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Asymmetric Synthesis of (−)-Brevipolide H through Cyclopropanation of the α,β-Unsaturated Ketone

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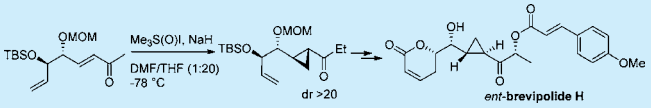
Supporting Information

ABSTRACT: Brevipolides are 5,6-dihydro-γ-pyrone derivatives, first reported in 2004 as the inhibitors of the chemokine receptor CCR5 and exhibiting cytotoxicity against cancer cells. Starting from the C_2 symmetric diene-diol **2**, *ent*-brevipolide H was synthesized for the first time in 11 steps. The *anti*-addition of the sulfur ylide to the α,β-unsaturated enones was developed to give the key cyclopropane moiety. The synthetic (−)-brevipolide H showed an IC_{50} value of 7.7 μM against PC-3 cells.



Brevipolides are bioactive, natural products, recently isolated from the tropical plants *Hyptis brevipes* and *Lippia alva*.[1,2] These compounds show moderate cytotoxicity against a variety of tumor cell lines (ED_{50} < 10 μM)[2,3] and were identified as inhibitors of the chemokine receptor CCR5. Therefore, they are potential agents for treating human immunodeficiency virus (HIV).[1,4] The framework of the brevipolides is a polyoxygenated 6-heptyl-5,6-dihydro-2-pyrone, bearing a cyclopropane moiety and a mono- or dioxygenated cinnamate group (Figure 1).[5] The stereochemistry of the

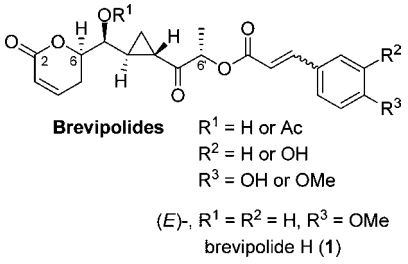
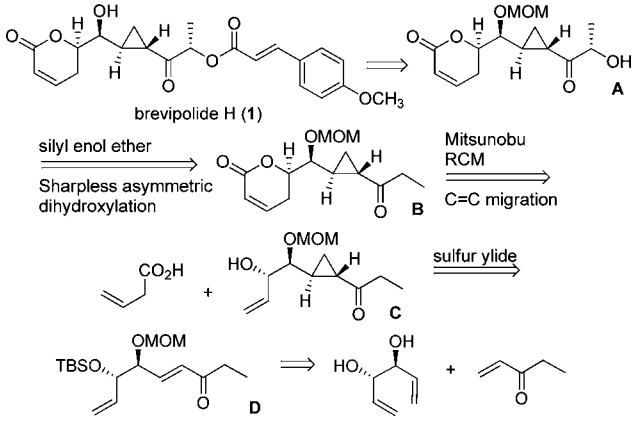


Figure 1. General structure of brebipolides and **1**.

reported brevipolides was initially established by NMR, CD spectroscopy, and Mosher ester formation except for the configuration of C-6′, which was found to undergo epimerization rapidly during the hydrolysis of the cinnamate ester.[2] Later, this stereocenter was determined by X-ray crystallography of the hydrogenated brevipolide derivative.[3] It is interesting to note that the stereocenters are conserved for all the known brevipolides. The newly discovered, interesting structure of the brevipolides and the need for further biological investigations prompted us to conduct synthetic studies. To our knowledge, the total synthesis of the brevipolides has not been reported.[6]

Scheme 1 outlines our approach to prepare brevipolides, as shown in the retrosynthetic analysis of brevipolide H. The

Scheme 1. Retrosynthetic Analysis of Brevipolide H



disconnection of the 4-methoxycinnamic ester would lead to the synthesis of the 12 carbon skeleton **A**. The α-hydroxyl group could be generated by Sharpless dihydroxylation of the silyl enol ether derived from the ketone **B**, and the 5,6-dihydro-2-pyrone could be prepared after the sequence of Mitsunobu esterification, ring-closing metathesis (RCM), and the base promoted olefin migration. The cyclopropane moiety could be derived from the reaction of sulfur ylides and the α,β-unsaturated ketone **D**, which could be assembled from the cross metatheseis (CM) between ethyl vinyl ketone and the C_2 symmetrical diene-diol.

The readily available (3*R*,4*R*)-1,5-hexadiene-3,4-diol (**2**)[7] was used as the starting material and protected as silyl ether **3** (Scheme 2).[8] We were glad to find that the addition of CuI as a cocatalyst, developed by Lipshutz's group, facilitated the CM between **3** and ethyl vinyl ketone in diethyl ether.[9] The

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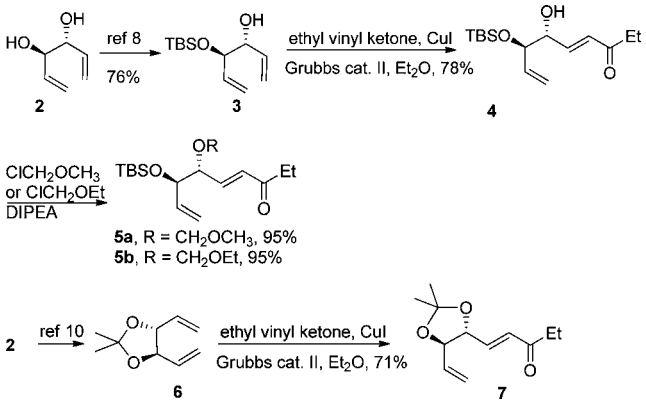
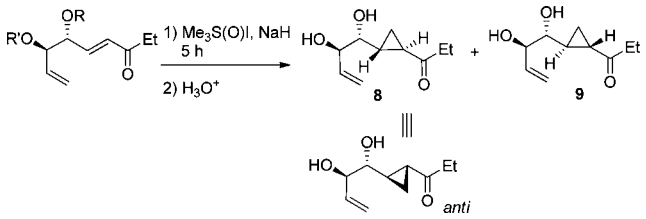
Scheme 2. Synthesis of α,β-Unsaturated Enones



remaining hydroxyl group was then protected as methoxymethyl (MOM) or ethoxymethyl ether to give the α,β-unsaturated enones **5a** and **5b**, respectively. The acetonide protected enone **7** was also prepared from the corresponding CM using the acetonide protected diene-diol **6**.[10] Our studies for the cyclopropanation of these enones **5a**, **5b**, and **7** using methylenedimethylsulfoxonium[11] are summarized in Table 1.

Table 1. Cyclopropanation of α,β-Unsaturated Enones



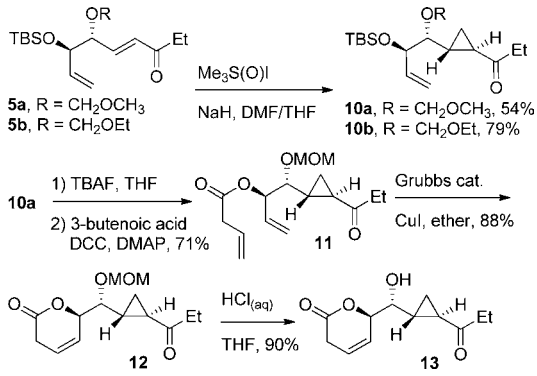
entry	enone	T (°C)	solvent	**8**:**9**[a]	yield (%)[b]
1	**5a**	25	DMF	5:1	54
2	**5a**	−10	DMF	6.3:1	42
3	**5b**	25	DMF	3.7:1	52
4	**5b**	0	DMF/THF[c]	6.3:1	56
5	**5b**	−30	DMF/THF[d]	17:1	77
6	**5b**	−78	DMF/THF[d]	>20:1	79
7	**5b**	25	THF	–	trace
8	**7**	25	DMF	1:1.9	59
9	**7**	0	DMF	1:2.4	71

[a]Determined by ^{1}H NMR of crude reaction mixtures. [b]Isolated yields. [c]DMF/THF = 1:6. [d]DMF/THF = 1:20.

We noticed that substrates **5** and **7** led to different stereochemical outcomes, which became evident after the removal of the protecting groups to the diastereomeric cyclopropane-diols **8** and **9** (entry 1 versus 8). The diastereomeric ratios derived from **5b** were further improved to >20:1 by lowering the reaction temperature and decreasing the portion of DMF in the DMF−THF mixed solvents (entries 3−6). This reaction became very sluggish when DMF was absent (entry 7). The cyclopropanation of the sulfur ylide to enones is known via Michael initiated ring closure to give the disubstituted, *trans*-cyclopropane;[12] however, the stereochemical outcome induced by the chiral enones was difficult to resolve. This issue was unequivocally determined when the X-ray crystallography of one derivative from **8** was obtained (*vide infra*).

Thus, the *tert*-butyldimethylsilyl group of cyclopropane **10a** was removed by TBAF and dicyclohexylcarbodiimide (DCC) was applied to link 3-butenoic acid to give the ester **11** (Scheme 3). The following RCM generated the 3,6-dihydro-

Scheme 3. Formation of the 5,6-Dihydro-2-pyrone



2*H*-pyran-2-one **12** and the removal of the MOM group under an acidic condition provided alcohol **13**, which allowed recrystallization and X-ray crystallography to determine the exact stereochemistry (Figure 2). However, we found that the 2-pyranone moiety of **12** was labile and decomposed during our attempts to afford the α-hydroxyl ketone.

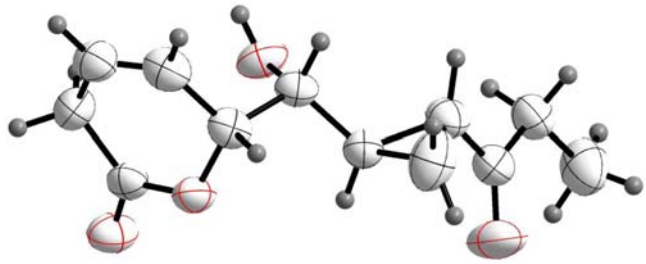


Figure 2. ORTEP of **13**.

The synthetic sequence was altered to introduce the α-hydroxyl group and incorporate the 4-methoxycinnamate first, rather than the formation of pyran-2-one (Scheme 4). The (*Z*)-silyl enol ether **14** was solely prepared by treating **10b** with lithium bis(trimethylsilyl)amide in HMPA/THF at −78 °C to generate the enolate, which was then trapped with *tert*-butyldimethylsilyl trifluoromethanesulfonate.[13,14] The following Sharpless asymmetric dihydroxylation, promoted by AD-mix β, gave the desired α-(*R*)-hydroxy-ketone **15** with moderate diastereoselectivity (dr = 2).[15,16] The formation of ester **16** was assisted by *N*,*N*′-diisopropylcarbodiimide and DMAP. The deprotection of the TBS group and the following Mitsunobu reaction went smoothly to give **17**, which contained all the stereochemical centers for the brevipolides but in the mirror image of the natural form. Then, the sequence of RCM and the DBU promoted olefin migration/conjugation giving the 2-pyanone **19**, where the two diastereomers generated in α-hydroxylation were separated by column chromatography. The deprotection of the ethoxymethyl ether provided the (−)-*ent*-brevipolide H. The spectroscopic data of **20** were consistent with the reported values except for the opposite optical rotation.[3] Preliminary assay of **20** against the cell proliferation of the human hormone-refractory prostate cancer cell line (PC-

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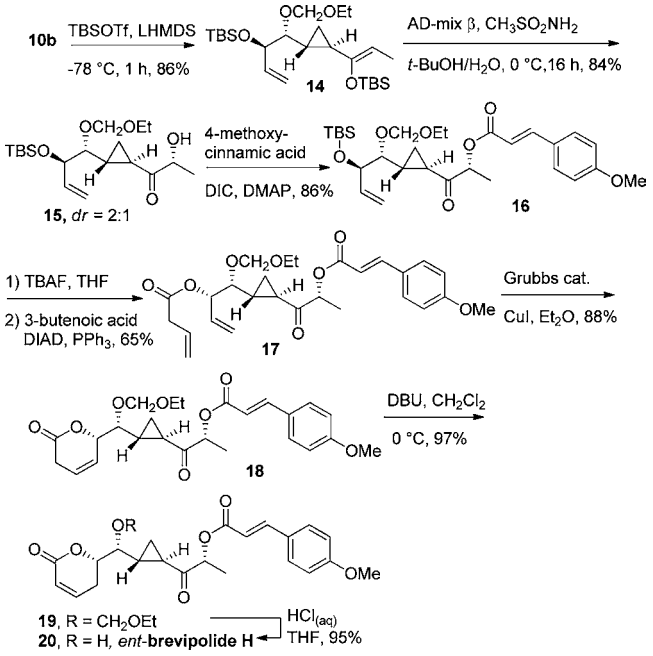
Scheme 4. Synthesis of *ent*-Brevipolide H



3) showed better activity (IC_{50} 7.7 μM) than the natural brevipolide H.

The X-ray crystallographic analysis of **13** and the spectroscopic agreement between the natural and synthetic brevipolide H clearly indicated the *anti*-addition of methylene-dimethylsulfoxonium to enone **5**. The trajectory for the ylide to *cyclic*, α,β-unsaturated ketones is known to go through the less hindered face of the conjugated systems, and good diastereoselectivities are often observed.[17] However, the corresponding reactions using *acyclic* enones or esters are less studied and contradictory results have been reported.[18,19] Here, we showed that the diastereoselectivity for the sulfoxide ylide addition is influenced by the protective groups, and the *anti*-addition with a good diastereomeric ratio was achieved for the first time for the acyclic substrate **5b**. The proposed model to account for the *anti*-addition is shown in Figure 3, where the OMOM

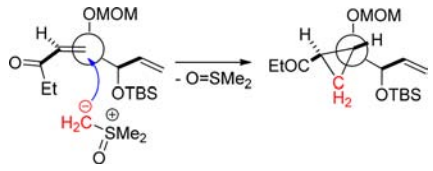


Figure 3. Proposed model for the addition of the sulfur ylide to **5a**.

group is perpendicular to the conjugated olefin to maximize the overlap between the C−O σ-bond and π^*-orbital of the enone.[5f] Thus, decreasing the solvent polarity should give better selectivity, which agrees with our experimental observations. On the other hand, the *syn*-addition, slightly preferred by the acetonide protected enone **7**, is consistent with Ma's and Gurjars' studies using the α,β-unsaturated carbonyl compounds derived from glyceraldehyde.[12b,19,20]

In summary, (−)-brevipolide H was synthesized for the first time in 11 steps with a 10% yield. The *anti*, conjugated addition of the sulfur ylide to the α,β-unsaturated enone provided the key cyclopropane moiety with the required stereochemistry. Since the procedures to prepare (*S,S*)-diene-diol **2** are also known[21] and all 10 reported brevipolides are consistent in their chirality centers, this synthesis should be applicable to prepare the natural (+)-brevipolide H and other members in this family.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data of compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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