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Total Synthesis and Absolute Configuration Determination of (+)-Bruguierol C

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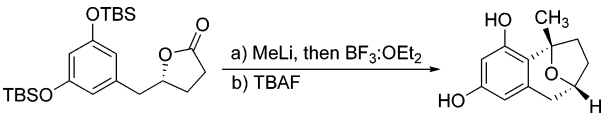


The first total synthesis and absolute configuration of bruguierol C are reported. The key step involved the diastereoselective capture of an in situ generated oxocarbenium ion via an intramolecular Friedel−Crafts alkylation.

In 2005, Sattler and co-workers isolated and disclosed an unusual family of aromatic β-*C*-glycoside natural products termed bruguierols A−C from the stem of the *Bruguiera gymmorrhiza* mangrove tree.[1] Within this family of natural products, as depicted in Figure 1, they had shown that the inclusion of the meta-substituted hydroxyl groups is crucial for the antimicrobial activity. Thus, only bruguierol C (**1**) was shown to exhibit modest antimicrobial activities (minimal inhibitory concentration, MIC: 12.5 μg/mL) against *Staphylococcus aureus* SG 511, *Micrococcus luteus* ATCC 10240, *Enterococcus faecalis* 1528 (vanA), *Escherichia coli* SG 458, and *Mycobacterium vaccae* (MT 10670). Two observations are quite remarkable. The first is that the antimicrobial activity of **1** against the *Enterococcus faecalis* 1528 microorganism is noteworthy, due to its resistance to other antibiotics such as gentamicin, teicoplanin, and vancomycin A.[2] Second, compound **1** shares the same MIC 12.5 μg/mL activity versus *Micrococcus luteus* ATCC 10240 with that of ciprofloxacin.[1,3] Based on the fact that **1** exhibits activity against both Gram-positive and Gram-negative bacteria, one could envision further investigations of bruguierol C or hybrid analogues thereof as broad spectrum antibiotics. Based not only on the biological profile of **1**, we were also attracted to pursuing the total synthesis of bruguierol C due to our own interest[4] in constructing quaternary centered β-*C*-glycoside moieties via oxocarbenium chemistry.

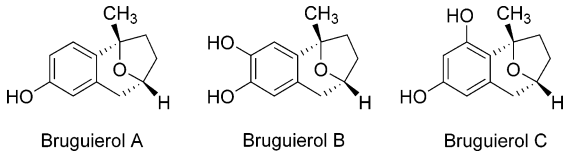
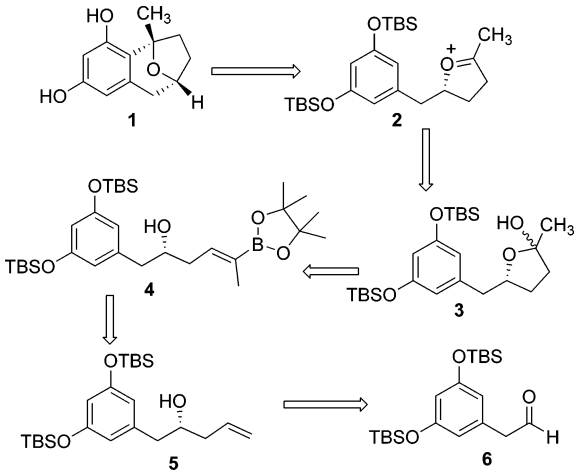


FIGURE 1. Structures of bruguierols A−C.

SCHEME 1. Retrosynthetic Analysis of 1



Herein, we report the first total synthesis and absolute configuration of bruguierol C. The key step involved the diastereoselective capture of an in situ generated oxocarbenium ion via an intramolecular Friedel−Crafts alkylation that ultimately delivered the targeted natural product.

Our initial synthetic blueprint of **1** was engineered to feature a domino reaction sequence via an oxidation of the vinylic boronate **4** to provide the γ-hydroxy ketone followed by cyclization to the lactol **3**. Final oxocarbenium formation under acidic conditions and an intramolecular Friedel−Crafts capture of the cationic intermediate **2** was envisioned to provide **1** as delineated in Scheme 1. The synthesis of the vinylic boronate **4** was envisioned to be derived from a cross metathesis between isopropenyl pinacol boronate and the homoallylic alcohol **5** which, in turn, could be readily obtained from the known aldehyde **6**[5] via asymmetric allylboration.[6]

With the initial blueprint in mind, focus was first placed on the synthesis of the required homoallylic alcohol **5**. Unfortunately, partial reduction of the known bis-TBS protected methyl ester **7**[5] directly to the aldehyde by means of DIBAL was problematic and over reduction was the principal reaction pathway leading to the primary alcohol **8**. On the basis of this observation, we decided to fully reduce **7** with LAH to the primary alcohol **8** and subsequent oxidation of the primary hydroxyl moiety was accomplished with PCC to provide the desired aldehyde **6** in 77% yield over the two steps as delineated in Scheme 2. An ensuing asymmetric allylboration of **6** was accomplished utilizing Brown's Ipc based allylborane reagent to furnish the homoallylic alcohol **5** in 70% yield with an er of

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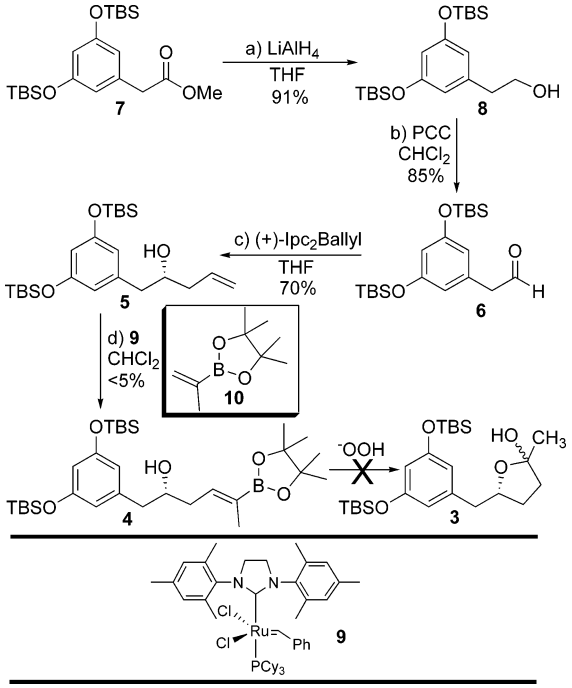
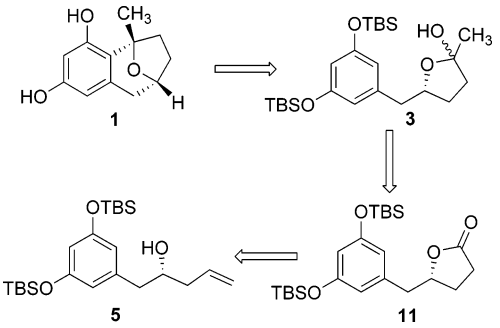
SCHEME 2. Failed Approach to Lactol 3



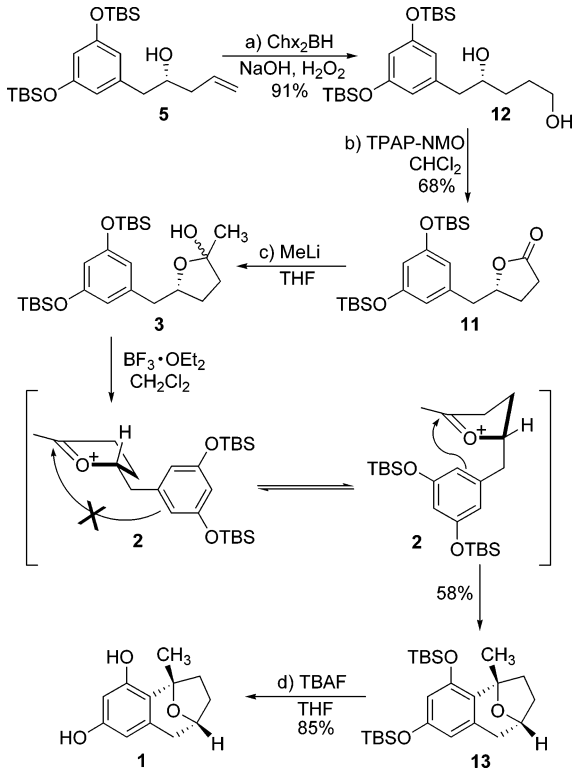
95:5, as determined by the Mosher ester. With the desired homoallylic alcohol in hand, the stage was set for the proposed cross-metathesis (CM) between isopropenyl pinacol boronate (**10**) and **5** in the presence of Grubbs' second-generation catalyst **9**. Inspired both by the Grubbs' account regarding the CM of type I alkenes with pinacol boronate **10**[7] and also the Sulikowski synthesis of apoptolidin in which they elegantly utilized a CM reaction with **10** and a type I olefin,[8] we envisioned little difficulty with a CM reaction sequence between **5** and **10** promoted by catalyst **9**. Much to our dismay, we observed less than 5% conversion of the homoallylic alcohol to the obligatory vinyl pinacol boronate ester **4**. Not surprisingly, further one-pot oxidation of the reaction mixture (pH 7 buffered or basic H_2O_2) of the in situ formed vinyl boronate failed to provide any trace amount of either the γ-hydroxy ketone or the cyclized lactol **3**.

Disappointed by the failure of the two preceding reactions to provide meaningful quantities of the desired lactol **3**, we reformulated a new approach to **1**. As shown in Scheme 3, our end game remained consistent with that of the first-generation retrosynthetic analysis. We envisaged that the final natural product would be furnished via the intramolecular trap of the incipient oxocarbenium cation by means of a Friedel−Crafts alkylation. The key distinction between the two strategies lies in the formation of lactol **3**. In the second-generation approach, we envisioned a sequential reaction that would ultimately form the oxocarbenium cation via a sequential methylation of lactone **11** followed by treatment of lactol **3** with an appropriate Lewis acid. In turn, lactone **11** could be readily derived from the previously prepared homoallylic alcohol **5** via a hydroboration−TPAP oxidation sequence.[9]

SCHEME 3. Second-Generation Retrosynthetic Analysis of 1



SCHEME 4. Completion of 1



With the second-generation strategy firmly in place, we focused our initial efforts on the formation of the desired lactone **11** as highlighted in Scheme 4. Thus, hydroboration of the olefinic portion of the previously synthesized homoallylic alcohol **5** with 3 equiv of dicyclohexyl borane (Chx_2BH) followed by basic oxidation provided the diol **12** in 91% yield. It is worth noting that attempted hydroboration of **5** with BH_3·THF, BH_3·DMS, or 9-BBN did not lead to a sufficient amount of the desired diol **12**.[10] Ensuing selective oxidation of the primary alcohol moiety of diol **12** to the aldehyde followed by intramolecular cyclization to the lactol and further oxidation to the obligatory lactone **11** was accomplished by means of Ley's TPAP-NMO protocol (5 mol %) in 68% yield.[11] With the

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(8) Wu, B.; Liu, Q.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6673.

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(10) The low product formation of **12** was attributed to the differences in reactivity of the mentioned boranes, as a majority of the alkene starting material was recovered. For a more in-depth discussion of kinetics and reactivities of different boranes see: (a) Ramachandran, P. V.; Jennings, M. P. *Chem. Commun.* **2002**, 386. (b) Brown, H. C.; Chandrasekharan, J.; Wang, K. K. *Pure Appl. Chem.* **1983**, *55*, 1387.

(11) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

synthesis of lactone **11**, the stage was set for our envisioned sequential reaction that would ultimately form the oxocarbenium cation via an ensuing methylation followed by treatment of lactol **3** with an appropriate Lewis acid. Finally, an intramolecular trap of the incipient oxocarbenium cation by means of a Marson-type Friedel−Crafts alkylation[12] should allow for the formation of the protected bruguierol C. With this idea in mind, treatment of lactone **11** with 1.3 equiv of MeLi in THF quantitatively furnished lactol **3**, which was then sequentially treated with $BF_3{\cdot}OEt_2$ and allowed to react at −20 °C for 2 h.

Much to our delight, the three-step reaction sequence (alkylation, oxocarbenium formation to afford **2**, and final intramolecular Friedel−Crafts alkylation) provided the desired *β-C*-glycoside product **13** with an overall 58% yield from lactone **11**. Last, treatment of **13** with 3 equiv of TBAF at rt in THF furnished the natural product **1** in a respectable 85% yield. The spectral data (^{1}H NMR, 360 MHz; ^{13}C NMR, 125 Mhz), optical rotation ($[\alpha]^{rt}_D$ +4.2°, *c* 0.0050 g/mL MeOH), and HRMS data of synthetic (+)-bruguierol C were in agreement with the natural sample.[1]

In conclusion, we have completed the total synthesis and determined the absolute configuration of (+)-bruguierol C (in 7 linear steps from the known compound **7**) by featuring a diastereoselective capture of an in situ generated oxocarbenium ion via an intramolecular Friedel−Crafts alkylation.

Experimental Section

5-[3,5-Bis(*tert*-butyldimethylsilanyloxy)phenyl]pentane-1,4-diol (12). To a solution of $BH_3{\cdot}S(CH_3)_2$ (0.36 mL, 10 M in Me_2S, 3 equiv) dissolved in anhydrous Et_2O (50 mL) was added cyclohexene (0.77 mL, 7.5923 mmol, 6.4 equiv) dropwise at 0 °C. The reaction was allowed to reach room temperature and then stirred for 2 h. The solution was then recooled to 0 °C followed by dropwise addition of the homoallylic alcohol **5** (500 mg, 1.1863 mmol, 1.0 equiv) as a 5 mL solution in Et_2O. The reaction was allowed to reach room temperature and left stirring for 10 h. The reaction was recooled to 0 °C and oxidized with 10 mL of 3 M NaOH and 5 mL of 30% H_2O_2 then the reaction mixture was allowed to reach room temperature and stirred for 4 h. The aqueous layer was extracted (3 × 20 mL) with Et_2O. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (silica, 40% ethyl acetate in hexanes) afforded diol **12** as a colorless oil (455 mg, 91%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.32 (d, 2H, J = 2.5 Hz), 6.22 (t, 1H, J = 2.2 Hz), 3.79 (m, 1H), 3.66 (m, 2H), 2.68 (dd, 1H, J = 13.3, 4.3 Hz), 2.57 (dd, 2H, J = 13.7, 7.9 Hz), 2.37 (br s, 2H), 1.71 (m, 3H), 1.51 (m, 1H), 0.97 (s, 18H), 0.18 (s, 12H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 156.6, 140.2, 114.5, 110.4, 72.5, 62.9, 44.1, 33.6, 29.3, 25.6, 18.2, −4.4. IR ($CHCl_3$) 3733, 3627, 3333, 2953, 2857, 2341, 1586, 1540, 1449, 1389, 1333, 1251, 1159, 1005, 939, 828, 778 cm $^{-1}$. R_f at 40% ethyl acetate in hexanes: 0.24. $[\alpha]^{25}_D$ −4.8 (*c* 0.02, CH_2Cl_2). HRMS (EI) calcd for $C_{23}H_{44}O_4Si_2$ (M^+) 440.2778, found 440.2786.

5-[3,5-Bis(*tert*-butyldimethylsilanyloxy)benzyl]dihydrofuran-2-one (11). To a solution of diol **12** (740 mg, 1.68 mmol) dissolved in anhydrous CH_2Cl_2 (8 mL) was added NMO (790 mg, 6.74 mmol, 4 equiv), TPAP (30 mg, 0.0842 mmol, 5% mol), and 4 Å MS (500 mg) at room temperature. The reaction mixture was left stirring until the starting material was consumed by TLC (∼12 h). The reaction mixture was filtered through a plug of silica gel and rinsed with Et_2O to give the crude product. The resulting solution was then concentrated under reduced pressure. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded lactone **11** as a yellowish oil (500 mg, 68%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.32 (d, 2H, J = 1.8 Hz), 6.24 (t, 1H, J = 2.2 Hz), 4.68 (m, 1H), 2.99 (dd, 1H, J = 13.3, 5.8 Hz), 2.75 (d, 1H, J = 13.7, 6.8 Hz), 2.43 (m, 2H), 2.21 (m, 1H), 1.92 (m, 1H), 0.97 (s, 18H), 0.18 (s, 12H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.9, 156.7, 137.6, 114.6, 110.8, 80.6, 41.2, 28.6, 27.1, 25.7, 18.2, −4.4. IR ($CHCl_3$) 2956, 2930, 2858, 1775, 1590, 1452, 1338, 1265, 1167, 1022, 832, 782, 741, 704 cm $^{-1}$. R_f at 20% ethyl acetate in hexanes: 0.4. $[\alpha]^{25}_D$ −5.6 (*c* 0.05, CH_2Cl_2). HRMS (EI) calcd for $C_{23}H_{40}O_4Si_2$ (M^+) 436.2465, found 436.2456.

3,5-Bis(*tert*-butyldimethylsilanyloxy)-1-methyl-12-oxatricyclo-[7.2.1.0^{2,7}]dodeca-2,4,6-triene (13). To a solution of lactone **11** (250 mg, 0.57 mmol) dissolved in anhydrous Et_2O (5 mL) was added MeLi (0.48 mL, 0.77 mmol, 1.3 equiv) dropwise under argon at −78 °C. The reaction was left stirring for 1.5 h until starting material was consumed at which time the reaction was quenched with $NH_4^+Cl^-$. The aqueous layer was then extracted (3 × 20 mL) with Et_2O. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure, which afforded the crude lactol product. To a solution of crude lactol dissolved in 5 mL of CH_2Cl_2 was added $BF_3{\cdot}OEt_2$ (0.14 mL, 1.14 mmol, 2.0 equiv) dropwise under argon at −20 °C. The solution was left stirring for 2 h and the reaction was quenched with sat. $NH_4^+Cl^-$. The aqueous layer was then extracted (3 × 20 mL) with Et_2O. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Flash chromatography (silica, 5% diethyl ether in hexanes) afforded the bis-TBS protected bruguierol C (**13**) as a colorless oil (143 mg, 58% over two steps). ^{1}H NMR (360 MHz, $CDCl_3$), δ 6.17 (d, 1H, J = 2.5 Hz), 6.12 (d, 1H, J = 2.2 Hz), 4.61 (dddd, 1H, J = 7.2, 5.4, 2.5, 1.8 Hz), 3.31 (dd, 1H, J = 16.2, 5.0), 2.34 (d, 1H, J = 16.2), 2.21 (m, 1H), 2.09 (dddd, 1H, J = 10.8, 9.4, 2.2, 1.4 Hz), 1.84 (s, 3H), 1.76 (m, 1H), 1.63 (m, 1H), 1.01 (s, 9H), 0.96 (s, 9H), 0.30 (s, 3H), 0.24 (s, 3H), 0.17 (s, 6H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 154.1, 152.2, 135.1, 126.8, 113.4, 108.5, 80.4, 73.1, 42.0, 37.8, 26.0, 25.6, 24.2, 18.5, 18.1, −3.5, −3.9, −4.4, −4.4. IR ($CHCl_3$) 2954, 2930, 2897, 2355, 1601, 1571, 1424, 1372, 1279, 1190, 1082, 894, 830, 778 cm $^{-1}$. R_f at 30% ethyl acetate in hexanes: 0.4. $[\alpha]^{25}_D$ +16.2 (*c* 0.03, CH_2Cl_2). HRMS (EI) calcd for $C_{24}H_{42}O_3Si_2$(M^+) 434.2673, found 434.2674.

(+)-Bruguierol C (1). To a solution of protected natural product **13** (90 mg, 0.21 mmol) dissolved in THF (5 mL) was added TBAF (0.63 mL, 0.63 mmol, 3.0 equiv) dropwise at rt. The reaction was left stirring for 1.5 h and the reaction was quenched with sat. $NH_4^+Cl^-$. The aqueous layer was then extracted (3 × 20 mL) with EtOAc. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure, which afforded the crude product. Flash chromatography (silica, 40% ethyl acetate in hexanes) afforded (+)-bruguierol C (**1**) as a white solid (37 mg, 85%). ^{1}H NMR (360 MHz, CD_3OD), δ 6.08 (d, 1H, J = 2.2 Hz), 6.02 (d, 1H, J = 2.5 Hz), 4.58 (dddd, 1H, J = 7.2, 5.4, 2.2, 1.8 Hz), 3.20 (dd, 1H, J = 16.2, 5.0 Hz), 2.35 (d, 1H, J = 16.2 Hz), 2.20 (m, 1H), 2.10 (m, 1H), 1.81 (s, 3H), 1.74 (m, 1H), 1.63 (m, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 157.5, 155.5, 136.0, 122.3, 108.1, 102.0, 82.3, 75.0, 42.9, 38.8, 31.0, 24.4. IR ($CHCl_3$) 3735, 3633, 3326, 2923, 2854, 2360, 1608, 1464, 1348, 1296, 1161, 1028, 997, 836 cm $^{-1}$. R_f at 50% ethyl acetate in hexanes: 0.4. $[\alpha]^{25}_D$ +4.2 (*c* 0.005, MeOH). HRMS (EI) calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943, found 206.0947.

Acknowledgment. Support was provided by the University of Alabama and the NSF (CHE-0115760) for the departmental NMR facility.

Supporting Information Available: Spectral data for all compounds are also accessible. This material is available free of charge via the Internet at http://pubs.acs.org.

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