*)- Proline [(*S*)-**195**]; (b) (*S*)-**467**.

Transition state models with (*S*) -proline [(*S*)-**195**]:

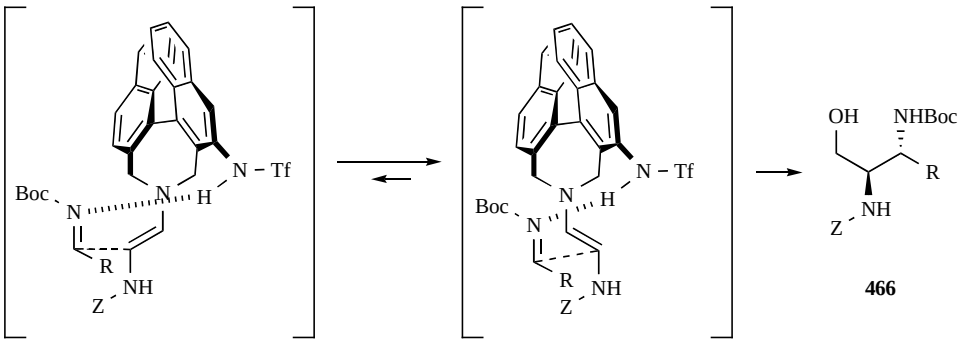


E-s-cis-enamine
TS-468

E-s-trans-enamine
TS-469

465

Transition state models with (*S*)-**467**:



E-s-cis-enamine
TS-470

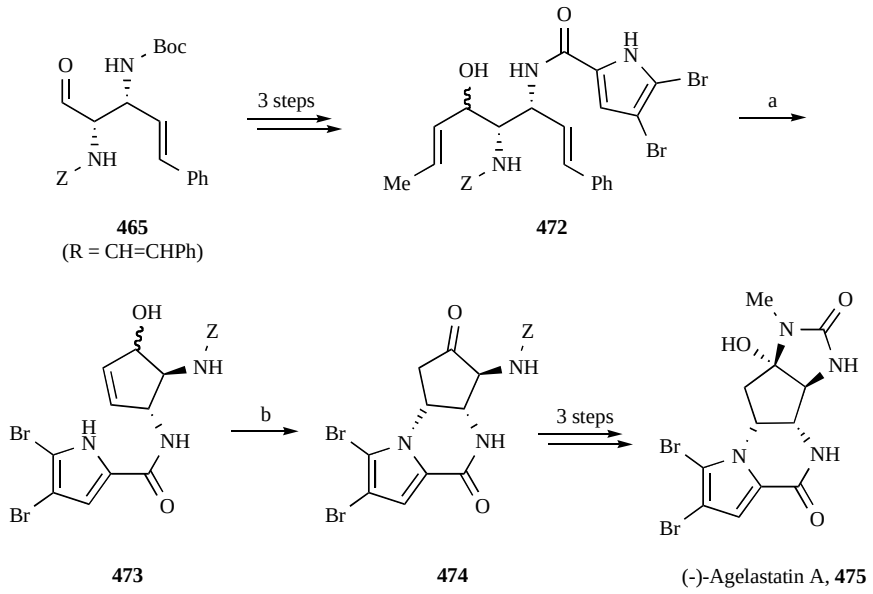
E-s-trans-enamine
TS-471

466

Scheme 66. Transition-state models.

enamine) as being the dominant species over the sterically encumbered **TS-469**. In other hands, both *E-s-cis*- and *E-s-trans*-enamines (**TS-470** and **TS-471**, Scheme **66**) can be formed when (*S*)-**467** is used. Nevertheless, the transition state **TS-470** (which has the imine moiety at the suitable position) delivers faster the anti-vicinal diamine adduct with respect **TS-471**.

In order to demonstrate the potential of such a transformation, a formal synthesis of (-)-agelastatin A, a marin alkaloid, which exhibits potent antitumor activity, was realized. The Mannich product **465**, obtained by means of (*S*)-proline catalysis (30 mol%), was isolated in 69% yield with high selectivities (*syn/anti* 6.4/1, 98% *ee*). Then, it was further engaged in a series of transformations (*eg* Nozaki-Hiyama-Takai-Kishi coupling, Boc deprotection and amide formation, Scheme **67**) to afford amide **472**. Treatment of **472** with Hoveyda-Grubbs second-generation catalyst affords cyclopentene **473** that was submitted to IBX oxidation and subsequent intramolecular conjugate addition of the pyrrole moiety. The obtained cyclopentanone **474** was used in a previous total synthesis of (–)-agelastatin A (**476**) by Ichikawa's group [241]. Then, in 5 steps from *syn*-vicinal diamine **465**, an elaborated intermediate **474** used in a former total synthesis of (–)-agelastatin A was successfully obtained in 21% overall yield from Z-protected aminoacetaldehyde with *N*-Boc-protected imine (Scheme **67**).



465
(R = CH=CHPh)

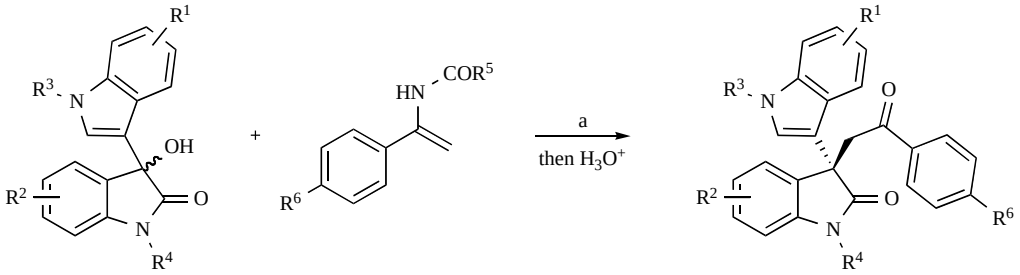
472

473

474

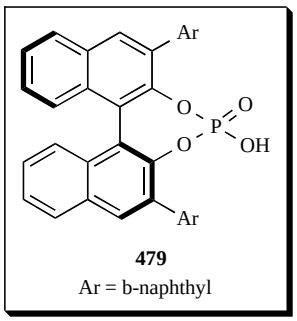
(-)-Agelastatin A, **475**

Scheme 67. Formal Synthesis of (-)-Agelastatin A. Reagents and conditions: (a) Hoveyda-Grubbs second-generation catalyst, toluene (78%); (b) IBX, DMSO then *i*Pr_2Net (81%).

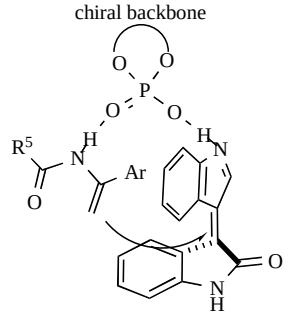


476 **477** **478**

R^1 = 5'-Br, 5'-MeO, 5'-Cl, 5'-F, 6'-Me, 6'-F, H R^2 = H, 5-Me, 5-F R^3 = H, Me R^4 = H, Bn, Boc
R^5 = OMe, OEt, OBn, Ph R^6 = H, Me, Cl



479
Ar = b-naphthyl

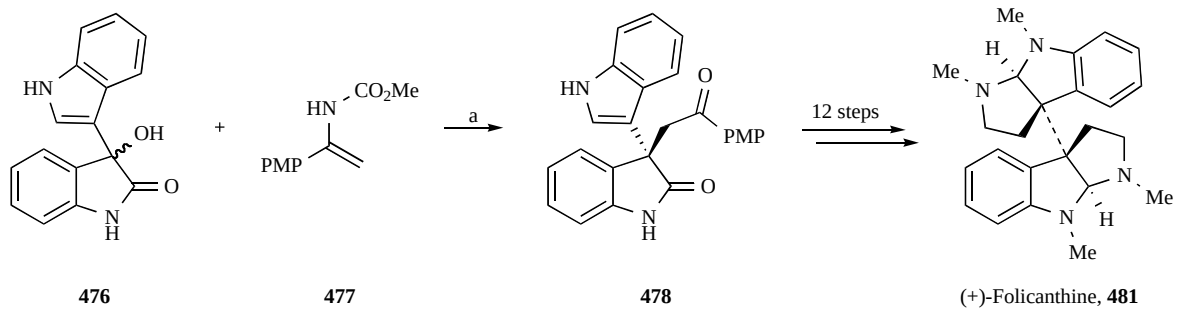


Favorable Transition State (**480**) that gives the *R*-configured product

Scheme 68. Synthesis of the key intermediate toward (+)-Folicanthine. Reagents and conditions: (a) **476** (1.0 eq.), **477** (1.5 eq.), **479** (10 mol%), CH_2Cl_2 (2 mL, on a 1 mmol scale with 100 mg of Na_2SO_4 (70-92%, 90-96% *ee*).

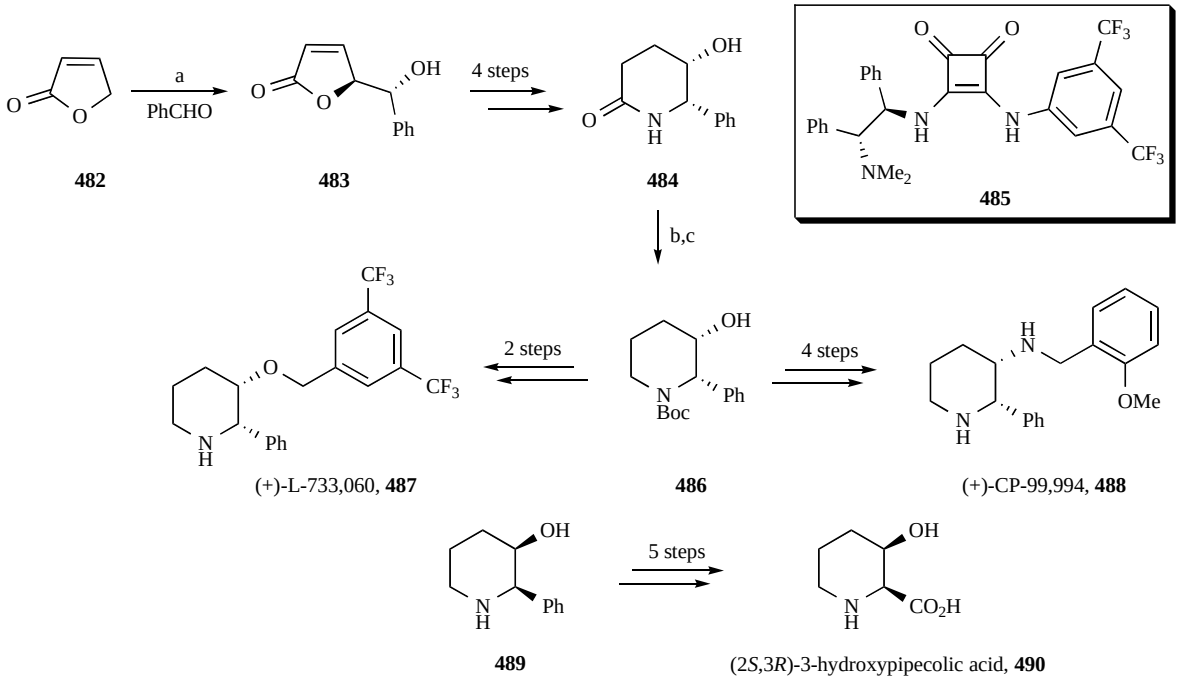
5.7. (+)-Folicanthine

Cyclotryptamine alkaloids have promising biological and pharmaceutical activities and very fascinating chemical structures. These compounds bear an octahydro-3a,3'a-bispyrrolo[2,3-*b*]indole subunit characterized by vicinal all-carbon quaternary stereogenic centers. Very recently, Gong and co-workers have devised an enantioselective catalytic method to access 3,3'-disubstituted oxindoles **478** with the concomitant creation of a quaternary all-carbon stereogenic center starting from 3-hydroxyindoles **476** and enecarbamates **477** by means of chiral phosphoric acids catalysis (**479**, 10 mol%) (Scheme **68**) [242]. It might be pointed out that when optimising the reaction conditions, the authors have observed that the addition of anhydrous sodium sulphate afforded higher product yield while maintaining the remarkable stereochemical outcome.



476 **477** **478** (+)-Folicanthine, **481**

Scheme 69. Synthesis of (+)-Folicanthine. Reagents and conditions: (a) **479** (10 mol%), CH_2Cl_2, Na_2SO_4 (82%, 90% *ee*).



482 **483** **484** **485**

(+)-L-733,060, **487** **486** (+)-CP-99,994, **488**

489 (2*S*,3*R*)-3-hydroxypipecolic acid, **490**

Scheme 70. Synthesis of three bioactive piperidines. Reagents and conditions: (a) **485** (20 mol%), CH_2Cl_2, rt (74%, d.r. = 8/1, e.r. = >100/1); (b) BH_3·THF; (c) $(Boc)_2O$ (82%, 2 steps).

They assumed that sodium sulphate serves as a water-scavenger, generated from dehydration reaction, and thus inhibits enamide decomposition.

Thereby, they have fruitfully applied their strategy to synthesize a key chiral building block **478** (R^1=R^2=R^3=R^4= H) in 82% yield and 90% *ee*, and to accomplish, after 12 additional steps, the first catalytic enantioselective total synthesis of (+)-folicanthine (Scheme **69**).

5.8. (+)-L-733,060, (+)-CP-99,994 and (2S,3R)-3-hydroxypipecolic Acid

An efficient and concise synthesis of bioactive piperidines was devised by Pansare and Paul [243] by means of organocatalytic direct vinylogous aldol (ODVA) reaction, a strategy that only recently has received attention [244, 245]. Indeed, the introduction of organocatalysts in such transformations paves the way to easier reaction conditions as the need for 2-siloxyfurans can be avoided (which is necessary for typical stereoselective Mukaiyama aldol reactions) and simpler γ-crotonolactone (commercially available) can be used. Thus, they have elaborated a synthetic strategy that highlights the convenience of such a method and synthesized three representative members of the 2,3-disubstituted class of bioactive piperidines (Scheme **70**). The synthesis of a common synthetic precursor for carrying on the preparation of (+)-L-733,060 and (+)-CP-99,994 was initiated by the direct vinylogous aldol reaction of γ-crotonolactone (**482**) and benzaldehyde in the presence of aminosquaramide catalyst **485** (20 mol%). By doing so, the butenolide **483** was isolated in good yield and diastereoselectivity (74%, *anti/syn* 8:1) and remarkable enantioselectivity (>99% *ee*). Four additional steps allowed the synthesis of piperidone **484** without purification of any of the intermediates (76% yield after four steps). Borane-mediated reduction followed by *N*-Boc protection give rise to the *N*-Boc derivative **486** which is successfully transformed into (+)-L-733,060 (**487**) and (+)-CP-99,994 (**488**) after 2 and 4 steps respectively.

The preparation of (2*S*,3*R*)-3-hydroxypipecolic acid (**490**) required the use (2*S*,3*R*)-2-phenyl-3-hydroxy piperidine **489** as starting material. This intermediate was prepared as described for **483** by employing the *ent*-**485**. After 5 sequential transformations, the desired hydroxypipecolic acid was isolated in 52% yield from **483**.

6. CONCLUSION

Throughout this review, selected successful examples on organocatalyzed asymmetric synthesis of natural products by means of methylene activation have been presented. Although it is not

always stated that methylene compounds are classical intermediates in some organocatalyzed transformations, it is clear that in many cases they are responsible, by coordination or reaction with the organocatalyst, for the stereochemical outcome. Accordingly, the construction of diversified functionalized moieties with high levels of asymmetric induction has been achieved. There is no doubt that organocatalysis only or in combination with other approaches, as for example transition-metal catalysis and sustainable chemistry, represents a real progress in the field of organic chemistry of the 21st century. Herein, our goal was to give a general overview on breakthroughs results from 2009 till April 2012 on the field of organocatalysis and total synthesis of natural products where at least one organocatalyzed step overtakes a methylene compound intermediate. The above considerations motivated us to highlight and review here some significant examples that from our point of view clearly show the impact of active methylene compounds as intermediates in total synthesis by means of organocatalysis. Indeed, to date, a range of procedures that is suitable for the asymmetric functionalization of simple and unsaturated enals and ketones in which methylene intermediates are involved gives access to a broad variety of important building blocks. Since the first seminal publications on organocatalysis [2, 3] have appeared in 2000, its application in total synthesis has followed soon after. Undoubtedly, the use of organocatalyzed approaches in the total synthesis of natural products can be considered as a tool of paramount importance where longstanding synthetic challenges were successfully surmounted and new disconnections are allowed so far. We are confident that the examples presented herein are just the beginning (as illustrated in Fig. **1**) and that new salient publications will reinforce the idea of how organocatalysis can be used to create new Carbon-Carbon and C-Heteroatoms bonds in a distinctive and very selective way by means of remarkable strategies.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

$(DHQ)_2PHAL$	=	Bis(dihydroquinidine)phthalizine
AchE	=	Acetylcholinesterase
AD	=	Asymmetric Dihydroxylation
BINOL	=	1,1'-Bi-2-naphthol
Boc	=	*tert*-butylcarbonyl
BSM	=	bis(phenylsulfonyl)methane
Bz	=	benzoyl
CAN	=	Cerium(IV) ammonium nitrate
Cbz	=	benzyloxycarbonyl
CD	=	cinchonidine
DAC	=	Donor-Acceptor Cyclopropane
DBN	=	1,5-diazabicycle[4.3.0]non-5-ene
DBU	=	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	=	1,2-dichloroethane
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	=	dimethylacetamide
DMAP	=	dimethylaminopyridine
DME	=	1,2-dimethoxyethane
DMF	=	dimethylformammide
DMP	=	Dess-Martin's periodinane
DMP	=	3,4-dimethoxyphenyl
DMSO	=	dimethylsulphoxide
FC	=	Friedel-Crafts
HFIPA	=	hexafluoroisopropyl acrylate
HMPA	=	Hexamethylphosphoramide
HWE	=	Horner-Wardsworth-Emmons
IBX	=	2-iodoxybenzoic acid
IMAMR	=	intramolecular aza-Michael reaction
IMDA	=	Intramolecular Diels-Alder
KAT	=	kinetic asymmetric transformation
KHMDS	=	potassium bis(trimethylsilyl)amide
LDA	=	Lithiumdiisopropylamide
LHMDS	=	Lithium bis(trimethylsilyl)amide
*m*CPBA	=	3-chloroperoxybenzoic Acid
MOM	=	Methoxymethyl
MS	=	molecular sieves
MTBE	=	methyl tert-butyl ether
MVK	=	methyl vinyl ketone
NBS	=	*N*-bromosuccinimide
NHC	=	nucleophilic heterocyclic carbene
NIS	=	*N*-iodosuccinimide
NMM	=	*N*-Methylmorpholine
NMO	=	4-methyl-morpholine N-oxide
NMP	=	1-methyl-2-pyrrolidinone
NMP	=	*N*-Methylpyrrolidone
ODVA	=	organocatalytic direct vinylogous aldol
PG	=	protecting group
PLP	=	Pirydoxal-Phosphate
PMB	=	*para*-methoxybenzyl**.**
PTC	=	phase-transfer catalysis
QD	=	Quinidine
RC	=	Rauhut-Courrier
RCM	=	ring closing methatesis
SET	=	single-electron transfer
SOMO	=	Singly Occupied Molecular Orbital
TASF	=	tris(dimethylamino)sulfonium difluoro-trimethylsilicate
TBA	=	tribromoacetic acid
TBDPS	=	*tert*-butyldiphenylsilyl
TES	=	triethylsilyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TMS	=	trimethylsilyl

TPAP	=	Tetra-N-propylammonium perruthenate
TRIP	=	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate
Troc	=	Trichloroethyl chloroformate
β-ICD	=	β-isocupreidine

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