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 water3 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[1.1.0]butane 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
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, we 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 L bottles with a solution of propellane that we routinely store in a fridge at −40 °C.

Scheme 2. Synthesis of Propellane (4)"  
*aPhoto: six 1 L bottles with a solution of propellane in diethyl ether stored in a fridge at −40 °C.

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
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

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. A solution of reagents in diethyl ether was pumped via a fluorinated ethylene propylene pipe (0.5 cm inner diameter) through a photoelement. 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 (total diode power: 670 W). Interestingly, after the photo-reaction, the original deep yellow color of diacetyl (5) became almost white, indicating disappearance of the starting material (Scheme 4). We used 80% of the nominal LED luminescence power (total diode power: 670 W). Interestingly, after the photo-reaction, the original deep yellow color of diacetyl (5) became almost white, indicating disappearance of the starting material (Scheme 4). We used 80% of the nominal LED luminescence power (total diode power: 670 W). Interestingly, after the photo-reaction, the original deep yellow color of diacetyl (5) became almost white, indicating disappearance of the starting material (Scheme 4). We used 80% of the nominal LED luminescence power (total diode power: 670 W). Interestingly, after the photo-reaction, the original deep yellow color of diacetyl (5) became almost white, indicating disappearance of the starting material (Scheme 4). We used 80% of the nominal LED luminescence power (total diode power: 670 W). Interestingly, after the photo-reaction, the original deep yellow color of diacetyl (5) became almost white, indicating disappearance of the starting material (Scheme 4). We used 80% of the nominal LED luminescence power (total diode power: 670 W). Interestingly, after the photo-reaction, the original deep yellow color of diacetyl (5) became almost white, indicating disappearance of the starting material (Scheme 4). We used 80% of the nominal LED luminescence power (total diode power: 670 W).

Multigram Synthesis of Diacid 1. Multigram synthesis of diacid 1 from ketone 6 was performed following the protocol of Michl 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-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 AgNO3 gave fluorine-substituted acid 8 in a 54 g scale (Scheme 6), a key intermediate in the synthesis of a 19F NMR label for solid state peptide studies. Activation of the carboxylic group in 8 with ClCO2Me 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-substituted amine 10 in a 13 g amount. Esterification of diacid 1 with methanol and monohydrolysis gave valuable linker 11 in 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 Pätzl as a mimetic of γ-aminobutyric acid (GABA) in peptides. Finally, acylation of N-hydroxyphthalimide with 11, followed by light-mediated decarboxylative borylation with B2Cat, 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, and recently, VanHeyst, Qi, and co-workers from Merck used it for practical photoredox cross-couplings of heterocycles.

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...
tryed hydrolysis of compound 15 in the presence of silver nitrate (Scheme 7). However, only ring-opened alkene 16 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. 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 undertook the synthesis of compound 16. The reaction mixture was titrated and transferred into 800 mL bottles for storage. The mixture was distilled to a 5 L flask and stored under argon. The yield: 3.75 L, 0.1 M of diketone 6 (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 halof orm reaction of the diketone in batch. Several representative multigram functionalizations of diacid 1 into medic hem-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). 1H NMR spectra were recorded at 400, 500, or 600 MHz (Varian); 13C NMR spectra were recorded at 100, 126, or 151 MHz (Varian); 19F NMR spectra were recorded at 376 MHz (Varian); and 15N NMR spectra were recorded at 100, 126, or 151 MHz (Varian). 1H NMR chemical shifts are calibrated with residual undeuterated solvents CHCl3 (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). 13C NMR chemical shifts for 1H NMR are reported relative to the central CHCl3 (δ = 77.16 ppm) or DMSO (δ = 39.52 ppm). 19F NMR chemical shifts are calibrated using CFCl3 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[1.1.1.1′-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 Et2O (2 L). The reaction 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 −78 °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%. *Titrination:* propellane was titrated with thiophenol. A degassed with argon solution of thiophenol (3.00 g) in Et2O was added to a solution of 4 (10 mL). The mixture was stirred for 15 min, concentrated, and subjected to 1H NMR. The ratio of the obtained PhS-BCP-H and remaining PhSH was calculated based on the product of the tertiary carbon in propellane at 2.72 ppm (s, 1H) and the proton in PhSH at 3.44 ppm (s, 1H).

![Scheme 7. Synthesis of BCP-Containing Hydroxy Acid 14](image-url)
A solution of NaOH (10 kg, 24.6 mol, 1.5 equiv) in water (3.5 L) was cooled to 20 °C, and Br₂ (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 CH₂Cl₂ (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 washed in hexane (1 L), then in CH₂Cl₂ (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. ¹H NMR (400 MHz, CDCl₃) δ 80.2, 76.8 (d, J = 20 Hz), 54.3 (d, J = 21 Hz), 37.6 (d, J = 17 Hz) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 156.9, 102.9, 80.2, 76.8 (d, J = 316 Hz), 55.3 (d, J = 20 Hz), 39.9 (d, J = 72 Hz), 28.5 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ −166.6 (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 MeOH (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. ¹H NMR (500 MHz, DMSO-d₆) δ 9.43 (s, 3H), 2.53 (s, 3H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆) δ 175.5 (s, J = 36 Hz), 74.8 (d, J = 329 Hz), 55.7 (d, J = 22 Hz), 28.2 (d, J = 48 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ −150.3 (s) ppm. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C₇H₁₂O₇ 192.0633; found 192.0630.

3-Fluorobicyclo[1.1.1]pentane-1-carboxylic Acid (8). Compound 1 (155.0 g, 0.99 mol, 1.0 equiv) and AgNO₃ (59.0 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 stirred at room temperature overnight and concentrated under reduced pressure. The residue was dissolved in EtOAc (1 L) and stirred at room temperature overnight and concentrated under reduced pressure. The mixture was dissolved in a mixture of hexane:MeOH = 1:1 (L) (filtrated, and concentrated under reduced pressure). The solution was heated in an oil bath with a thermocouple at 50 °C for 24 h, then cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in water (1 L) and extracted with MeOH (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 P₂O₅. Yield: 163.3 g, 0.96 mol, 90%. Yellow solid. Mp = 126–127 °C. ¹H NMR (400 MHz, CDCl₃) δ 11.15 (br s, 1H), 3.69 (s, 3H), 2.34 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 175.2, 169.8, 52.9, 52.1, 37.7, 37.6 ppm. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C₁₅H₂₀N₂O₇ 357.1264; found 357.1247.

3-(Tert-Butyloxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylic Acid (12). Compound 11 (40.0 g, 0.23 mol, 1.0 equiv) was dissolved in iBuOH (1 L). Et₂N (280.0 g, 0.27 mol, 1.2 equiv) and (PhO)₂P(O)N₃ (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 NaHCO₃ (2 L), water (500 mL), and brine (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 Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in dioxane (500 mL) and washed with MeOH (500 mL) and extracted with MeOH (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 Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (gradient, hexane:MeOH = 19 to 1:1). Yield: 44.0 g, 0.19 mol, 80%, white solid. Mp = 138–139 °C. ¹H NMR (400 MHz, CDCl₃) δ 5.00 (br s, 1H), 3.67 (s, 3H), 2.27 (s, 3H), 1.43 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 169.8, 53.0, 51.9, 37.7 ppm. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C₁₅H₂₂N₂O₇ 341.1666; found 341.1662. The purified sample was further purified by a preparative reverse phase HPLC with a gradient elution (water: acetonitrile = 8:2) to give pure N,N-diisopropylcarbodiimide, DIC (44.0 g, 0.35 mol, 1.2 equiv) as a colorless oil.
methyl ether (2) dried over Na2SO4, dissolved in CH2Cl2 and washed with a sat. solution of Na2CO3 (3 × combined organic layers were washed with water (2 × 300 mL) and brine (300 mL), dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude product was dissolved in MeOH:H2O = 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 P2O5 during 24 h. The product was washed in MeOH:Bu (3 × 100 mL), 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. 1H NMR (400 MHz, DMSO-d6) δ 3.31 (s, 3H), 1.59 (s, 6H) ppm. 13C{1H} NMR (126 MHz, DMSO-d6) δ 170.5, 50.7, 50.4 ppm. 19F{1H} NMR (376 MHz, DMSO-d6) δ -143.5 (s) ppm. Anal. Calc. for C14H14F2O4: C, 49.00; H, 3.47; F, 11.65. Found: C, 49.00; H, 3.50; F, 11.65.

1-Benzyl 3-(1,3-Dioxoisooindolin-2-yl) bicyclo[1.1.1]-pentane-1,3-dicarboxylate (21). To a solution of 20 (7.0 g, 0.0179 mol, 1.0 equiv) and 2,2′-bis(1,3,2-benzodioxaborole) (5.0 g, 0.0211 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: 50% of nominal, the temperature of the reaction mixture: 35 °C. After completion of the reaction, Et3N (5.4 g, 0.0537 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 filtered, washed with MeOH, 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 Na2SO4, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH:MeOD-H2O = 2:1 (200 mL). The mixture was hydrogenated under a rubber ball (50 mL) was added 10% Pd/C (0.25 g, 0.00234 mol, 0.1 equiv). The mixture was stirred at room temperature overnight and then concentrated. The residue was filtered out, and the reaction mixture was concentrated. The additional solvent was removed by sublimation. Yield: 3.6 g, 0.011 mol, 61%, white solid. 1H NMR (500 MHz, CDCl3) δ 7.41–7.23 (m, 5H), 5.08 (s, 2H), 1.22 (s, 12H) ppm. 13C{1H} NMR (126 MHz, CDCl3) δ 169.5, 136.3, 128.6, 128.2, 83.7, 65.9, 52.5, 43.1 ppm. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for C16H15BO3: 285.0997; found 285.0997. Benzyl 3-Hydroxybicyclo[1.1.1]-pentane-1-carboxylate (23). To a solution of KH2PO4 (15.92 g, 0.117 mol, 3.0 equiv) in a mixture of H2O (160 mL) and THF (240 mL) was added H2O2 (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 MeOH (2 × 300 mL). The combined organic layers were washed with water (1 × 500 mL) and extracted with MeOH:MeOD-H2O = 2:1 (200 mL). The solution was filtered through SiO2, and concentrated under reduced pressure. The residue was dissolved in a mixture of hexane:MeOH:Bu (1:1:100 mL) and filtered. Yield: 1.0 g, 35%, white solid. 1H NMR (400 MHz, MeOD-d4) δ 7.39–7.17 (m, 5H), 5.36 (s, 1H), 5.10 (s, 2H), 2.21 (s, 6H) ppm. 13C{1H} NMR (101 MHz, CDCl3) δ 170.4, 135.4, 128.3, 127.0, 70.5, 61.8, 55.3, 30.3 ppm. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for C7H15NO2: 119.0532; found 119.0543.
The authors declare no competing financial interest.

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