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Natural Products

SPECIAL ISSUE

Synthesis of the Bicyclic Lactone Core of Leonuketal, Enabled by a Telescoped Diels–Alder Reaction Sequence

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Abstract: The Diels–Alder cycloaddition reaction has become established as a fundamental approach for the preparation of complex natural products; however, successful application of the intermolecular Diels–Alder cycloaddition reaction to the synthesis of particularly congested scaffolds remains surprisingly problematic. Inspired by the terpenoid spiroketal natural product leonuketal, a challenging telescoped reaction sequence has been realized to access the core [2.2.2]-bicyclic lactone ring system and its [3.2.1] isomer. Our four-step, protecting-group-free process required detailed investigation to circumvent the problems of adduct fragmentation and intermediate instability. Successful solution of these practical issues, along with unambiguous structural determination of the target structures, provide useful insights that will facilitate future applications of the Diels–Alder cycloaddition reaction to challenging, highly congested molecular scaffolds and ongoing synthetic efforts towards this natural product.

1. Introduction

In 2015, Peng and co-workers reported the isolation of the unique diterpenoid natural product leonuketal (**1**) from the herb *Leonurus japonicus* (Figure 1).[1] Leonuketal has displayed significant vasorelaxant activity against the KCl-induced contraction of rat aorta (EC_{50} = 2.32 μM), and was assigned an unprecedented tetracyclic structure.

The bridged spiroketal core of compound **1** was proposed by Peng and co-workers to originate from oxidative cleavage of the B ring of a labdane-type precursor that contained a double bond to give compound **2**, followed by spirocyclization. To date, no studies regarding the preparation of leonuketal have been reported. The synthetic challenge that is posed by its unique and complex architecture attracted our interest,

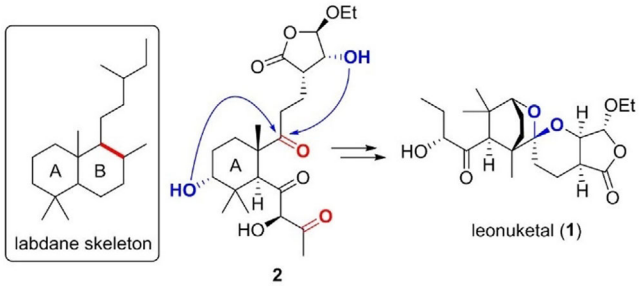

Figure 1. Biosynthesis of leonuketal (**1**), as proposed by Peng and co-workers.[1]

along with the potential for new synthetic and pharmacological discoveries. Initially, our attention focused on identifying a viable route to the key densely functionalized [2.2.2]-oxabicyclic core ring system. Larsen et al. had earlier reported the synthesis of bicyclic carbohydrate-derived [2.2.2]-lactone **4** from keto anhydride **3** (Scheme 1 A).[2–5] Their studies revealed that reduction of the C5-ketone (red; Scheme 1 A) proceeded with complete diastereoselectivity to afford a single alcohol epimer, which underwent spontaneous 6-*exo*-*trig* cyclization at the distal carbonyl group of the anhydride (blue; Scheme 1 A). This approach appeared to offer a plausible synthetic route to bicyclic lactone **5**, which forms the core of leonuketal (Scheme 1 B), through an analogous cyclization reaction of alcohol **6**, if the requisite precursor ketone (**7**) could be secured.

We anticipated that bicyclic anhydride **7**, or a suitable synthon, would be accessible through a Diels–Alder cycloaddition reaction (Scheme 2). The cycloaddition of 1,1-dimethyl Danishefsky-type diene **8** with methyl-substituted fumarate **9** should lead to 3,4-*trans*-**10**, a synthetic equivalent of **7** with the appropriate relative stereochemistry for leonuketal (**1**).

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Supporting information and the ORCID identification number(s) for the author(s) of this article, including experimental procedures, analytical data, copies of the ^{1}H and ^{13}C NMR spectra for new compounds, and ORTEPs of compounds **25** and **28**, can be found under: https://doi.org/10.1002/asia.201800903.

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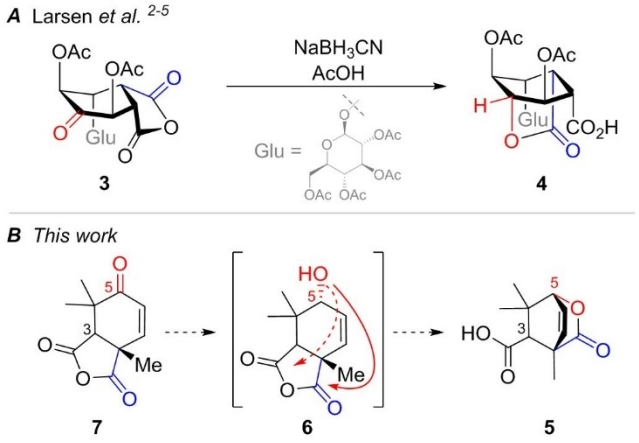
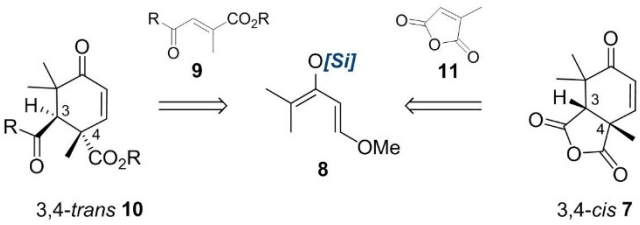


Scheme 1. Various approaches to the [2.2.2]-bicyclic lactone core of compound **1**; the atom numbering relates to the positions in the natural product, leonuketal. OAc = acetoxy.



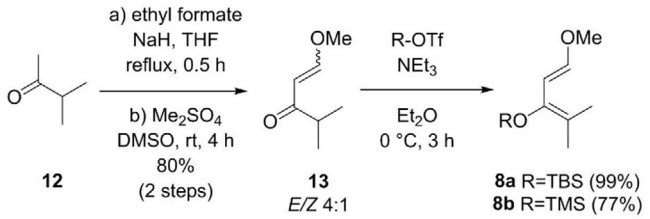
Scheme 2. Our retrosynthetic analysis.

However, there have been very few reports of successful cycloaddition reactions that involve such highly substituted diene/*trans*-dienophile combinations. As an alternative, we also envisaged that a cycloaddition reaction of compound **8** with the more-reactive commercially available cyclic *cis*-dienophile citraconic anhydride (**11**; ca. US$0.70 g^{-1}) should give access to the fused cyclic anhydride 3,4-*cis*-**7**, with the additional benefit of shortening the number of synthetic steps. The stereochemistry of 3,4-*cis*-**7** by following this latter sequence would be C3-epimeric with respect to compound **1**. Therefore, an additional epimerization step would be required later in the synthesis.

2. Results and Discussion

The requisite 2-silyloxy butadienes (**8a** and **8b**) were readily prepared by using an adapted literature procedure (Scheme 3).[6] Thus, deprotonation of compound **12** with sodium hydride, followed by treatment with ethyl formate and subsequent methylation, afforded ketone **13** in high yield (*E*/*Z* = 4:1). Subsequent treatment of the *E*/*Z* mixture with the appropriate silyl triflate afforded 2-silyloxy butadienes **8a** and **8b** as single stereoisomers. These modified conditions were more successful and reliable in our hands than the previously reported procedure.

At the outset of our study of the Diels–Alder cycloaddition reaction, we anticipated two principal challenges: 1) high steric demand in forming two tertiary–quaternary C–C bonds; and



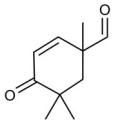
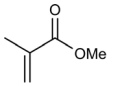
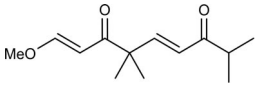
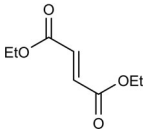
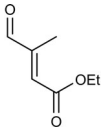
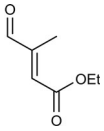
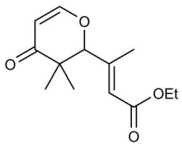
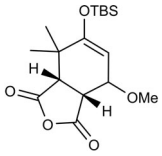
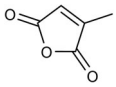
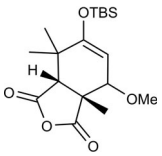
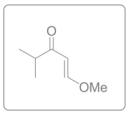
Scheme 3. Preparation of dienes **8a** and **8b**. Tf = trifluoromethanesulfonyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

2) the possible formation of regioisomeric mixtures, owing to the use of unsymmetrical 1,2-doubly activated dienophiles, such as compound **11**. Literature precedents for [4+2] cycloaddition reactions that form such densely substituted cyclohexenes are scarce, despite their abundance in terpenoid scaffolds.[7] Reports of related cycloaddition reactions that involved either a 1,1-dimethylated 2-silyloxy butadiene or a fumarate or citraconic anhydride (**11**) dienophile suggested that all of these components were problematic reaction partners.[8] Indeed, at the outset of our studies, the work of Sarpong's group towards prenylated indole alkaloids represented, to the best of our knowledge, the only related example, in which a 1,1-dimethylated 2-silyloxy butadiene system underwent a productive intermolecular cycloaddition reaction with a trisubstituted dienophile.[9,10] During the preparation of this manuscript, a very closely related example that involved an aryl-substituted maleic anhydride dienophile was described by the Dong group, which formed the foundation of a highly efficient total synthesis of three complex natural products: (−)-enmein, (−)-isodocarpin, and (−)-sculponin.[11] Interestingly, no problems in terms of product fragmentation or instability were reported in the development of this reaction, which was successfully performed on a multigram scale. In general, [4+2] cycloaddition reactions that involved citraconic anhydride (**11**) are significantly rarer that those of its simpler symmetrical congener, maleic anhydride (**14**).[12–14]

2.1. *Trans*-Dienophiles

Our initial investigations into the cycloaddition reactions of dienes **8a** and **8b** were disappointing (Table 1). Although the cycloaddition reaction between compound **8a** and the simple dienophile methyl methacrolein (**15**) proceeded readily to directly afford cyclic enone **16** in excellent yield (Table 1, entry 1), the reaction with the corresponding acrylate ester, methyl methacrolate (**17**), was unsuccessful, instead leading only to dimerization of the diene (**18**; Table 1, entry 2). Variation of the Lewis acid catalyst did not alter the course of this reaction. The thermal cycloaddition reaction of compound **8a** with either of the *trans*-dienophiles, diethyl fumarate (**19**; Table 1, entry 3) or 3-methyl-4-oxocrotonate (**20**; Table 1, entry 4), failed to give any of the desired products. However, in the presence of the Lewis acid catalyst scandium triflate, compound **8a** underwent an undesired hetero-Diels–Alder addition reaction to give compound **21** in moderate yield (Table 1, entry 5). Given our lack of success with the *trans*-dienophile

Table 1. Diels–Alder cycloaddition reactions of 1,1-dimethyl butadienes **8a** and **8b** with a range of dienophiles.

Entry	Dienophile		Conditions	Product		Yield [%]	Result Reaction type
1		**15**	$ZnCl_2$, CH_2Cl_2, 0 °C, 3 h		**16**	84	Diels–Alder reaction
2		**17**	1) $SnCl_4$, CH_2Cl_2, −78 °C, 3 h; then 0 °C, 1 h 2) Et_3N, 0 °C		**18**	51[a]	diene dimerization[b]
3		**19**	40 h, 150 °C	–		–	–
4		**20**	40 h, 150 °C	–		–	–
5		**20**	1) $Sc(OTf)_3$, CH_2Cl_2, −78 °C, 3 h 2) Et_3N, RT		**21**	43	hetero-Diels–Alder reaction
6		**14**	toluene, 100 °C, 2 h		**22**	36	Diels–Alder reaction
							Ratio of **23**/**13**[c]
7		**11**	neat, 40 h, 150 °C				80:20[a]
8			neat, 16 h, 150 °C, **11** (2 equiv)				30:70[a,d]
9			neat, 16 h, 150 °C, **11** (4 equiv)		**23**		10:90[a,d]
10			neat, 16 h, 140 °C				92:8[a,e]
11			neat, 16 h, 140 °C		**13**[g]		90:10[a,e,f]

[a] Product distribution was determined by using ^{1}H NMR following complete conversion; [b] dimerization product of diene **8a**; [c] ratio of the Diels–Alder product (**23**) to the desilylation byproduct (**13**); [d] butylated hydroxytoluene (BHT) was used instead of hydroquinone; [e] distilled citraconic anhydride (**11**) was used; [f] diene **8b** was used; [g] desilylation byproduct.

series, we turned our attention to the use of the *cis* alternatives: maleic anhydride (**14**) and citraconic anhydride (**11**).

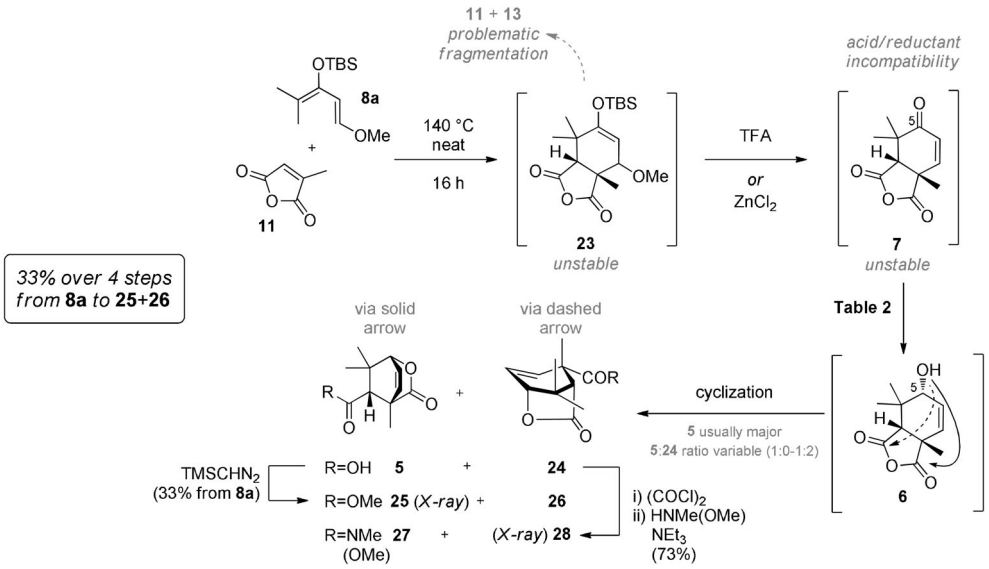
2.2. *Cis*-Dienophiles

Pleasingly, in contrast to the *trans*-dienophiles, the thermal reaction of compound **8a** with the model *cis*-dienophile maleic anhydride (**14**) proceeded cleanly to afford the corresponding cycloadduct (**22**) in 36% yield (Table 1, entry 6). More pleasingly, on heating with diene **8a** at 150 °C in toluene, citraconic anhydride (**11**) also underwent complete conversion into the desired cycloaddition product (**23**), as established by using ^{1}H NMR analysis (Table 1, entry 7). Importantly, this result also revealed complete regioselectivity for the desired cycloadduct regioisomer, likely driven by unfavorable steric interactions between the 1,1-dimethyl groups of the diene and the methyl group of dienophile **11** in the transition state for the undesired regioisomer. Notwithstanding this encouraging result, our optimization of the reaction was hampered by the concomitant desilylation of diene **8a** to give compound **13**, as well as by

the instability of compound **23** during its isolation and purification on silica gel, which resulted in very low yields of the isolated product (<5%). We observed that the desilylation of diene **8a** to give ketone **13** was less prevalent when an equimolar amount of dienophile **11** was used, as opposed to a two- or four-fold excess (Table 1, entry 7 versus entries 8 and 9). This result suggested that acidic impurities in the commercially sourced dienophile **11**, possibly citraconic acid, was promoting the undesired side reaction. Accordingly, we distilled citraconic anhydride (**11**) prior to use, and we observed a decrease in the desilylation side-reaction in subsequent runs (Table 1, entries 10 and 11). A subtle lowering of the reaction temperature was also beneficial (Table 1, entry 10). These optimized conditions were also found to be compatible with TMS diene **8b** (Table 1, entry 11).

Although conditions for the formation of the target Diels–Alder cycloadduct (**23**) had been identified, the problem of product isolation remained to be resolved to complete a productive routine synthesis. We immediately encountered difficulties in the desilylation/elimination reaction of cycloadduct **23** to afford ketone **7**. Following close investigation of the reaction process, we determined that compound **23** underwent a retro-Diels–Alder/diene-desilylation reaction to give citraconic anhydride (**11**) and ketone **13**, upon cooling in the reaction solvent, toluene. This effect was not observed when the crude adduct was quickly redissolved in deuterated chloroform for NMR analysis, thus implying the presence of a solvent effect in the fragmentation process. Interestingly, maleic anhydride cycloadduct **22** (Table 1, entry 6) did not undergo a retro-Diels–Alder/desilylation reaction and was stable to purification on silica gel. This result suggested that the angular methyl group at the ring junction also contributed to fragmentation, and further demonstrated the increase in difficulty on moving from maleic to citraconic anhydride. After a detailed dissection of the Diels–Alder reaction procedure, it was eventually possible to circumvent these issues by conducting the cycloaddition step in the absence of solvent, to avoid toluene-induced fragmentation. Subsequent direct treatment of the crude reaction mixture with TFA in chloroform successfully afforded ketone **7** (Scheme 4). This compound was also unstable to purification on silica gel or alumina, and was accordingly used directly in the next step.

Having established access to crude ketone **7**, we turned our attention to the formation of the [2.2.2]-oxabicyclic core of leonuketal (**1**). Reduction of the α,β-unsaturated ketone with sodium cyanoborohydride in acetic acid afforded an inseparable mixture of the desired product [2.2.2]-**5** with a second product, [3.2.1]-**24**. This reaction favored the formation of compound **5** in an approximately 2:1 ratio in most cases; however, this selectivity was somewhat variable and was occasionally reversed, for reasons that remain to be identified.[15] The reduction step was found to proceed with complete *exo*-selectivity to give a single C5-alcohol epimer (**6**), but a competing cyclization reaction on either carbonyl group of the cyclic anhydride led to the concomitant formation of either a six-membered lactone (solid arrow; Scheme 4) to give the favored, desired product [2.2.2]-**5**, or a five-membered lactone (dashed arrow; Scheme 4) to afford [3.2.1]-**24**. Similar competitive cyclization had previously been observed by Larsen et al. on a substitution-dependent basis.[5] We recognized that [3.2.1]-**24** could still potentially be a useful intermediate in later studies if necessary, through a *trans*-esterification step later in the synthesis. Carboxylic acids [2.2.2]-**5** and [3.2.1]-**24** were ultimately separable by derivatization into their respective esters, **25** and **26**, which were obtained in 17% and 7% overall yield from citraconic anhydride, respectively. The corresponding Weinreb amides (**27** and **28**) were also prepared by conversion of the crude mixture of acids **5** and **24** into the corresponding acid chlorides, followed by amide formation with *N*,*O*-dimethylhydroxylamine, in 24% combined yield from citraconic anhydride (Scheme 4). Single-crystal X-ray structures of [2.2.2]-**25** and [3.2.1]-**28**, which represented both isomeric manifolds, were



Scheme 4. Optimized telescoped four-step Diels–Alder sequence to afford the bicyclic lactone core of leonuketal (**1**). TFA = trifluoroacetic acid.

obtained and allowed unambiguous confirmation of the structural assignment and relative stereochemistry.

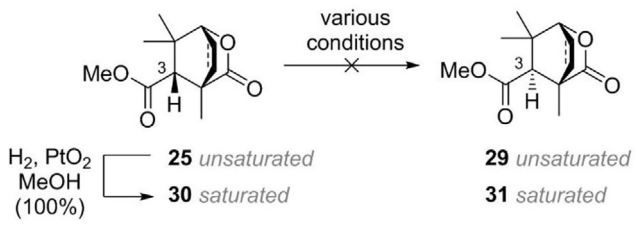
Having identified synthetic methods to access bicyclic lactones **25**–**28** and confirmed their structures, from a process point of view, it appeared that a telescoped reaction sequence for the preparation of compounds **25** and **26** directly from compounds **11** and **8a** without isolation would avoid the purification issues that were encountered for cycloadduct **23** and ketone **7**. The key to achieving this goal involved identifying suitable conditions for formation of ketone **7** from the crude Diels–Alder reaction mixture that would be compatible with the subsequent reductive lactonization reaction. After exploring a number of alternative conditions for the reduction of the C5-ketone (Table 2), we found that the desilylation of compound **23** could be achieved by using zinc chloride, without disrupting the subsequent reduction/lactonization step if the latter reaction were performed by using sodium cyanoborohydride in acetic acid (Table 2, entry 4). By using this telescoped sequence, it was possible to obtain compounds **25** and **26** in a pleasing combined yield of 33% over four steps from diene **8a** with variable selectivity between bicyclic products [2.2.2]-**25** and [3.2.1]-**26**, as previously observed for the multistep sequence.

Table 2. Optimization of the reduction step (**7**→**6**) in the presence of $ZnCl_2$ for the telescoped reaction sequence (Scheme 4).

Entry	Reductant	Solvent	Yield [%][b,c]
1	$NaBH_4$	$CHCl_3$	–
2	$NaBH_3CN$	$CHCl_3$/THF (1:1)[a]	–
3	$NaBH_3CN$	$CHCl_3$/THF/AcOH (1:1:0.1)	33
4	$NaBH_3CN$	$CHCl_3$/AcOH (1:1)	quant.

[a] AcOH (1 drop) was added; [b] yield was determined by using NMR spectroscopy with an internal standard; [c] combined yield of compounds **5** and **24** versus substrate **11**. quant. = quantitative yield.

Finally, our focus was directed towards inversion of the stereochemistry at the C3 position, which was required to access the correct relative stereochemistry for the bicyclic core of leonuketal (**1**). Disappointingly, despite an extensive screening of basic and other conditions to promote the epimerization reaction, we could not access the target C3-epimer **29** (Scheme 5 and the Supporting Information, Table S1). Furthermore, no inclusion of deuterium was observed upon quenching a mixture of compound **25** and sodium hydride, which had been heated at reflux in 1,4-dioxane, with deuterium oxide. To rule out the possibility of unfavorable π interactions of the endocyclic alkene, compound **25** was hydrogenated into its saturated analogue (**30**). However, disappointingly, compound **30** was likewise resistant to deprotonation. These data suggest that the formation of the enolate is not possible, owing to either the high steric demand of deprotonation, or to the requirement of a prohibitively strained geometry for the enolate. Inversion of the stereochemistry at the C3 position through the decarboxylative formation of an alkyl radical from activated esters of compound **5** was also briefly pursued, but this strategy was also ultimately unfruitful.[16–21]



Scheme 5. Attempted C3-epimerization of compounds **25** and **30**.

3. Conclusion

In summary, an efficient telescoped four-step procedure for the synthesis of highly congested bicyclic lactone ring systems similar to that possessed by leonuketal (**1**) has been developed that does not rely on protecting groups. This sequence proceeded through unstable intermediates that were highly prone to fragmentation and decomposition, and was only achieved after close dissection of each individual transformation. The structure and relative stereochemistry of the highly congested [2.2.2]- and [3.2.1]-bicyclic lactone products were unambiguously determined by X-ray crystallography. Surprisingly, it was not possible to achieve the planned C3-epimerization to access the required relative stereochemistry for leonuketal. The insights that have been gained in realizing this challenging approach should facilitate wider application of the Diels–Alder cycloaddition reaction to highly congested molecular scaffolds and other ongoing synthetic efforts towards this natural product.

Experimental Section

General

Unless otherwise noted, all of the reactions were performed under an oxygen-free nitrogen atmosphere by using standard techniques. THF and CH_2Cl_2 were dried by passing through a column of activated alumina under a nitrogen atmosphere by using an LC Technology solvent-purification system. All other reagents were used as received unless otherwise noted. Yields are of chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by using thin-layer chromatography (TLC) on silica gel plates, by using UV light as the visualizing agent and potassium permanganate as a developing agent. Silica gel 60 (230–400 mesh) was used for flash column chromatography unless otherwise stated. NMR spectra were recorded at RT in $CDCl_3$ on a Bruker 400 MHz instrument. Chemical shifts (δ) are reported in parts per million; coupling constants (J) are in Hertz. Multiplicities are reported as follows: s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), and m (multiplet). Where distinct from resonances owing to the major diastereomer, resonances owing to minor diastereomers are denoted by an asterisk. ^{1}H and ^{13}C NMR resonances were assigned by using a combination of DEPT-135, COSY, HSQC, HMBC, and NOESY spectroscopic techniques. IR spectra were recorded on a thin film on a composite of zinc selenide and diamond crystal, on an FTIR spectrometer. Melt-

ing points are uncorrected. HRMS was performed on a spectrometer operating at a nominal accelerating voltage of 70 eV or on a TOF-Q mass spectrometer.

Ketone 13

A suspension of 3-methyl-2-butanone (6.21 mL, 58.1 mmol), ethyl formate (8.58 mL, 116 mmol), and NaH (1.53 g, 63.9 mmol; 60% dispersion in mineral oil) in THF (120 mL) was heated to reflux and stirred for 30 min. The solution turned from cloudy gray to yellow, and was allowed to cool to RT before concentrating in vacuo. The resultant yellow gum was dissolved in DMSO (120 mL) under an inert atmosphere, dimethyl sulfate (5.51 mL, 58.1 mmol) was added, and the reaction was stirred for 4 h at RT. The reaction was quenched with water (150 mL) and extracted with CH_2Cl_2 (3× 150 mL); the combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. The resultant oil was purified by vacuum distillation (80 °C, 1.5 mbar) to give ketone **13** as a clear oil (5.92 g, 80% yield, *E*/*Z* = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 12.6 Hz, 1 H), 6.40* (d, *J* = 7.2 Hz, 0.24 H), 5.62 (d, *J* = 12.5 Hz, 1 H), 5.08* (d, *J* = 7.2 Hz, 0.23 H), 3.85* (s, 0.83 H), 3.70 (s, 3 H), 2.87* (dq, *J* = 13.9, 6.9 Hz, 0.23 H), 2.65 (dq, *J* = 7.0 Hz, 1 H), 1.10 (s, 3 H), 1.09 (s, 3 H), 1.07* (s, 0.74 H), 1.05 ppm* (s, 0.68 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.6, 162.7, 158.2*, 105.3*, 103.5, 57.7, 41.2, 39.7*, 18.8, 18.6 ppm; * denote resonances that correspond to the minor isomer. The spectroscopic data were in good agreement with a previous report.[6]

Diene 8a

TBSOTf (5.38 mL, 23.4 mmol) was added dropwise to a stirring solution of ketone **13** (2.50 g, 15.6 mmol) and Et_3N (6.52 mL, 46.8 mmol) in Et_2O (50 mL) at 0 °C under a nitrogen atmosphere. After 10 min, the solution was allowed to warm to RT and stirred for a further 3 h, by which point two layers had formed. The bottom layer was removed by using a pipette and the top layer was concentrated in vacuo. The resultant crude oil was purified by flash chromatography on neutral alumina (EtOAc/petroleum ether, 6%) to give diene **8a** as a clear oil (3.75 g, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.63 (d, *J* = 12.3 Hz, 1 H), 5.63 (d, *J* = 12.4 Hz, 1 H), 3.58 (s, 3 H), 1.67 (s, 6 H), 0.99 (s, 9 H), 0.10 ppm (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.4, 140.2, 111.2, 101.0, 56.7, 26.2, 19.1, 19.0, 18.5, −3.3 ppm. A small impurity that corresponded to TBS–X persisted after purification, as per the previous report by Jewett and Rawal.[6] The spectroscopic data were in good agreement with a previous report.[6]

Diene 8b

TMSOTf (1.55 mL, 8.58 mmol) was added dropwise to a stirring solution of ketone **13** (1.00 g, 7.80 mmol) and Et_3N (3.26 mL, 23.4 mmol) in Et_2O (90 mL) at 0 °C under a nitrogen atmosphere. After 10 min, the solution was allowed to warm to RT and stirred for a further 3 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL) and pentane (30 mL) was added. The organic layer was separated and the aqueous phase was extracted with pentane (30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2×30 mL), water (2×30 mL), and brine (2×30 mL), and dried over $MgSO_4$. The solvent was removed in vacuo and the resultant brown oil was purified by vacuum distillation (110 °C, 50 mbar) to afford diene **8b** as a clear oil (1.20 g, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (d, *J* = 12.6 Hz, 1 H), 5.68 (d, *J* = 12.2 Hz, 1 H), 3.58 (s, 3 H), 1.66 (s, 3 H), 1.66 (s, 3 H), 0.18 ppm (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.9, 140.6, 111.0, 101.2, 56.8, 18.9, 18.7, 0.82 ppm; IR (film): $\tilde{\nu}_{max}$ = 2981, 2936, 1627, 1380, 1045 cm^{-1}.

Adduct 16

Diene **8a** (40 mg, 0.16 mmol) was added to a solution of methacrolein (30 μL, 0.33 mmol) and $ZnCl_2$ (4.5 mg, 0.033 mmol) at 0 °C in CH_2Cl_2 (0.5 mL). The resultant solution was stirred for 3 h, a saturated aqueous solution of Na_2CO_3 (5 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was concentrated in vacuo and the crude oil was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 20%) to give adduct **16** as a clear oil (23 mg, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1 H), 6.72 (dd, *J* = 10.2, 1.8 Hz, 1 H), 6.04 (d, *J* = 10.2 Hz, 1 H), 2.34 (dd, *J* = 14.5, 1.8 Hz, 2 H), 1.82 (d, *J* = 14.5 Hz, 1 H), 1.27 (s, 3 H) 1.16 (s, 3 H), 1.02 ppm (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.4, 201.5, 148.0, 128.8, 48.6, 43.9, 41.4, 26.7, 25.7, 24.0 ppm; IR (film): $\tilde{\nu}_{max}$ = 2971, 2931, 1711, 1457, 1386, 1369, 1240, 1166 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{10}H_{15}O_2$: 167.1067 $[M+H]^+$; found: 167.0714.

Ketone 18

$SnCl_4$ (0.1 M in CH_2Cl_2, 30 μL, 0.06 mmol) was added to a solution of diene **8a** (40 mg, 0.16 mmol) and methyl methacrylate (35 μL, 0.32 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C. The resulting solution was stirred for 3 h at −78 °C and then warmed to 0 °C and stirred for a further 1 h before the addition of Et_3N (69 μL, 0.49 mmol). The mixture was concentrated in vacuo and purified by flash chromatography on silica gel (EtOAc/petroleum ether, 20%) resulting in the isolation of unexpected dimerization product **18** as a clear oil (51% conversion by ^{1}H NMR of the crude reaction mixture containing an internal standard). An analytical sample gave the following data:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 12.1 Hz, 1 H), 6.95 (d, *J* = 16.1 Hz, 1 H), 6.21 (d, *J* = 16.0 Hz, 1 H), 5.73 (d, *J* = 12.1 Hz, 1 H), 3.71 (s, 3 H), 2.85 (sept, *J* = 6.9 Hz, 1 H), 1.30 (s, 6 H), 1.12 ppm (d, *J* = 7.0 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.9, 199.8, 164.2, 150.2, 126.9, 100.7, 58.3, 49.6, 39.0, 23.9, 18.5 ppm; IR (film): $\tilde{\nu}_{max}$ = 2973, 2936, 1672, 1270, 1032, 816 cm^{-1}.

Adduct 21

Diene **8a** (40 mg, 0.16 mmol) was added to a solution of ethyl 3-methyl-4-oxocrotonate (44 μL, 0.33 mmol) and $Sc(OTf)_3$ (16 mg, 20 mol%) in CH_2Cl_2 at −78 °C. The resultant mixture was stirred for 3 h and then allowed to warm to RT and quenched with Et_3N (69 μL, 0.49 mmol). The mixture was extracted with a saturated aqueous solution of NH_4Cl, washed with brine, and dried over Mg_4SO_4. The organic phase was concentrated in vacuo and purified by flash chromatography on silica gel (EtOAc/petroleum ether, 30%) to give adduct **21** as a clear oil (23 mg, 43% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 6.6 Hz, 1 H), 5.94 (q, *J* = 1.1 Hz, 1 H), 5.39 (d, *J* = 5.9 Hz, 1 H), 4.54 (s, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 2.25 (d, *J* = 1.5, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.11 (s, 3 H) 1.06 ppm (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.6, 166.0, 161.5, 151.1, 120.7, 105.5, 90.4, 60.3, 44.8, 20.0, 19.0, 18.0, 14.4 ppm; IR (film): $\tilde{\nu}_{max}$ = 2978, 2937, 1716, 1466, 1385, 1369, 1269, 1162 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{18}NaO_4$: 261.1097 $[M+Na]^+$; found: 261.1091.

Adduct 22

A solution of diene **8a** (61 mg, 0.25 mmol) and freshly sublimed maleic anhydride (49 mg, 0.50 mmol) in toluene (1 mL) was stirred in a round-bottomed flask at 100 °C for 2 h. After cooling to RT, the solution was concentrated in vacuo and purified by flash chromatography on silica gel (EtOAc/petroleum ether, 15%) to afford adduct **14** as a colorless oil (31 mg, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.97 (d, J = 6.4 Hz, 1H), 4.25 (dd, J = 6.4, 5.0 Hz, 1H), 3.36 (dd, J = 10.8, 4.9 Hz, 1H), 3.21 (s, 3H), 3.18 (d, J = 10.9 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H), 0.95 (s, 9H), 0.22 ppm (d, J = 1.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 170.3, 163.1, 97.3, 71.5, 55.5, 49.4, 46.7, 36.8, 28.8, 25.7, 25.2, 18.3, −4.3, −5.1 ppm; IR (film): $\tilde{\nu}_{max}$ = 2933, 1715, 1637, 1255, 1089 cm^{-1}; HRMS (ESI+): *m/z* calcd for $C_{17}H_{28}NaO_5Si$: 363.1598 $[M+Na]^+$; found: 363.1598.

Lactones 25 and 26

Method A: A mixture of diene **8a** (1.17 g, 4.82 mmol), distilled citraconic anhydride (400 mg, 3.57 mmol), and hydroquinone (9.8 mg, 0.09 mmol) was degassed in a Schlenk tube by prolonged evacuation and back-filling with nitrogen gas three times. Then, the reaction mixture was stirred at 140 °C overnight. After cooling to RT, chloroform (35 mL) and TFA (1.05 mL) were added, the resulting mixture was stirred for 5 min at RT, and then concentrated in vacuo. The crude mixture was dissolved in AcOH (40 mL) and $NaBH_3CN$ (1.24 g, 17.9 mmol) was added. The reaction mixture was stirred at RT for a further 2 h and then concentration in vacuo. The crude mixture was dissolved in CH_2Cl_2 (150 mL) and washed with 1 M aqueous HCl (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The collected organic phases were washed with brine (1×150 mL), dried over $MgSO_4$, and concentrated in vacuo to afford a crude mixture of acids **5** and **24**. The crude mixture was suspended in MeOH/benzene (30 mL, 2:1 v/v) and (diazomethyl)trimethylsilane (2.15 mL, 2 M in Et_2O) was added. The resultant mixture was stirred for 15 min and then quenched with AcOH. The reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel (EtOAc/petroleum ether, 35%) to afford a mixture of lactones **25** (136 mg, 17% yield) and **26** (60 mg, 7% yield) as yellow oils.

Method B (one-pot optimized procedure): A mixture of diene **8a** (141 mg, 0.58 mmol), distilled citraconic anhydride (**11**; 45 mg, 0.40 mmol), and hydroquinone (1 mg, 0.01 mmol) was degassed in a Schlenk tube by prolonged evacuation and back-filling with nitrogen gas three times. Then, the reaction mixture was stirred at 140 °C overnight. After cooling to RT, chloroform (5 mL) and $ZnCl_2$ (1.0 M in Et_2O, 150 μL) were added and the resulting mixture was stirred for 20 min. Then, AcOH (2 mL) and $NaBH_3CN$ (182 mg, 2.9 mmol) were added and the mixture was stirred at RT for a further 30 min and then quenched with 1 M aqueous HCl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3×15 mL). The collected organic phase was washed with brine (1×30 mL), dried over $MgSO_4$, and concentrated in vacuo. Esterification with (diazomethyl)trimethylsilane and purification according to the procedure described in Method A afforded a mixture of lactones **25** (8.0 mg, 9% yield) and **26** (22 mg, 24% yield) as yellow oils.

[2.2.2]-**25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (dd, J = 7.6, 5.0 Hz, 1H), 6.14 (dd, J = 7.6, 1.9 Hz, 1H), 4.58 (dd, J = 5.0, 2.0 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 1H), 1.41 (s, 3H), 1.16 (s, 3H), 1.11 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.2, 171.7, 136.8, 133.1, 82.0, 56.6, 51.9, 46.2, 41.4, 29.5, 23.4, 17.2 ppm; IR (film): $\tilde{\nu}_{max}$ = 2957, 1436, 1353, 1211, 1100, 1021 cm^{-1}; HRMS (ESI+): *m/z* calcd for $C_{12}H_{16}NaO_4$: 247.0941 $[M+Na]^+$; found: 247.0944. Single crystals suitable for XRD analysis were obtained by evaporation from a solution in $CHCl_3$/*n*-hexane (m.p. 104–107 °C).

[3.2.1]-**26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.19 (dd, J = 9.6, 5.8 Hz, 1H), 5.96 (ddd, J = 9.6, 1.7, 0.9 Hz, 1H), 4.26 (d, J = 5.9, 1H), 3.72 (s, 3H), 2.52 (s, 1H), 1.49 (s, 3H), 1.27 (s, 3H), 1.26 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2, 173.9, 133.7, 126.8, 80.4, 55.6, 52.8, 47.8, 43.4, 27.0, 22.6, 22.0 ppm; IR (film): $\tilde{\nu}_{max}$ = 2956, 1780, 1436, 1262, 1109, 1025 cm^{-1}; HRMS (ESI+): *m/z* calcd for $C_{12}H_{16}NaO_4$: 247.0941 $[M+Na]^+$; found: 247.0949.

Weinreb Amides 27 and 28

Oxalyl chloride (0.24 mL, 2.85 mmol) and DMF (1 drop) were added to a solution of crude acids **5** and **24** (ca. 0.71 mmol; from method B) in CH_2Cl_2 (7.5 mL) under a nitrogen atmosphere and the resulting mixture was stirred at RT for 4 h and concentrated in vacuo. The crude mixture was dissolved in CH_2Cl_2 (7.5 mL), HN(Me)OMe·HCl (139 mg, 1.43 mmol) and Et_3N (0.40 mL, 2.85 mmol) were added, and the mixture was stirred for a further 24 hours at RT. Then, the mixture was washed with a saturated aqueous solution of NH_4Cl (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude oil was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 70%) to afford Weinreb amides **27** (25 mg, 14% yield from citraconic anhydride) and **28** (19 mg, 10% yield from citraconic anhydride) as white solids.

[2.2.2] Weinreb amide **27**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (dd, J = 7.5, 5.0 Hz, 1H), 6.13 (dd, J = 7.6, 2.0 Hz, 1H), 4.51 (dd, J = 5.0, 2.0 Hz, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 2.61 (s, 1H), 1.39 (s, 3H), 1.12 (s, 3H), 1.11 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0, 172.9, 136.5, 133.5, 82.2, 61.4, 52.4, 46.6, 41.4, 32.4, 29.2, 24.0, 17.5 ppm; IR (film): $\tilde{\nu}_{max}$ = 2944, 1777, 1745, 1646, 1089, cm^{-1}; HRMS (ESI+): *m/z* calcd for $C_{13}H_{20}NO_4$: 254.1387 $[M+H]^+$; found: 254.1386.

[3.2.1] Weinreb amide **28**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.11 (dd, J = 9.6, 5.7 Hz, 1H), 6.02 (ddd, J = 9.7, 1.7, 1.0 Hz, 1H), 4.24 (d, J = 5.8 Hz, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 2.91 (t, J = 1.6 Hz, 1H), 1.53 (s, 3H), 1.28 (s, 3H), 1.24 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.9, 174.8, 135.5, 124.2, 80.6, 60.7, 54.4, 48.3, 43.7, 34.2, 27.2, 22.1, 22.0 ppm; IR (film): $\tilde{\nu}_{max}$ = 2960, 1760, 1643, 1080 cm^{-1}; HRMS (ESI+): *m/z* calcd for $C_{13}H_{20}NO_4$: 254.1387 $[M+H]^+$; found: 254.1390. Single crystals suitable for XRD analysis were obtained by evaporation from a solution in Et_2O (m.p. 135–137 °C).

Lactone 30

A mixture of lactone **25** (9.4 mg, 0.042 mmol) and a catalytic amount of PtO_2·H_2O in MeOH (1 mL) was stirred at RT under a H_2 atmosphere (balloon) for 16 h. The mixture was filtered through Celite® and the filtrate was concentrated in vacuo to give ester **30** as an amorphous white solid (10 mg, quantitative yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (dd, J = 3.8, 1.7 Hz, 1H), 3.68 (s, 3H), 2.51 (s, 1H), 2.12–2.02 (m, 1H), 1.94 (dddd, J = 14.5, 11.7, 6.6, 3.7 Hz, 1H), 1.81–1.60 (m, 2H), 1.22 (s, 3H), 1.16 (s, 3H), 1.06 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.5, 171.3, 83.3, 60.5, 51.6, 40.2, 37.0, 30.6, 28.9, 24.0, 22.5, 19.6 ppm; IR (film): $\tilde{\nu}_{max}$ = 2953, 1755, 1367, 1098, 1040 cm^{-1}; HRMS (ESI+): *m/z* calcd for $C_{12}H_{19}O_4$: 227.1278 $[M+H]^+$; found: 227.1271.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cycloaddition · leonuketal · multistep reactions · natural products · synthetic methods

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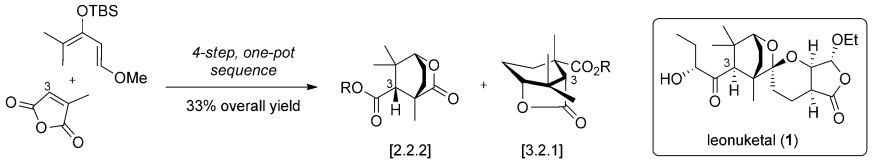

Star gazers: Protecting group free synthesis of the bicyclic core of the terpenoid natural product leonuketal was achieved by optimization of a four-step, one pot reaction sequence based on a challenging Diels-Alder cycloaddition.

Natural Products

Phillip S. Grant, Margaret A. Brimble, Daniel P. Furkert**

■■ – ■■

Synthesis of the Bicyclic Lactone Core of Leonuketal, Enabled by a Telescoped Diels–Alder Reaction Sequence