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Large-Scale Synthesis and Modifications of Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acid (BCP)

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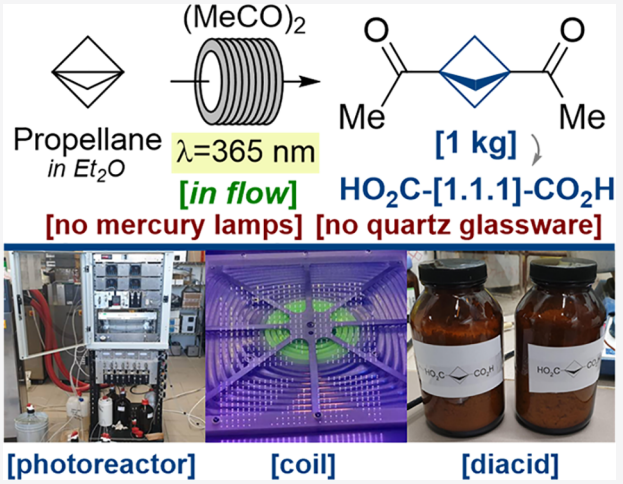
ABSTRACT: *In flow* photochemical addition of propellane to diacetyl allowed construction of the bicyclo[1.1.1]pentane (BCP) core in a 1 kg scale within 1 day. Haloform reaction of the formed diketone in batch afforded bicyclo[1.1.1]pentane-1,3-dicarboxylic acid in a multigram amount. Representative gram scale transformations of the diacid were also performed to obtain various BCP-containing building blocks—alcohols, acids, amines, trifluoroborates, amino acids, *etc.*—for medicinal chemistry.



INTRODUCTION

Benzene is the most popular ring in bioactive compounds.[1] In particular, the structure of more than 500 drugs comprises the motif of benzene.[2] However, bioactive compounds with several phenyl rings often have low solubility in water[3] and high toxicity due to rapid oxidation *in vivo* into quinones.[4] On the other hand, because of the recently emerged concept *Escape from Flatland*,[5] today medicinal chemists often replace benzene rings in bioactive compounds with saturated bioisosteres. Apart from improving physicochemical properties—better solubility, lower lipophilicity, and higher metabolic stability—this tactic is also often used to come out of the patented chemical space.[6] In particular, in 2012, Stepan and co-workers substituted the phenyl fragment in a γ-secretase inhibitor with the bicyclo[1.1.1]pentyl (BCP) skeleton.[7] The obtained analogue showed higher activity, better solubility, and improved metabolic stability. Since then, bicyclo[1.1.1]pentyl-containing derivatives have been playing an important role in medicinal chemistry.[8] They have already been mentioned in more than 200 patents (Figure 1).

Indeed, an increasing demand from pharmaceutical institutions initiated many academic groups to work on elaboration of novel synthetic approaches to substituted bicyclo[1.1.1]pentanes and their analogues.[9−11]

Despite the huge development in recent years on the synthesis of bicyclo[1.1.1]pentanes, however, still the most popular approach to them relies on the stepwise modifications of carboxylic groups in diacid **1** (Figure 1).[11b] In recent years, we received a lot of requests from pharmaceutical companies on various BCP-containing building blocks. Therefore, we needed a practical method to rapidly access multigram quantities of diacid **1**.

The first synthesis of diacid **1** was described in 1982 by Applequist.[12] The authors converted cyclobutanone **2** into the substituted bicyclo[1.1.0]butane **3** (Scheme 1).[13] From that intermediate, diacid **1** was synthesized in five steps in a 400 mg amount. In 1988, Michl developed a practical approach to access diacid **1** (Scheme 1).[14,15] The authors performed the photochemical reaction between propellane (**4**) and diacetyl (**5**) to produce diketone **6** in 58% yield (2 steps from dibromide **7**). The synthesis was performed in batch, and 26 g of the product was obtained in a single run. The photochemical step was performed with a medium-pressure Hanovia mercury lamp in a Pyrex vessel. Haloform reaction of **6** gave the needed diacid **1** in a 25 g scale. In 2014, Booker-Milburn performed a reaction between propellane (**4**) and diacetyl (**5**) *in flow* to obtain 52 g of product **6** (Scheme 1).[16] Irradiation

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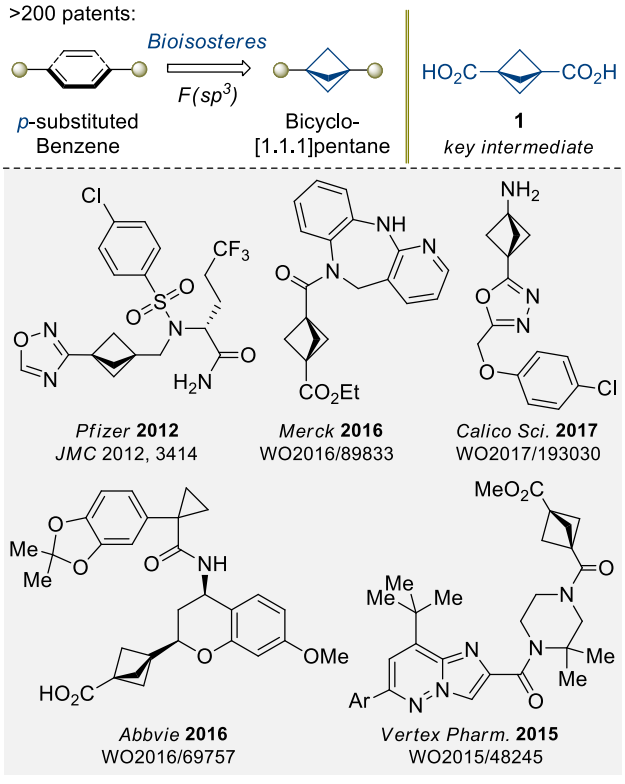
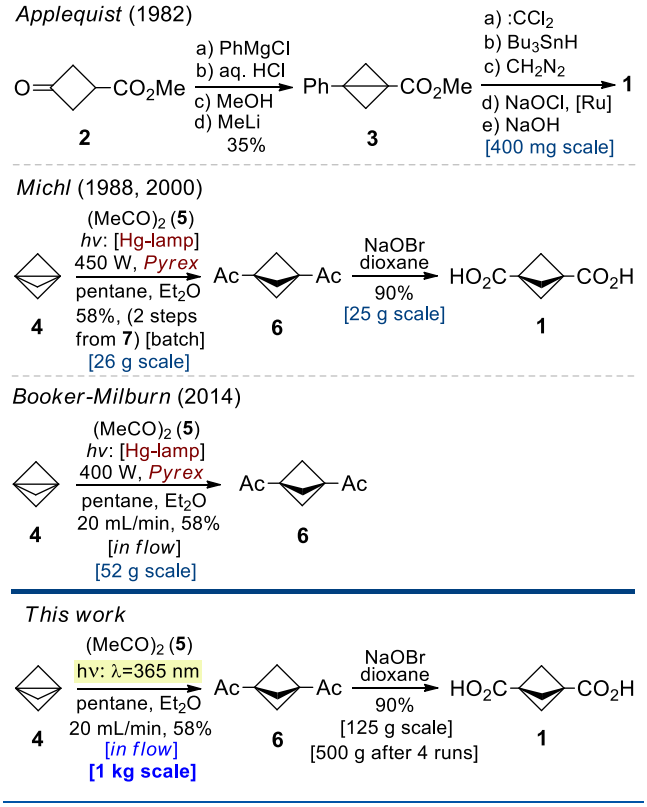


Figure 1. Bioactive derivatives of bicyclo[1.1.1]pentane (BCP).

Scheme 1. Approaches to Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acid (1)



was again performed with a medium-pressure Hanovia mercury lamp in Pyrex glassware.

Recently, Baumann also developed an elegant photochemical addition of oxalic acid derivatives to propellane *in flow* using a medium-pressure mercury lamp with filters.[17,18]

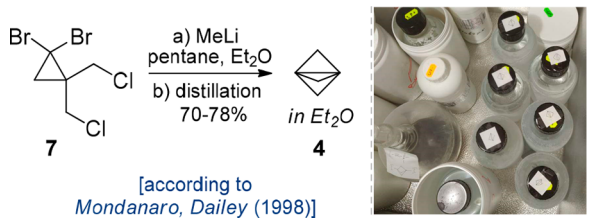
In our first attempts, we repeated the protocol of Kaszynski and Michl which allowed preparing diacid **1** in gram quantities.[14,15] However, the need to perform irradiation with (a) a Hanovia mercury lamp (b) in Pyrex glassware prevented further scale-up of this method. Herein, therefore would like to disclose our results and unexpected observations on the rapid practical synthesis of diacid **1**. Our protocol employs common LED (365 nm) irradiation with no need to use Pyrex glassware. Because it is still the most popular precursor to BCP derivatives (Figure 1), we believe that these results will be interesting to many organic chemists and medicinal chemists in both industrial and academic institutions.

RESULTS AND DISCUSSION

Synthesis and Storage of Propellane (4). Propellane **4** was first reported in 1982 by Wiberg.[19] In 1985, Szeimies developed an alternative synthesis of **4** from dibromide **7**,[20] and in 1988, Michl optimized it.[14] In 1998, Mondanaro and Dailey further optimized the protocol.[21]

For the synthesis of propellane, we used the procedure of Mondanaro and Dailey.[21] Previous reports suggested direct use of propellane after the preparation, because of its extensive polymerization under contact with air.[22] We found that the solution of propellane (**4**) in diethyl ether can be stored at −40 °C for several weeks. Titration with thiophenol revealed that, after 1 month in a fridge, the concentration of **4** in a solution dropped from 0.75 to 0.60 N. Scheme 2 shows a photo of six 1

Scheme 2. Synthesis of Propellane (4)[a]



[a]Photo: six 1 L bottles with a solution of propellane in diethyl ether stored in a fridge at −40 °C.

L bottles with a solution of propellane that we routinely store in a fridge. It is very convenient not to prepare propellane every time, but to keep its stock solution and use when needed. Indeed, the solution in the bottle must be kept under an argon atmosphere.

Multigram Photochemical Preparation of Diketone 6. Initially, we performed photochemical reactions between propellane (**4**) and diacetyl (**5**) *in batch* following the protocol of Michl.[14] However, the need to use (a) the broad wavelength mercury lamp and (b) Pyrex glassware somewhat complicated the practical aspects of the procedure. Out of curiosity,[23] we tried other standard wavelengths—420 and 365 nm—that are compatible with standard chemical glassware and do not require Pyrex vessels. Under irradiation with 420 nm (blue LED), the reaction did not proceed. However, irradiation with 365 nm led to smooth formation of product **6** at room temperature. Performing the reaction in batch, we could easily

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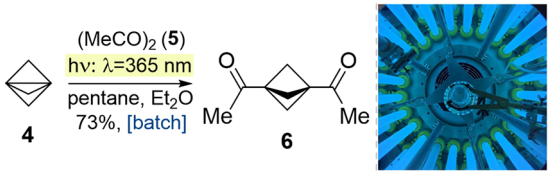
synthesize 10 g of diketone **6** (Scheme 3). The reaction was performed in a standard chemical glass flask.

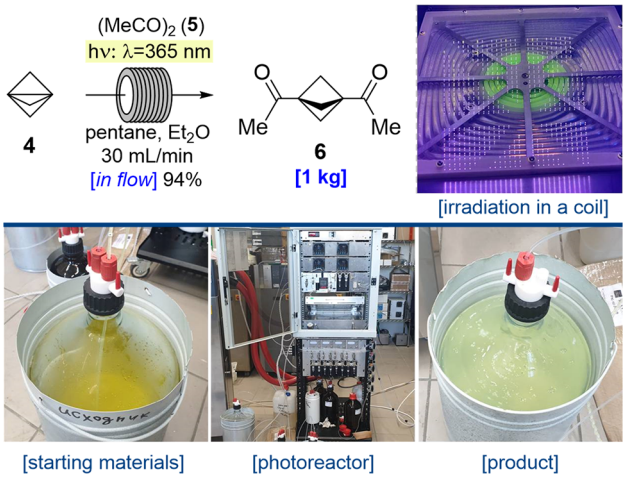
Scheme 3. Photochemical Synthesis of Diketone 6 in Batch[a]



[a]Irradiation is performed at 365 nm in a standard chemical glass flask.

Having an optimized batch procedure in hand, we attempted next the photochemical reaction *in flow*. The irradiation was performed at 365 nm.[24] A solution of reagents in diethyl ether was pumped via a fluorinated ethylene propylene pipe (0.5 cm inner diameter) through a photoelement.[25] After some optimization, we found that the transformation was complete with a 30 mL/min flow rate (**4**:**5** = 1:1; conc. = 0.7 M, Scheme 4). We used 80% of the nominal LED luminescence power

Scheme 4. Photochemical Synthesis of Diketone 6 *in Flow*[a]



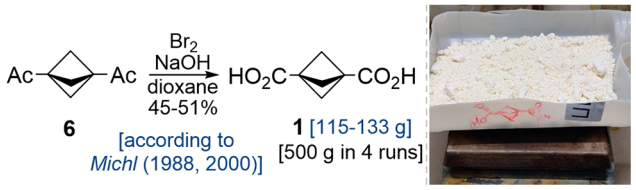
[a]Irradiation is performed at 365 nm in a coil.

(total diode power: 670 W). Interestingly, after the photoreaction, the original deep yellow color of diacetyl (**5**) became almost white, indicating disappearance of the starting material (Scheme 4: left and right). Using that *in flow* protocol, we could easily pump 9 L of the reaction mixture through a photoelement and produce ca. 1 kg of diketone **6** within 6 h.

Multigram Synthesis of Diacid 1. Multigram synthesis of diacid **1** from ketone **6** was performed following the protocol of Michl[14] with a slight modification. Previously, authors purified diketone **6** and then performed the haloform reaction. We found, however, that a higher yield of diacid **1** could be obtained by performing the reaction with crude **6** (obtained by evaporation of the reaction mixture after irradiation). In fact, performing the reaction in a 6 L flask, we could start from ca. 250 g of crude **6** and synthesize 115−133 g of diacid **1** in a single run depending on the batch. Repeating the synthesis four times in total allowed us to synthesize ca. 500 g of diacid **1** (Scheme 5).

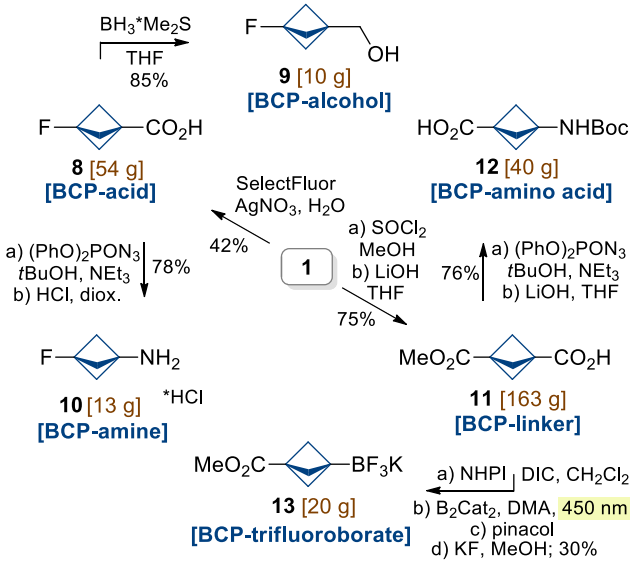
Multigram Synthesis of BCP-Containing Building Blocks. As it was mentioned earlier, most of the medchem-

Scheme 5. Multigram Scale Synthesis of Diacid 1 in Batch



related building blocks are still being produced from diacid **1**. Having synthesized a significant amount of diacid **1**, we would also like to present here its representative multigram functionalizations that were performed before on a smaller scale. Treatment of **1** with SelectFluor (1.2 equiv) in the presence of a catalytic amount of $AgNO_3$ gave fluorine-substituted acid **8**[26] in a 54 g scale (Scheme 6), a key

Scheme 6. Multigram Scale Synthesis of BCP-Containing Building Blocks 8−13 from Diacid 1



intermediate in the synthesis of a ^{19}F NMR label for solid state peptide studies.[10a] Activation of the carboxylic group in **8** with $ClCO_2Me$ and reduction with sodium borohydride gave interesting alcohol **9** in a 10 g amount. Curtius rearrangement of acid **8**, followed by acidic *N*-Boc deprotection, afforded fluoro-substitued amine **10** in a 13 g amount. Esterification of diacid **1** with methanol and monohydrolysis gave valuable linker **11**[14] in a 163 g scale. Curtius rearrangement of **11**, followed by alkali hydrolysis of the ester group, gave *N*-Boc amino acid **12** in 40 g quantities. It is worth noting that amino acid **12** was previously used by Pätzel as a mimetic of γ-aminobutyric acid (GABA) in peptides.[27] Finally, acylation of *N*-hydroxyphthalimide with **11**, followed by light-mediated decarboxylative borylation with B_2Cat_2, addition of pinacol, and subsequent treatment with potassium fluoride, gave valuable organotrifluoroborate **13** in a 20 g amount. The compound was first synthesized by Aggarwal,[28] and recently, VanHeyst, Qi, and co-workers from Merck used it for practical photoredox cross-couplings of heterocycles.[29]

In addition, we wanted also to disclose here the synthesis of hydroxy acid **14**, the compound that, in the unprotected form, was unknown before. There were several attempts before to access the needed core. In 1982, Applequist and colleagues

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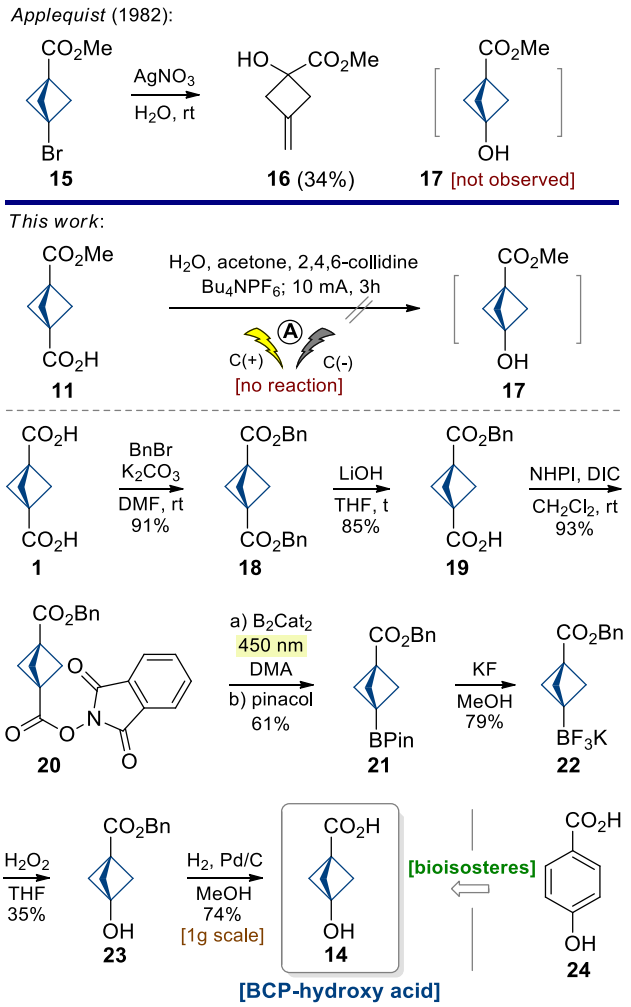
tried hydrolysis of compound **15** in the presence of silver nitrate (Scheme 7).[12] However, only ring-opened alkene **16**

Scheme 7. Synthesis of BCP-Containing Hydroxy Acid 14



was isolated in 34% yield, while formation of alcohol **17** was not observed. Recently, Baran and co-workers developed an electrochemical synthesis of hindered ethers and alcohols from carboxylic acids.[30] Being involved in this project, we also tried to expand this methodology onto acid **11**. For that, a mixture of acid **11** and water in acetone was electrolyzed under a constant current of 10 mA during 3 h (Scheme 7). Unfortunately, formation of the desired product was not observed. Under prolonged electrolysis, only slow decomposition of the starting material took place. Finally, we undertook the synthesis of compound **14** from diacid **1** (Scheme 7). Alkylation of the latter with an excess of benzyl bromide smoothly gave diester **18**. Selective alkali monohydrolysis afforded acid **19**. Acylation of *N*-hydroxyphthalimide (via **20**), followed by light-mediated decarboxylative borylation with B_2Cat_2 and addition of pinacol, gave organoboron derivative **21**. Reaction with potassium fluoride provided trifluoroborate **22**. The key oxidation with hydrogen peroxide formed alcohol **23** in 35% yield. Finally, cleavage of the *O*−Bn bond by hydrogenation on Pd/C in methanol gave the desired molecule **14** in a 1 g amount. Compound **14** can be viewed as the saturated bioisostere of popular 4-hydroxybenzoic acid (**24**). Moreover, similar bioisosteric replacement of phenols was recently validated by Adsool and colleagues.[31]

CONCLUSION

Most of the medchem-relevant BCP-containing derivatives are obtained today from bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (**1**) (Figure 1). In this work, we developed its practical synthesis on a multigram scale. The key step was *in flow* photochemical reaction between propellane (**4**) and diacetyl (**5**) under irradiation with 365 nm *in flow*. Importantly, the procedure was mercury lamp-free and quartz vessels-free. The developed protocol allowed for the rapid production of ca. 1 kg of diketone **6** during 6 h. The target diacid **1** was subsequently synthesized in a 500 g scale by haloform reaction of the diketone in batch. Several representative multigram functionalizations of diacid **1** into medchem-relevant BCP building blocks were also demonstrated (Schemes 6 and 7). We believe that, with the robust practical protocol described here, medicinal chemists worldwide in both industry and academia could easily now synthesize and use BCP molecules routinely.

EXPERIMENTAL SECTION

General Considerations. All chemicals were provided by Enamine Ltd. (www.enamine.net). All solvents were treated according to standard methods. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was performed using silica gel column chromatography. TLC characterization was performed with precoated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100−200 mesh). ^{1}H NMR spectra were recorded at 400, 500, or 600 MHz (Varian); ^{19}F NMR spectra were recorded at 376 MHz (Varian); and ^{13}C NMR spectra were recorded at 100, 126, or 151 MHz (Varian). ^{1}H NMR chemical shifts are calibrated using residual undeuterated solvents $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). ^{13}C NMR chemical shifts for ^{13}C NMR are reported relative to the central $CHCl_3$ (δ = 77.16 ppm) or DMSO (δ = 39.52 ppm). ^{19}F NMR chemical shifts are calibrated using $CFCl_3$ as an internal standard. Coupling constants are given in Hz. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight reflectron experiments.

Tricyclo[1.1.1]pentane (Propellane) (4). A dry three-neck round-bottom flask (6 L) equipped with an overhead stirrer was charged with 1,1-bis(chloromethyl)-2,2-dibromocyclopropane (**7**) (800.0 g, 2.7 mol, 1.0 equiv) in Et_2O (2 L). The mixture was cooled to −78 °C, and MeLi (3 M, 2 L, 6.0 mol, 2.2 equiv) was added dropwise at the same temperature under argon. The mixture was stirred for 30 min at −75 °C, then warmed to 0 °C, and stirred for 1.5 h. The mixture was distilled to a 5 L flask and stored under argon. The mixture was titrated and transferred into 800 mL bottles for storage. Yield: 3.75 L, 0.1 M of **4**, 78%. *Titration*: propellane was titrated with thiophenol. A degassed with argon solution of thiophenol (3.00 g) in Et_2O was added to a solution of **4** (10 mL). The mixture was stirred for 15 min, concentrated, and subjected to ^{1}H NMR. The ratio of the obtained PhS-BCP-H and remaining PhSH was calculated based on the proton of the tertiary carbon in propellane at 2.72 ppm (s, 1H) and the proton in PhSH at 3.44 ppm (s, 1H).

1,1′-(Bicyclo[1.1.1]pentane-1,3-diyl)bis(ethan-1-one) (6). To a solution of **4** (0.7 M, 8 L, 5.6 mol, 1.0 equiv) was added a degassed with argon solution of $(MeCO_2)_2$ (482.0 g, 5.6 mol, 1.0 equiv) in Et_2O (500 mL). The reaction mixture (9 L) was passed through a photoreactor during 6 h with a flow rate of ca. 30 mL/min. The volume of the illuminated area is 160 mL, and that of the nonilluminated area is 50 mL. The wavelength is 365 nm, and the LED luminescence power is 80% of the nominal (total diode power: 670 W). The mixture was concentrated under reduced pressure. Yield: 821.2 g, 5.4 mol, 94%. This product was used in the next step

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without additional purification. An analytically pure sample can be obtained by crystallization of the compound from pentane:diethyl ether = 2:1. Mp = 69−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.09 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 205.8, 51.9, 43.3, 26.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_9H_{13}O_2$ 153.0916; found 153.0910.

Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acid (1). A solution of NaOH (1 kg, 24.6 mol, 15.0 equiv) in water (3.5 L) was cooled to 20 °C, and Br_2 (2 kg, 12.3 mol, 7.5 equiv) was added to the solution dropwise. The mixture was stirred for 3 h, then cooled to 0 °C, and a solution of ketone **6** (250.0 g, 1.64 mol, 1.0 equiv) in dioxane (1 L) was added dropwise. The mixture was stirred overnight and extracted with CH_2Cl_2 (3 × 3 L). An aqueous solution was acidified and extracted with EtOAc (3 × 3 L). The organic layers were concentrated under reduced pressure. The residue was mashed in hexane (1 L), then in CH_2Cl_2 (1 L), and a white precipitate was filtered off. The aqueous layer was also concentrated and additionally extracted with EtOAc (2 × 1 L). Yield: 115.5−133.1 g, 0.74−0.85 mol, 45−51% depending on a batch. After four runs, ca. 500 g of the diacid was obtained. Mp = 169−170 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (br s, 2H), 2.14 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 170.6, 51.8, 37.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_7H_9O_4$ 157.0501; found 157.0508.

3-Fluorobicyclo[1.1.1]pentane-1-carboxylic Acid (8). Compound **1** (155.0 g, 0.99 mol, 1.0 equiv) and $AgNO_3$ (39.0 g, 0.23 mol, 0.2 equiv) were dissolved in distilled water (3 L). The mixture was degassed with argon (5 times), and Selectfluor (416.0 g, 1.18 mol, 1.2 equiv) was added. The mixture was degassed with argon (2 times) and heated at 70 °C in an oil bath with a thermocouple for 24 h. The solution was cooled to room temperature and extracted with MeO*t*Bu (3 × 1 L). The organic layer was concentrated under reduced pressure. The solid residue was recrystallized from a mixture of MeO*t*Bu:pentane = 1:9 to give the title product as a yellow solid. Mp = 95−97 °C. Yield: 54.0 g, 0.41 mol, 42%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (br s, 1H), 2.39 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 175.5 (d, J = 37 Hz), 74.8 (d, J = 329 Hz), 55.7 (d, J = 22 Hz), 28.2 (d, J = 48 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −150.3 (s) ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_6H_7FO_2$ 130.0430; found 130.0432.

(3-Fluorobicyclo[1.1.1]pentan-1-yl)methanol (9). Compound **8** (13.0 g, 0.100 mol, 1.0 equiv) was dissolved in THF (200 mL). The solution was degassed with argon and cooled to 0 °C, and $BH_3{\cdot}Me_2S$ (11.7 g, 0.15 mol, 1.5 equiv) was added dropwise. The mixture was stirred at room temperature overnight, then cooled to 0 °C, and dry MeOH (100 mL) was added dropwise. The mixture was stirred for 5 h at room temperature and concentrated under reduced pressure. The residue was distilled at 1 mmHg. Yield: 10.1 g, 0.087 mol, 86%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 2H), 1.99 (d, J = 2.5 Hz, 6H), 1.81 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 75.9 (d, J = 329 Hz), 60.8 (d, J = 27 Hz), 52.4 (d, J = 21 Hz), 29.3 (d, J = 41 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −145.7 (s) ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_6H_{10}FO$ 117.0716; found 117.0712.

3-Fluorobicyclo[1.1.1]pentan-1-amine Hydrochloride (10). Compound **8** (16.0 g, 0.125 mol, 1.0 equiv) was dissolved in *t*BuOH (500 mL). Et_3N (15.0 g, 0.150 mol, 1.2 equiv) and $(PhO)_2P(O)N_3$ (38.0 g, 0.137 mol, 1.1 equiv) were added to the solution. The mixture was heated at 85 °C in an oil bath with a thermocouple for 24 h, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in EtOAc (500 mL) and washed with a sat. solution of $NaHCO_3$ (200 mL), water (250 mL), and brine (250 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (gradient, hexane:MeO*t*Bu = 1:9 to 1:1). Yield: 21.2 g, 0.105 mol, 83%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (br s, 1H), 2.30 (s, 6H), 1.42 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.9, 80.2, 76.8 (d, J = 316 Hz), 55.3 (d, J = 20 Hz), 39.9 (d, J = 72 Hz), 28.5 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −169.6 (s) ppm. The total amount of the product was dissolved in 5 M HCl in dioxane (500 mL) and stirred at room temperature overnight. The mixture was concentrated under reduced pressure. The solid residue was washed with MeO*t*Bu (1 L) and dried (under reduced pressure, 1 mmHg at 50 °C in a heating mantle). Yield: 13.5 g, 0.098 mol, 95%, white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (s, 3H), 2.33 (s, 6H). ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 75.6 (d, J = 321 Hz), 54.3 (d, J = 21 Hz), 37.6 (d, J = 72 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −166.6 (s) ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for C_5H_9FN 102.0719; found 102.0715.

3-(Methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic Acid (11). Compound **1** (200.0 g, 1.28 mol, 1.0 equiv) was dissolved in MeOH (3 L), and $SOCl_2$ (457.0 g, 3.84 mol, 3.0 equiv) was added dropwise at 20−40 °C. The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The mixture was dissolved in a mixture of hexane:MeO*t*Bu = 1:1 (1 L), filtered through SiO_2 (∼500 g), and concentrated. Yield: 196.1 g, 1.06 mol, 83%, white solid, mp 90−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.31 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 170.3, 54.3, 51.9, 45.8, 28.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_9H_{13}O_4$ 185.0814; found 185.0810. The product (196.1 g, 1.06 mol, 1.0 equiv) was dissolved in THF (2 L), and $LiOH{\cdot}H_2O$ (40.0 g, 0.95 mol, 0.9 equiv) was added to the mixture. The mixture was heated in an oil bath with a thermocouple at 50 °C for 72 h, then cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in water (1 L) and extracted with MeO*t*Bu (3 × 500 mL). The aqueous layer was acidified with HCl to pH ∼3−4. The precipitate was filtered off and dried at 1 mmHg over P_2O_5. Yield: 163.3 g, 0.96 mol, 90%. Yellow solid. Mp = 126−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (br s, 1H), 3.69 (s, 3H), 2.34 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 175.2, 169.8, 52.9, 52.1, 37.7, 37.6 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_{11}O_4$ 171.0657; found 171.0655.

3-((*tert*-Butoxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylic Acid (12). Compound **11** (40.0 g, 0.23 mol, 1.0 equiv) was dissolved in *t*BuOH (1 L). Et_3N (28.0 g, 0.27 mol, 1.2 equiv) and $(PhO)_2P(O)N_3$ (70.0 g, 0.25 mol, 1.1 equiv) were added to the solution. The mixture was heated in an oil bath with a thermocouple at 85 °C for 24 h, then cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in EtOAc (1 L) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 400 mL), water (500 mL), and brine (500 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (gradient, hexane:MeO*t*Bu = 1:9 to 1:1). Yield: 44.0 g, 0.19 mol, 80%, white solid. Mp = 138−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (br s, 1H), 3.67 (s, 3H), 2.27 (s, 6H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 169.8, 53.0, 51.9, 37.7 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{20}NO_4$ 242.1392; found 242.1399. The product was dissolved in a mixture of THF and H_2O (7:3, 500 mL), and $LiOH{\cdot}H_2O$ (11.5 g, 0.28 mol, 1.5 equiv) was added to the mixture. The mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was dissolved in distilled water (500 mL) and extracted with MeO*t*Bu (3 × 500 mL). The aqueous layer was acidified with citric acid to pH ∼ 6 and extracted with EtOAc (3 × 300 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was recrystallized from a mixture of hexane:EtOAc = 7:3 (the product was boiled in hexane and EtOAc was added in portions). Yield: 40.0 g, 0.176 mol, 95%, white solid. Mp = 176−177 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (br s, 1H), 7.58 (br s, 1H), 2.08 (s, 6H), 1.37 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 170.9, 154.5, 53.4, 45.1, 28.2 ppm. LCMS $(M - H)^-$: 226. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{18}NO_4$ 228.1236; found 228.1239.

Potassium Trifluoro[3-(methoxycarbonyl)bicyclo[1.1.1]-pentan-1-yl]boranuide (13). Compound **11** (50.0 g, 0.29 mol, 1.0 equiv) was dissolved in CH_2Cl_2 (1 L), and *N*-hydroxyphthalimide (48.0 g, 0.29 mol, 1 equiv), 4-(dimethylamino)pyridine, and DMAP (3.51 g, 0.029 mol, 0.1 equiv) were added. *N*,*N*′-diisopropylcarbodiimide, DIC (44.0 g, 0.35 mol, 1.2 equiv), was added to the mixture dropwise at room temperature. The mixture was stirred at room

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temperature overnight. The mixture was filtered, and a filtrate was concentrated under reduced pressure. ^{1}H NMR (500 MHz $CDCl_3$) δ 7.86 (dt, J = 7.0, 3.5 Hz, 2H), 7.77 (dd, J = 5.6, 3.1 Hz, 2H), 3.70 (s, 3H), 2.53 (s, 6H) ppm. The crude product (100.1 g, 0.29 mol, 1.0 equiv) and 2,2′-bis(1,3,2-benzodioxaborole), B_2Cat_2 (83.0 g, 0.35 mol, 1.2 equiv), were dissolved in DMA (3 L). The mixture was degassed with argon (5 times) then irradiated *in flow*. Irradiation: blue LED: 450 nm, spiral volume: 320 mL, flow rate: 10 mL/min, radiation intensity: 50% of nominal (total diode power: 850 W), residence time in the spiral: 32 min, temperature on the cooler: −20 °C, the temperature of the reaction mixture at the outlet: 16 °C. After completion of the reaction, Et_3N (88.0 g, 125 mL, 0.87 mol, 3.0 equiv) and pinacol (51.0 g, 0.435 mol, 1.5 equiv) were added to the reaction mixture, and it was stirred overnight at room temperature. The mixture was extracted with a mixture hexane:EtOAc = 9:1 (5 × 500 mL) and concentrated. The residue was extracted with hexane (3 × 500 mL). The combined organic layers were washed with water (2 × 300 mL) and brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The final product had ca. 85% purity according to ^{1}H NMR. Yield 38.2 g, 0.12 mol, 45%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.14 (s, 6H), 1.24 (s, 12H) ppm. The obtained crude product (38.2 g, 0.12 mol, 1.0 equiv) was dissolved in a mixture of MeOH:H_2O = 8:2 (400 mL), and KF·HF (25.0 g, 0.32 mol, 2.5 equiv) was added. The mixture was stirred at room temperature overnight and then concentrated. The final product was dried at 1 mmHg over P_2O_5 during 24 h. The product was mashed in MeO*t*Bu (3 L), and the precipitate was extracted with acetone using a Soxhlet extractor for 48 h. Yield: 20.0 g, 67%, white solid. Mp = 264−265 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.51 (s, 3H), 1.59 (s, 6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 170.5, 50.7, 50.4 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −143.5 (s) ppm. Anal. Calcd for $C_7H_9BF_3KO_2$: C, 36.23; H, 3.91. Found: C, 36.10; H, 4.05.

Dibenzyl Bicyclo[1.1.1]pentane-1,3-dicarboxylate (18). To a solution of compound **11** (50.00 g, 0.32 mol, 1.0 equiv) and K_2CO_3 (101.79 g, 0.74 mol, 2.3 equiv) in DMF (500 mL) was added BnBr (120.41 g, 0.70 mol, 2.2 equiv) at room temperature. The mixture was stirred overnight and filtered. The filtrate was diluted with water (1 L) and extracted with *tert*-butyl methyl ether (3 × 300 mL). The combined organic layers were washed with water (2 × 600 mL) and brine (1 × 600 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was mashed in hexane, filtered, washed with hexane, and dried. Yield: 97.44 g, 0.29 mol, 91%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (m, 10H), 5.15 (s, 4H), 2.39 (s, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.7, 135.6, 128.4, 128.1, 127.9, 77.2, 52.7, 37.6 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{21}O_4$ 337.1440; found 337.1445.

3-((Benzyloxy)carbonyl)bicyclo[1.1.1]pentane-1-carboxylic Acid (19). To a solution of **18** (25.0 g, 0.074 mol, 1.0 equiv) in dry THF (680 mL) was added LiOH·H_2O (2.8 g, 0.067 mol, 0.9 equiv). The mixture was heated in an oil bath with a thermocouple at 50 °C for 72 h. The mixture was concentrated under reduced pressure. The residue was diluted with water (400 mL) and extracted with *tert*-butyl methyl ether (2 × 300 mL). The aqueous layer was acidified with 1 M HCl to pH ∼ 3. The precipitate was filtered, washed with distilled water (100 mL), and dissolved in EtOAc (400 mL). The solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield: 15.7 g, 0.0638 mol, 86%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.65 (br s, 1H), 7.35 (s, 5H), 5.14 (s, 2H), 2.37 (s, 6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.8, 169.1, 135.5, 128.6, 128.3, 128.0, 77.2, 66.5, 52.8, 37.6, 37.5 ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{14}H_{14}NaO_4$ 269.0790; found 269.0792.

1-Benzyl 3-(1,3-Dioxoisoindolin-2-yl) bicyclo[1.1.1]pentane-1,3-dicarboxylate (20). To a solution of **19** (25.00 g, 0.100 mol, 1.0 equiv), *N*-hydroxyphthalimide (17.39 g, 0.107 mol, 1.05 equiv), and DMAP (1.22 g, 0.015 mol, 1.05 equiv) was added DIC (13.45 g, 0.107 mol, 1.05 equiv) dropwise at room temperature. The mixture was stirred overnight. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with a sat. solution of Na_2CO_3 (3 × 200 mL) and 1 M HCl (3 × 200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield: 36.40 g, 0.039 mol, 93%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99−7.82 (m, 2H), 7.82−7.68 (m, 2H), 7.48−6.99 (m, 5H), 5.15 (s, 2H), 2.57 (s, 6H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 164.7, 161.7, 135.6, 134.9, 128.9, 128.7, 128.4, 128.1, 124.0, 77.2, 66.6, 53.7, 38.8, 35.5 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{18}NO_6$ 392.1134; found 392.1130.

1-Benzyl 3-(1,3-Dioxoisoindolin-2-yl) bicyclo[1.1.1]pentane-1,3-dicarboxylate (21). A solution of **20** (7.0 g, 0.0179 mol, 1.0 equiv) and 2,2′-bis(1,3,2-benzodioxaborole) (5.0 g, 0.021 mol, 1.2 equiv) in DMA (90 mL) was degassed with argon (5 times) then irradiated *in flow*. Irradiation: blue LED: 450 nm, radiation intensity: 15% of nominal, the temperature of the reaction mixture: 35 °C. After completion of the reaction, Et_3N (5.4 g, 00537 mol, 3.0 equiv) and pinacol (3.1 g, 0.026 mol, 1.5 equiv) were added. The mixture was stirred at room temperature overnight. The mixture was extracted with a mixture of hexane:EtOAc, 9:1 (2 × 500 mL), and concentrated under reduced pressure. The residue was extracted with hexane (3 × 300 mL), and the combined layers were washed with water (2 × 300 mL) and brine (1 × 300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The excess of pinacol was removed by sublimation. Yield: 3.6 g, 0.011 mol, 61%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.23 (m, 5H), 5.08 (s, 2H), 2.15 (s, 6H), 1.22 (s, 12H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5, 136.3, 128.6, 128.2, 128.0, 83.7, 65.9, 52.5, 43.1 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{26}BO_4$ 329.1924; found 329.1918.

Potassium (3-((Benzyloxy)carbonyl)bicyclo[1.1.1]pentan-1-yl)trifluoroborate (22). To a solution of **21** (10.0 g, 0.03 mol, 1.0 equiv) in a mixture of MeOH:H_2O = 8:2 (100 mL) was added KF·HF (5.46 g, 0.07 mol, 2.5 equiv). The mixture was stirred at room temperature overnight and then concentrated. The final product was dried at 1 mmHg over P_2O_5 during 24 h. The product was mashed in MeO*t*Bu (250 mL), and the precipitate was dissolved in acetone, decanted, and concentrated under reduced pressure. Yield: 7.30 g, 0.0237 mol, 79%, white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42−7.24 (m, 5H), 5.03 (s, 2H), 1.64 (s, 6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 169.9, 136.6, 128.5, 127.9, 127.7, 64.7, 50.5 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −143.0 (s) ppm. Anal. Calcd for $C_{13}H_{13}BF_3KO_2$: C, 50.67; H, 4.25. Found: C, 50.50; H, 4.35.

Benzyl 3-Hydroxybicyclo[1.1.1]pentane-1-carboxylate (23). To a solution of KH_2PO_4 (15.92 g, 0.117 mol, 3.0 equiv) and compound **22** (12.00 g, 0.039 mol, 1.0 equiv) in a mixture of H_2O (160 mL) and THF (240 mL) was added H_2O_2 (30%, 44.21 g, 0.390 mol, 10.0 equiv) dropwise at 0 °C. The mixture was stirred at room temperature overnight. The mixture was diluted with water (400 mL) and extracted with MeO*t*Bu (2 × 300 mL). The combined organic layers were washed with water (1 × 500 mL) and a sat. solution of $NaHSO_3$ (1 × 500 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in a mixture of hexane:MeO*t*Bu, 1:1 (60 mL), filtered through SiO_2, and concentrated under reduced pressure. Yield: 3.0 g, 0.0137 mol, 35%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.17 (m, 5H), 5.36 (s, 1H), 5.10 (s, 2H), 2.21 (s, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.4, 135.4, 128.3, 128.0, 127.7, 66.3, 61.8, 55.3, 30.3 ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{13}H_{14}NaO_3$ 241.0841; found 241.0833.

3-Hydroxybicyclo[1.1.1]pentane-1-carboxylic Acid (14). To a solution of compound **23** (3.0 g, 0.0137 mol, 1.0 equiv) in MeOH (50 mL) was added 10% Pd/C (0.25 g, 0.00234 mol, 0.1 equiv). The mixture was hydrogenated under a rubber ball filled with H_2 at rt overnight. Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure. Yield: 1.3 g, 0.01 mol, 74%, white solid. Mp = 98−99 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (br s, 1H), 6.40 (br s, 1H), 1.98 (s, 6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.5, 61.7, 54.9, 30.6 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_6H_9O_3$ 129.0552; found 129.0543.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00977.

Copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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