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Enantiocontrolled Total Syntheses of Breviones A, B, and C

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Supporting Information

ABSTRACT: Enantiocontrolled total syntheses of the breviones A, B, and C have been accomplished using a highly diastereoselective oxidative coupling of an α-pyrone with a tricyclic diene prepared from an optically pure Wieland−Miescher ketone derivative through the 7-endo-trig mode of acyl radical cyclization.

Breviones A−E (**1**−**5**, Figure 1),[1] the diterpene/polyketide hybrid natural products also called meroterpenoids,[2] were first isolated from *Penicillium brevicompactum* Dierckx by Macías et al.[1] Their structures were elucidated by chemical transformations and extensive 2D NMR studies. Breviones F−H (**6**−**8**)[3] were recently isolated from the marine deep-sea fungus *Penicillium* sp. (MCCC3A00005). These compounds contain unprecedented penta- (**1**−**4**, **6**, and **7**), hexa- (**5**), and heptacyclic (**8**) basic carbon frameworks, and in **1**−**4**, **6**, and **7**, the framework includes a characteristic oxygen-containing spiro CD ring. **1**−**5** inhibit etiolated wheat coleoptile growth,[1b] while **6**−**8** exhibit cytotoxic activity against HeLa cells and **6** has an inhibitory effect on HIV-1 replication in C8166 cells.[3] Because of their intriguing structural features, biological profiles, and limited availability, these natural products represent attractive targets for total synthesis. To date, several synthetic studies have been reported,[4,5] including the total synthesis of optically active brevione B (**2**),[5c] in which the absolute structure was determined. Here we describe the first enantioselective total synthesis of brevione C (**3**) and highly efficient enantioselective total syntheses of breviones A (**1**) and B (**2**) employing a regioselective 7-endo acyl radical cyclization[6] to assemble the seven-membered A ring (for brevione C) and a diastereoselective oxidative coupling[7] of an exocyclic olefin and an α-pyrone[8] for the construction of the spiro ring[9] as the key steps.[10] For the initial target, we chose brevione C, reasoning that if a synthetic route to brevione C could be established, it would then be easier to prepare breviones A and B.

Our strategies for the syntheses of breviones C (**3**), A (**1**), and B (**2**) are illustrated in Scheme 1. For the synthesis of **3**, we chose as the key intermediate the pentacyclic compound **9**, which would be converted to **3** by oxidation. It was thought that **9** could be constructed by the oxidative coupling of tricyclic compound **10**, a diterpene moiety, with α-pyrone **11**, a polyketide unit. The seven-membered A ring of **10** would be assembled using a highly regioselective 7-endo-trig mode of cyclization of the acyl radical **12**, which was previously developed in our laboratory.[11] Aldehyde **13**, a precursor of the acyl radical,[12] would in turn be prepared from the optically active Wieland−Miescher ketone derivative **15**[13] via tricyclic compound **14**. For the synthesis of **1** and **2**, it

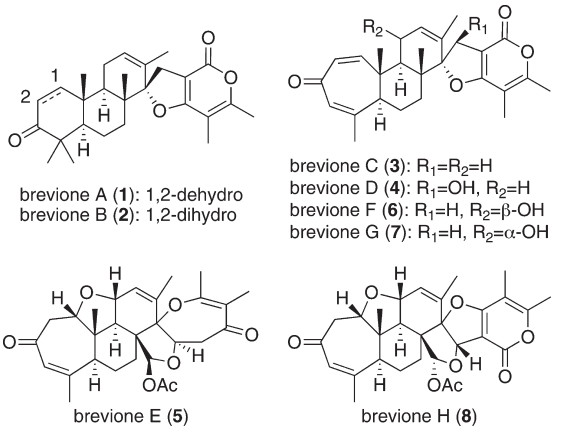
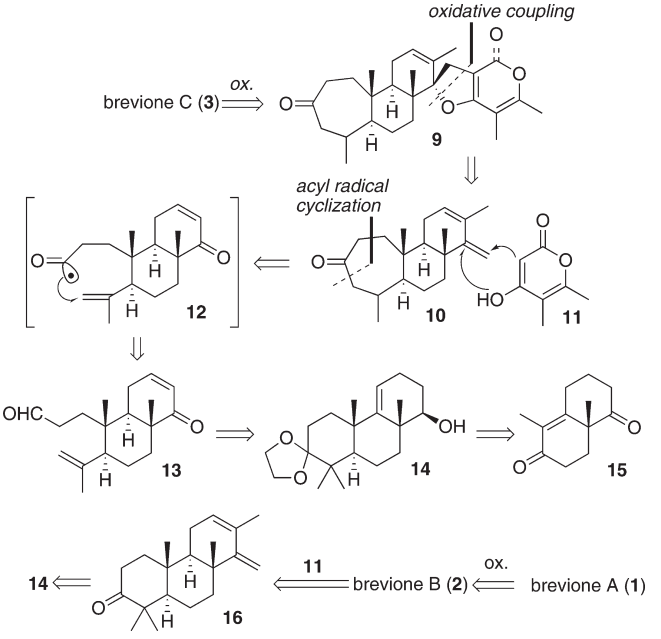


Figure 1. Structures of the breviones.

Scheme 1. Retrosynthetic Analysis



was thought that **14** could serve as the common intermediate; it would be converted to diene **16**, which would then be coupled

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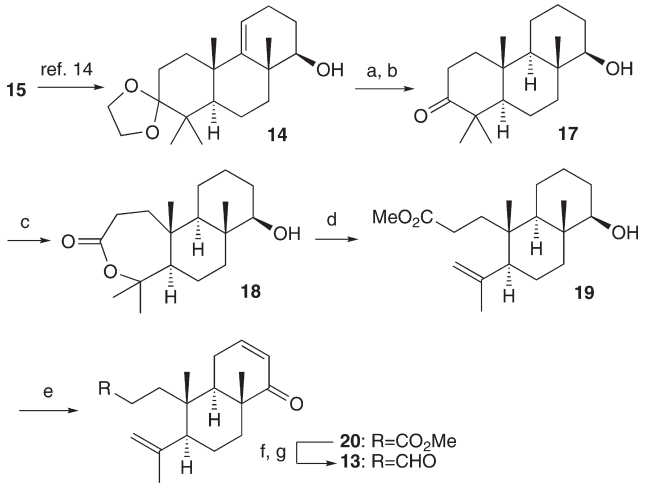
Scheme 2. Synthesis of Aldehyde 13[a]



[a] Reagents and conditions: (a) 2 M HCl, THF, reflux, 50 min. (b) Pd/C, AcOEt, rt, 57 h; 91% (two steps). (c) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 18 h, 95%. (d) *p*-TsOH·H_2O, MeOH, rt, 4 h, 98%. (e) IBX, DMSO, 85 °C, 12 h, 86%. (f) DIBAH, toluene, −78 °C, 10 min. (g) DMP, CH_2Cl_2, rt, 2 h; quant (two steps).

with **11** to produce **2**. Finally, **2** would be dehydrogenated to give **1**.

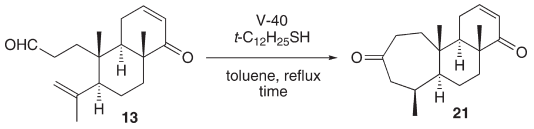
The Wieland−Miescher ketone derivative **15** (>99% ee) was converted to the optically pure tricyclic alcohol **14** via a four-step sequence.[14] Acidic hydrolysis followed by hydrogenation afforded keto alcohol **17**, which was subjected to Baeyer−Villiger oxidation to give lactone **18** (Scheme 2). The lactone was treated with *p*-toluenesulfonic acid in MeOH[15] to produce alkenyl ester **19** in excellent yield. IBX oxidation gave enone **20**, which was converted to aldehyde **13** by sequential treatment with DIBAH and Dess−Martin periodinane.

With the acyl radical precursor in hand, we next investigated the 7-endo-trig cyclization[16] used to assemble the A ring of **21**, a seven-membered cyclic ketone. Treatment of aldehyde **13** with *tert*-dodecanethiol (*t*-$C_{12}H_{25}SH$) (0.5 equiv) and the radical initiator 1,1′-azobis(cyclohexane-1-carbonitrile) (V-40) (0.5 equiv) in refluxing toluene[17] produced **21** in 47% yield as a single product through the 7-endo-trig cyclization of the acyl radical intermediate **12**. The configuration of the newly generated tertiary stereogenic center in **21** was deduced to be *S* on the basis of the previous results.[11] Encouraged by these findings, we next proceeded to examine more closely the reaction conditions (Table 1). The best result was obtained when **13** was treated with *t*-$C_{12}H_{25}SH$ (3 equiv) and V-40 (3 equiv) in refluxing toluene for 2 h, which afforded **21** in 82% yield (entry 6). It should be emphasized that the reaction proceeded selectively even in the presence of an enone moiety.

After protection of the A-ring ketone in **21**, an iodide was introduced at the α-carbon of the enone[18] to give **22**, which was methylated by Stille coupling to provide **23** (Scheme 3). Attempts at direct methylenation of **23** using a variety of methods failed to afford the carbonyl-protected analogue of **10.** Therefore, **23** was treated with methyllithium, and the resulting tertiary alcohol **24** was dehydrated under thermal conditions to produce in good yield tricyclic diene **10** containing an exocyclic olefin (the diterpene segment).

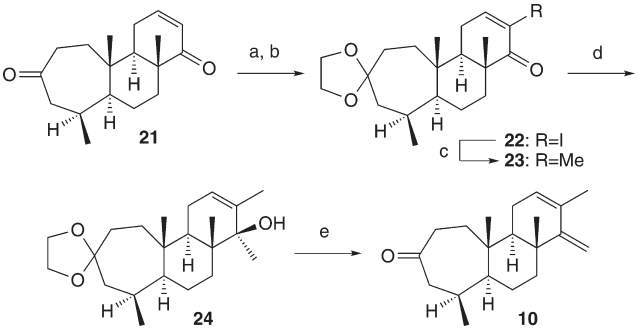
Next we examined the synthesis of α-pyrone **11**, a compound known in the literature.[8] However, the literature procedure

Table 1. Acyl Radical Cyclization of 13



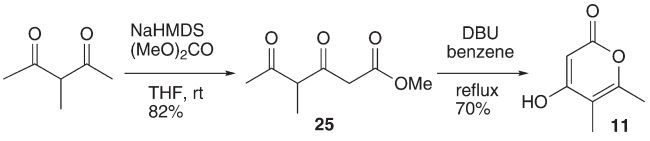
entry	equiv of V-40	equiv of *t*-$C_{12}H_{25}SH$	time (h)	yield (%)
1	0.5	0.5	12	47
2	1	1	12	59
3	1.5	1.5	3	70
4	3	15	2	72
5	3	3	2	82

Scheme 3. Synthesis of the Diterpene Segment 10[a]



[a] Reagents and conditions: (a) Ethylene glycol, PPTS, benzene, reflux, 4 h, 98%. (b) I_2, $TMSN_3$, pyridine, rt, 12 h. (c) Me_4Sn, CuI, Ph_3As, $Pd_2(dba)_3$·$CHCl_3$, NMP, 80 °C, 3 h; 87% (two steps). (d) MeLi, THF, −78 °C, 1 h, 98%, (e) Ac_2O, 270 °C then H_3O^+, 80%.

Scheme 4. Synthesis of α-Pyrone 11



resulted in low yields of the product and was not reproducible. Consequently, we set out to develop a more general and efficient method. After several attempts, we found that sequential carbomethoxylation[19] of the dianion generated from 3-methylpentane-2,4-dione and cyclization of the resulting diketo ester **25** using DBU in refluxing benzene efficiently provided **11** (Scheme 4).[20]

Having made the two segments, we next examined the key oxidative coupling. The results are shown in Table 2. Treatment of tricyclic diene **10** with α-pyrone **11** using ceric ammonium nitrate (CAN)[7f] in CH_3CN at 0 °C gave the desired pentacyclic compound **9** in 65% yield as a separable 10:1 diastereomeric mixture. X-ray crystallographic analysis[21] of the major diastereoisomer revealed it to be the desired pentacycle, as shown in Figure 2. To improve the chemical yield, we examined many oxidizing agents [e.g., $Mn(OAc)_3$ (entry 2),[7a] $Mn(pic)_3$,[7b] Ag_2CO_3/Celite,[7e] etc.] as well as the reaction conditions and found that using a 2:1 mixture of CAN and $Cu(OAc)_2$[22] resulted in a dramatic improvement in the yield to 84% with the same diastereoselectivity of 10:1. As for the diastereoselectivity,[23] the

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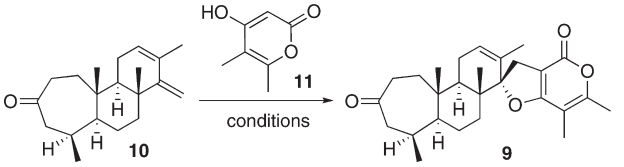
Table 2. Oxidative Coupling of 10 with 11



entry	conditions	time (h)	yield (%)[a]	dr[b]
1	CAN, CH_3CN, 0 °C	1.2	65	10:1
2	$Mn(OAc)_3 \cdot 2H_2O$, benzene, reflux	21	dec	—
3	CAN, $Cu(OAc)_2$, CH_3CN, 0 °C	1.3	84	10:1
4	CAN, [bdmin]BF_4/CH_2Cl_2 (1:5), 0 °C∼rt	4.8	45	>20:1
5	CAN, [bmin]BF_4/CH_2Cl_2 (1:5), 0 °C∼rt	3	78	>20:1
6	CAN, $Cu(OAc)_2$ [bmin]BF_4/CH_2Cl_2 (1:5), 0 °C∼rt	4	81	>20:1

[a] Isolated yields. [b] Determined by ^1H NMR analysis of the crude product.

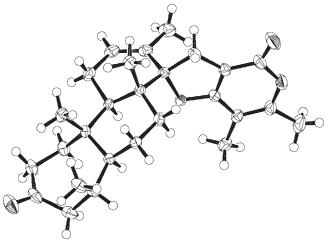
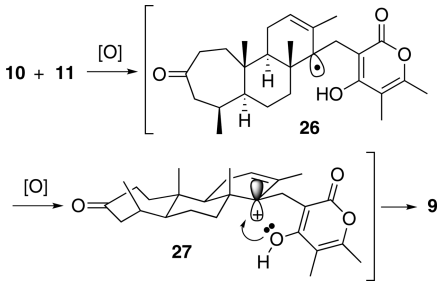


Figure 2. ORTEP drawing of **9**.

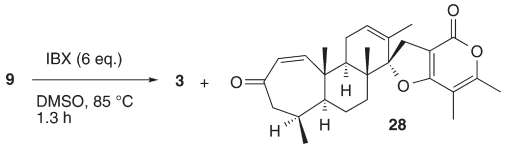
Scheme 5. Presumed Mechanism



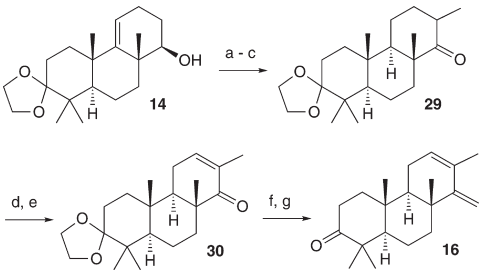
addition of an ionic liquid, [bdmin]BF_4, as the solvent elicited a dramatic improvement in the annulation efficiency, affording **9** exclusively, but the yield remained at 45% (entry 4). However, excellent results (exclusive formation of **9** in 81% yield) were obtained when the reaction was conducted with CAN/$Cu(OAc)_2$ in a 1:5 mixture of the ionic liquid [bmin]BF_4 and CH_2Cl_2[7i] (entry 6). Comparable diastereoselectivities and yields were obtained even using only CAN (entry 5).

The diastereoselective formation of the CD spiro ring can be explained by considering the conformation of the intermediate carbocation **27** that would be generated from the initially formed allyl radical intermediate **26** by oxidation (Scheme 5). The hydroxyl oxygen atom of the α-pyrone in **27** would attack from the sterically less hindered bottom face of the molecule to give **9** with the *S* configuration at the spiro stereogenic center preferentially.

Scheme 6. Total Synthesis of Brevione C (3)

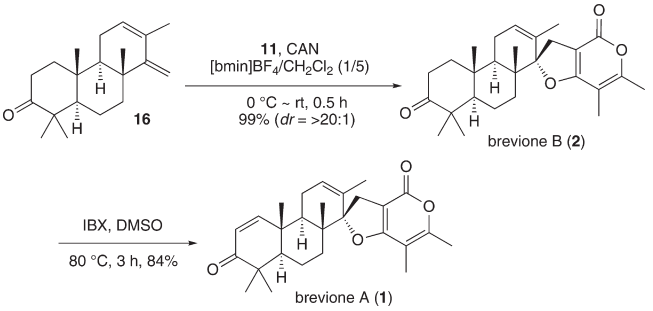


Scheme 7. Synthesis of Diene 16[a]



[a] Reagents and conditions: (a) H_2, Pd/C, EtOH, rt, 71 h, 95%. (b) Dess−Martin periodinane, CH_2Cl_2, rt, 30 min, 96%, (c) LDA, MeI, HMPA, THF, 0 °C, 2 h, 91%, (d) LDA, TMSCl, THF, −20 to −10 °C, 2 h, 98%. (e) $Pd(OAc)_2$, O_2, DMSO, 80 °C, 15 h, 75%, (f) MeLi, THF, −78 °C, 1 h, 96%, (g) Ac_2O, 270 °C, sealed tube, then H_3O^+; 86% (two steps).

Scheme 8. Total Synthesis of Breviones A (1) and B (2)



The pentacyclic ketone **9** thus prepared was treated with IBX[24] in DMSO at 80 °C for 1.3 h to provide brevione C (**3**) along with enone **28** in 44 and 54% yield, respectively (Scheme 6).[25] The semioxidized enone **28** was converted to **3** in 37% yield by subsequent treatment with IBX. The spectral properties and optical rotation of the synthetic material were identical with those of natural brevione C.[1b]

The syntheses of the breviones A (**1**) and B (**2**) started from optically pure alcohol **14**, which was used for the synthesis of brevione C. Sequential hydrogenation, Dess−Martin oxidation, and methylation furnished ketone **29** (Scheme 7). Attempted IBX oxidation gave unsatisfactory results, so **29** was converted to the silyl enol ether, which was then exposed to oxidation conditions using $Pd(OAc)_2$ and O_2 in DMSO[26] at 80 °C to obtain enone **30**.[5b,c] The enone was likewise transformed to the 1,3-diene **16** in two steps.

Oxidative coupling of diene **16** and α-pyrone **11** with CAN and $Cu(OAc)_2$ in CH_3CN at 0 °C for 2.5 h gave a mixture of brevione B (**2**) and its diastereoisomer in a 10:1 ratio in 96% yield (Scheme 8). When the reaction was conducted with CAN in a 1:5 mixture of [bmin]BF_4/CH_2Cl_2 at 0 °C ∼ rt for 0.5 h,[27] **2** was

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obtained in 99% yield as a single product. The brevione B thus obtained was treated with IBX in DMSO to give brevione A (**1**) in 84% yield. The spectral properties and optical rotations of both compounds were identical to those for natural breviones A[1a] and B.[1b]

In summary, we have completed the first enantiocontrolled total synthesis of brevione C using a highly diastereoselective oxidative coupling of α-pyrone **11** with tricyclic diene **10**, which was readily prepared from an optically pure Wieland−Miescher ketone derivative via a regioselective 7-endo-trig mode of acyl radical cyclization as the key reaction step in a longest linear sequence of 14 steps with an overall yield of 17%. Using a similar strategy, we have completed efficient and enantiocontrolled total syntheses of breviones A and B, in 42% yield and nine steps and 50% yield and eight steps, respectively, starting from a compound known in the literature, **14**,[13] which is an intermediate in the synthesis of brevione C. The synthetic route developed here is general and efficient and could also be applied to the syntheses of other breviones with more complicated structures and interesting biological profiles.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) CCDC 807997 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(22) One example of the use of a CAN/$Cu(OAc)_2$ mixture has been reported in which an intramolecular cyclization of an alkenyl diester provided a bicyclic lactone in a reasonable yield of 58.3%. Without $Cu(OAc)_2$, the bicycle was obtained in only 19.8% yield along with a single cyclized nitronate (22.5%). See: Baciocchi, E.; Paolobelli, A. B.; Ruzziconi, R. *Tetrahedron* **1992**, *48*, 4617. There have been no reports of the application of mixed oxidizing agents for intermolecular coupling.

(23) Interestingly, when the reaction was conducted with $Fe(phen)_3(PF_6)_3$ as the oxidizing agent (see: Wong, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 5593) in acetonitrile at room temperature for 0.3 h, it provided **9** as a single product in 36% yield.

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(27) The reaction with CAN/$Cu(OAc)_2$ in a 1:5 [bmin]BF_4/CH_2Cl_2 mixture at 0 °C ∼ rt for 0.3 h produced **2** in 85% yield with a lower diastereoselectivity of 13:1.