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A Short Asymmetric Route to the Bromophycolide A and D Skeleton

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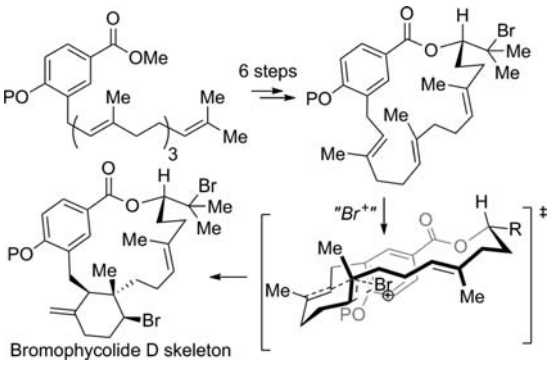
ABSTRACT



An asymmetric synthesis of the bromophycolide D ring system has been achieved in seven steps from a known geranylgeranylated benzoate, via bromonium-promoted transannular cyclization of a macrocyclic intermediate.

In 2005, Kubanek and co-workers isolated bromophycolides A and B (Figure 1) from the Fijian red algae *Callophycus Serratus*.[1a] Although instantly appealing to the organic chemist's eye, these novel structures are the first macrocyclic halogenated terpene-benzoate structures that have been isolated. Additionally, they and subsequently discovered bromophycolides C−Q show interesting biological activity, including growth inhibition of resistant bacterial strains (MRSA and VREF) as well as antitumor and antimalarial activity.[1]

No report of synthetic approaches to these molecules has yet appeared, perhaps because their multiple halogenated stereocenters make the bromophycolides intimidating targets. However, the stereochemical pattern of bromination suggested to us that a concise strategy might

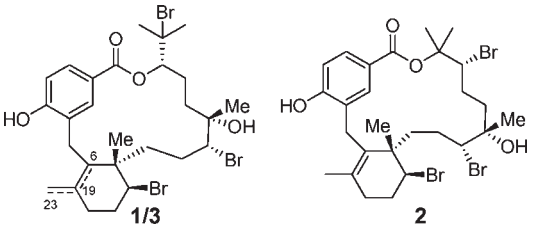


Figure 1. Bromphycolides A (**1**, $\Delta^{6,19}$), B (**2**), and D (**3**, $\Delta^{19,23}$).

be feasible (Scheme 1). As shown in structure **4**, not all stereocenters in **3** are derived from brominations on the same alkene face. This leads to the biosynthetic question of whether (1) multiple brominating enzymes are responsible for conferring opposite selectivity for the various positions or (2) a single enzyme brominates multiple positions but is capable of brominating either face when the substrate is heavily biased. We imagined that if a macrocycle such as **5** were the biosynthetic precursor to **3**, alkene positions 1, 2, and 3 might be well enough differentiated to undergo

(1) (a) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Hardcastle, K. I.; Fairchild, C. R.; Aalbersberg, W.; Raventos-Suarez, C.; Hay, M. E. *Org. Lett.* **2005**, *7*, 5261–5264. (b) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalbersberg, W.; Hay, M. H. *J. Nat. Prod.* **2006**, *69*, 731–735. (c) Lane, A. L.; Stout, E. P.; Lin, A.-S.; Prudhomme, J.; Le Roch, K.; Fairchild, C. R.; Franzblau, S. G.; Hay, M. E.; Aalbersberg, W.; Kubanek, J. *J. Org. Chem.* **2009**, *74*, 2736–2742. (d) Lin, A. S.; Stout, E. P.; Prudhomme, J.; Le Roch, K.; Fairchild, C. R.; Franzblau, S. G.; Aalbersberg, W.; Hay, M. E.; Kubanek, J. *J. Nat. Prod.* **2010**, *73*, 275–278.

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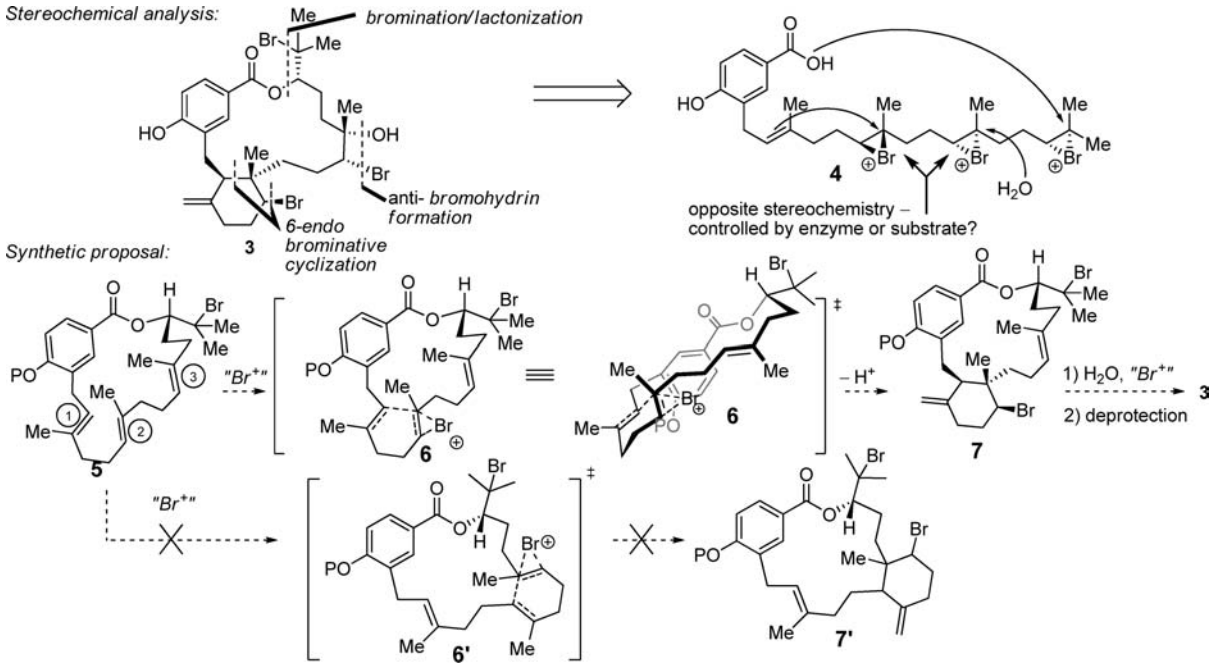
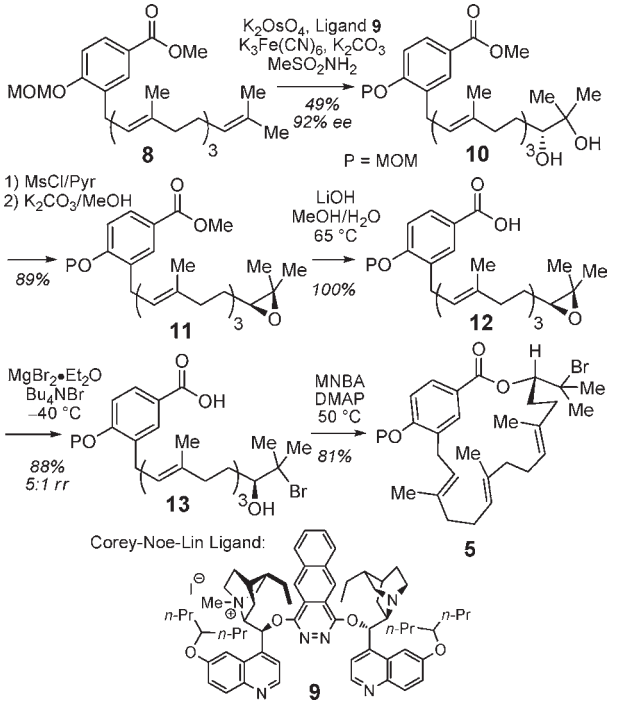
Scheme 1. Stereochemical Analysis and Synthetic Proposal



regio- and diastereoselective reactions with a bromonium source even outside the context of an enzyme pocket.[2] Although **5** is a 19-membered macrocycle, numerous elements limit its conformational flexibility. Three *E*-configured double bonds define arrays of four coplanar carbon atoms with locked 180° torsion angles, and the benzoate contributes another coplanar array of five atoms. Additionally, the large *tert*-butyl-like substituent should prefer a pseudoequatorial orientation. Examination of models suggested that intermediate **5** should undergo regio- and diastereoselective transannular cyclization between alkenes 1 and 2 (TS **6**) much more readily than between alkenes 2 and 3 (TS **6′**) to accommodate a chair transition state and all of the above-mentioned constraints. If successful, this strategy would provide a concise route to the desired ring system **7** (and not **7′**).

We thus set about to synthesize transannular cyclization substrate **5** (Scheme 2). Known geranylgeranylbenzoate **8** was prepared in three steps from commercially available starting materials.[3] The first asymmetric center was conveniently installed by Sharpless asymmetric dihydroxylation. To address the regiochemical problem of differentiating the "terminal" trisubstituted alkene from the other three, we employed ligand **9**, developed specifically for this purpose by Corey.[4] By running the reaction to ~70% conversion, we were able to isolate the desired regioisomer **10** in 49% yield (71% brsm) and 92% ee.[5]

Scheme 2. Preparation of Substrate **4**



(2) Though alkenes 1, 2, and 3 are likely to form cyclic bromonium ions at similar rates, bromonium transfer between alkenes is likely to be rapidly reversible, so that the reaction outcome is determined by the relative rates at which these various species react further: (a) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233. (b) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131–137. (c) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1996**, *61*, 962–968. (d) Neverov, A. A.; Muise, T. L.; Brown, R. S. *Can. J. Chem.* **1997**, *75*, 1844–1850. (e) Rodebaugh, R.; Fraser-Reid, B. *Tetrahedron* **1996**, *52*, 7663–7678.

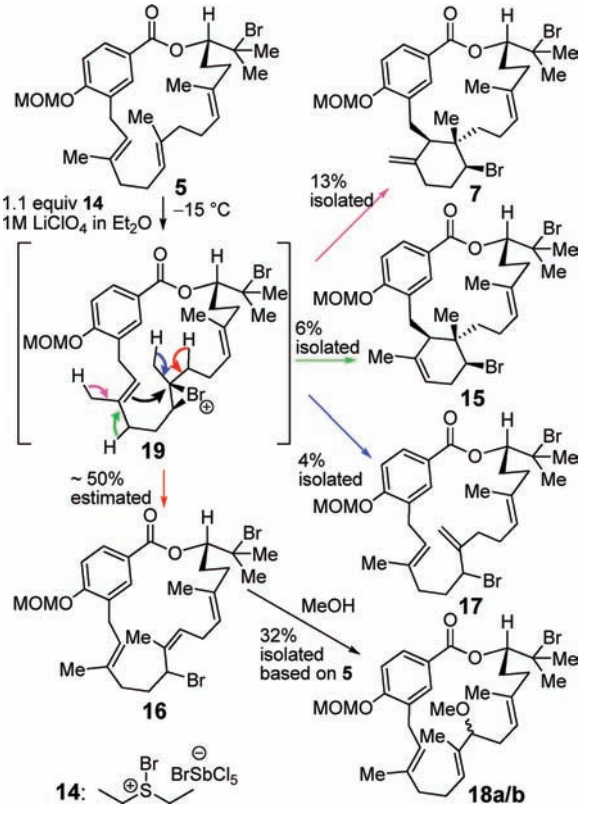
(3) Lang, M.; Steglich, W. *Synthesis* **2005**, *6*, 1019–1027.

The *R*- alcohol of **10** was inverted in the process of installing the tertiary bromide. Thus, mesylation of the secondary alcohol of **10** and ring closure with K_2CO_3 cleanly afforded epoxide **11**. Saponification at the optimal temperature of 65 °C cleanly afforded acid **12** without harming the epoxide. There was precedent suggesting that $MgBr_2 \cdot Et_2O$ would open the epoxide of **12** regioselectively to give tertiary bromide **13**.[6] However, we anticipated competing polyene cyclizations upon Lewis acid activation of the epoxide.[7] Indeed, addition of a full equivalent of Bu_4NBr was necessary to suppress polyene cyclizations; presumably bromide in high concentrations can compete with intramolecular alkene attack on the activated epoxide. Under these conditions, we could obtain bromohydrin **13** in good yield and regioselectivity.

Despite the hindered nature of the secondary neopentyl alcohol of **13** and the observed base sensitivity of its vicinal bromohydrin,[8] Shiina macrolactonization[9] proceeded in high yield.[10] The resulting macrocycle **5** crystallized during storage at −20 °C, and X-ray crystal structure determination confirmed its *S*- absolute configuration.[11]

With facile access to hundreds of milligrams of **5**, we investigated bromonium-initiated transannular cyclization (Scheme 3). After significant experimentation,[12] we found that 1.1 equiv of Snyder's recently reported reagent **14** (bromodiethylsulfonium bromopentachloroantimonate, BDSB)[13] in 1 M $LiClO_4/Et_2O$[14] afforded a 19% combined isolated yield of the desired products **7** and **15**. NMR and LC analysis of the crude product showed it to be a ∼9:3:2:1 mixture of **16:7:15:17**. The major product, **16**, however, invariably decomposed during normal and reversed-phase chromatography. Because we suspected **16** was an allylic bromide, we selectively solvolyzed it by treatment of the crude product mixture with methanol. From the solvolyzed mixture we isolated and identified five compounds: **7** and **15**, as well as moderately stable allylic bromide **17** and 32% of **18a/b**, the two major new

Scheme 3. Transannular Cyclization of **4**



compounds produced during methanolysis. Since we could not characterize **16** as a pure compound, its structure is tentatively assigned based on its known conversion to **18a/b**. The reaction of **5** with **14** evidently proceeds primarily through bromonium intermediate **19** (Scheme 3). Likely due to geometry, attack on this bromonium by the alkene (black arrow) is not fast enough to compete with loss of a proton from either of two positions (red or blue arrow), giving rise to **16** and **17**. The superiority of **14** compared with brominating reagents such as NBS is likely due to the absence of any basic leaving group that could accelerate processes leading to **16** and **17**.[15] In the bromonium polyene cyclization literature,[16] low yields are typical, likely due to the prevalence of deprotonation, although **14** has been shown to improve yields in unconstrained systems.[13]

Careful NMR analysis confirmed our assignment of structure **7**. It was easily distinguished from regioisomeric structure **7′** (see Scheme 1) based on HMBC correlations.[17] It was more difficult to rule out the possibility of diastereomeric structure **7″**, in which the configuration of the cyclohexane ring is reversed relative to the ester stereocenter (Scheme 4). MMFF-based Monte Carlo conformational

(4) Ligand **9**: (a) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741–8744. A related ligand: (b) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211–3214.

(5) Determined by Mosher ester analysis (see Supporting Information).

(6) Morimoto, Y.; Okita, T.; Takaishi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1132–1135.

(7) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730–4756.

(8) The bromohydrin derived from ester **11** could not be converted to acid **13**, due to multiple side reactions under a variety of basic and Lewis acidic ester cleavage conditions.

(9) (a) Shiina, I.; Fukui, H.; Sasaki, A. *Nat. Protoc.* **2007**, *2*, 2312–2317. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830.

(10) Slow addition of substrate (48 h) and elevated temperature (50 °C) were critical in order to ensure that the seco acid was consumed faster than it was added, preventing diolide formation. These conditions were robust on a scale of several hundered milligrams.

(11) See Supporting Information.

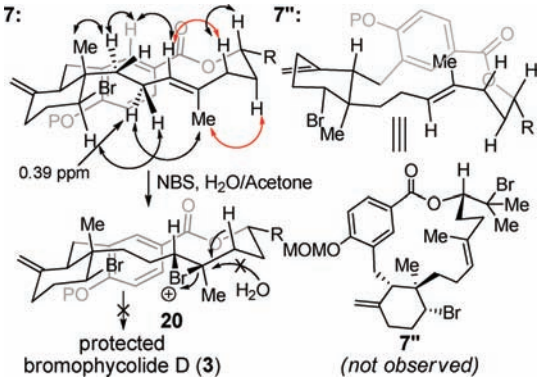
(12) Other reagents employed included NBS, NBS/acids, NBS/phosphines, and TBCHD (2,4,4,6-tetrabromocyclohexadienone).

(13) (a) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314. (b) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899–7903.

(14) We presume this highly polar solvent mixture to be helpful in prolonging the life of the cationic intermediate **19** long enough for the slow cyclization step to occur. Potentially, this solvent may also promote a compact and more cyclization-prone conformation of **19** via hydrophobic effects.

(15) The pK_a of the conjugate acid of dimethylsulfide is −5 (see: Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223–403), making it far less basic than leaving groups derived from other bromonium sources. A reviewer has suggested that BDSB may generally give cleaner reactions because its high reactivity allows the use of lower temperatures.

Scheme 4. Conformation and NMR Characteristics of **7**



searches of **7** and **7″** found the minimum-energy conformations shown in Scheme 4. The depicted structure and conformation of **7** are tentatively assigned based on chemical shift, coupling constant, and 800 MHz COSY, TOCSY, HSQC, HMQC, and ROESY data. One allylic methylene proton resonates unusually upfield at 0.39 δ, indicating its proximity to the aromatic pi cloud. Importantly, the NOE features highlighted in red would be difficult to observe in **7″**. We thus conclude that, to the extent cyclization occurs, it does so regio- and diastereoselectively,[18] according to our predicted model.

Conversion of the trisubstituted alkene of **7** to a bromohydrin with the correct stereochemistry would give protected bromophycolide D (**3**). Interestingly, the conformation of **7** is such that the trisubstituted alkene points its methyl "down", exposing the *Re* face to solvent. Bromonium formation on this face would give intermediate **20**, and subsequent *anti* attack by water would give the requisite bromohydrin in **3**. However, the back side of this brominium is apparently too blocked for water to attack, as treatment of **7** with bromonium sources in aqueous/organic solvent mixtures afforded primarily products resulting from deprotonation of **20**.[19]

In conclusion, we have developed a very concise asymmetric approach to bromophycolide skeleta, in only seven steps from known geranylgeranyl benzoate **8**. Our approach demonstrates a remarkable degree of regio- and diastereocontrol in the differentiation of three nearly identical alkenes within a macrocycle. Advances toward completion of the synthesis will be reported in due course.

Acknowledgment. Brandeis University is acknowledged for generous support. We thank Prof. Bruce Foxman (Brandeis Chemistry Department) for X-ray diffraction studies of **5**. The 800 MHz spectrometer in the Landsman Research Facility, Brandeis University was purchased under the NIH RR High-End Instrumentation program, 1S10RR017269-01.

Supporting Information Available. Complete experimental procedures and copies of ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Selected examples: (a) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900–903. (b) Tanaka, A.; Oritani, T. *Biosci. Biotech. Biochem.* **1995**, *59*, 516–517. (c) Tanaka, A.; Sato, M.; Yamashita, K. *Agric. Biol. Chem.* **1990**, *54*, 121–123. (d) Niwa, H.; Ieda, S.; Inagaki, H.; Yamada, K. *Tetrahedron Lett.* **1990**, *31*, 7157–7158. (e) Collado, I. G.; Madero, J. G.; Massanet, G. M.; Luis, F. R. *Tetrahedron Lett.* **1990**, *31*, 563–564. (f) Fujiwara, S.; Takeda, K.; Uyehara, T.; Kato, T. *Chem. Lett.* **1986**, *15*, 1763–1766. (g) Yamaguchi, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1985**, *26*, 343–346. (h) Kato, T.; Mochizuki, M.; Hirano, T.; Fujiwara, S.; Uyehara, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1077–1078. (i) Shieh, H.-M.; Prestwich, G. D. *Tetrahedron Lett.* **1982**, *23*, 4643–4646. (j) Kato, T.; Ichinose, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1051–1056. (k) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978**, *43*, 3693–3697. (l) González, A. G.; Martín, J. D.; Pérez, C.; Ramírez, M. A. *Tetrahedron Lett.* **1976**, *17*, 137–138. (m) Wolinsky, L. E.; Faulkner, D. J. *J. Org. Chem.* **1976**, *41*, 597–600. (n) Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 518–519. (o) Kato, T.; Ichinose, I.; Kumazawa, S.; Kitahara, Y. *Bioorg. Chem.* **1975**, *4*, 188–193. (p) Greenwood, J. M.; Solomon, M. D.; Sutherland, J. K.; Torre, A. *J. Chem. Soc. C* **1968**, 3004–3008. (q) van Tamelen, E. E.; Hessler, E. J. *Chem. Commun.* **1966**, 411–413.

(17) See Supporting Information for a full discussion of NMR data.

(18) To claim selectivity, we must claim the absence of significant regio- and diastereomers of **7** and **15**. LC of the crude product mixture shows no significant quantities of additional cyclization products. The identified products comprise > 80% of the crude LC; the only unidentified product present at greater than 3% abundance is quickly solvolyzed in methanol and is presumably a diastereo- or regioisomer of allylic bromide **16**.

(19) Products isolated so far are allylic bromides analogous to **16**, as well as allylic alcohols resulting from their hydrolysis in the aqueous medium. MOM-deprotected **7** also does not afford bromohydrins under similar conditions. As expected, the trisubstituted alkene of **7** can be selectively epoxidized, probably from the *Re* face. MOM deprotection of this epoxide yields a compound whose ^{1}H NMR spectrum is consistent with its being C_{10},C_{11}-*bis*-*epi*-Bromophycolide S.