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Toward the synthesis of brevipolide H

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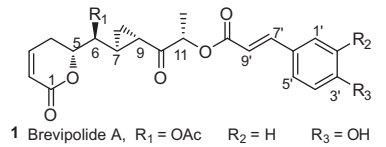
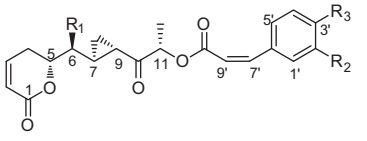
ABSTRACT

A linear diastereoselective synthesis of C_1–C_{12} fragment of brevipolide H is described. The key reactions include Jørgensen's asymmetric epoxidation, palladium-catalyzed regioselective opening of α,β-unsaturated γ,δ-epoxide, Charette's modified Simmons–Smith cyclopropanation, *anti*-selective reduction of cyclopropyl containing α,β-unsaturated ketone, Brown allylation, and ring-closing metathesis reaction.

In 2009, Douglas Kinghorn,[1] isolated brevipolides A–F from the entire plant of *Hyptis brevipes*, an invasive plant species which belongs to the genus *Hyptis* (Lamiaceae), distributed mainly in the tropical region around the world. Recently, Miranda[2] and co-workers also isolated related compounds brevipolides A–J (Fig. 1) from the same species and the absolute configuration was assigned as 5*R*, 6*S*, 7*S*, 9*S*, and 11*S* which was confirmed by the combination of X-ray diffraction analysis, chiroptical measurements, chemical correlations, and Mosher's ester analysis. The structural features of the brevipolides A–J family contain the cyclopropyl group attached to β-substituted cinnamylcarboxyketo unit on one side and on the other side a hydroxymethine containing an unsaturated δ-lactone. Brevipolides (A–J) showed excellent biological activity which includes inhibitory activity against bacterial, fungal growth, DNA intercalation activity, cytotoxicity against HT-29 and the MCF-7 human breast cancer cell line. In particular, compounds **7**, **8**, and **9** were isolated from Peruvian plant *Lippia alva* sp. (Verbenaceae),[3] which was identified as an inhibitory of chemokine receptor 5 (IC_{50} values CCR5, IC_{50} = 5.5, 6.0 and 7.2 μg mL^{-1}) and it leads for inhibiting HIV infection. Additionally, Compound **7** was also found to be active in an enzyme-based ELISA NF-κB assay.



1 Brevipolide A, R_1 = OAc R_2 = H R_3 = OH
2 Brevipolide C, R_1 = OH R_2 = OH R_3 = OH
3 Brevipolide E, R_1 = OAc R_2 = OH R_3 = OH
7 Brevipolide G, R_1 = OH R_2 = H R_3 = OH
8 Brevipolide H, R_1 = OH R_2 = H R_3 = OMe
10 Brevipolide J, R_1 = OH R_2 = OH R_3 = OMe



4 Brevipolide B, R_1 = OAc R_2 = H R_3 = OH
5 Brevipolide D, R_1 = OH R_2 = OH R_3 = OH
6 Brevipolide F, R_1 = OAc R_2 = H R_3 = OH
9 Brevipolide I, R_1 = OH R_2 = H R_3 = OMe

Figure 1. Structure of brevipolides A–J.

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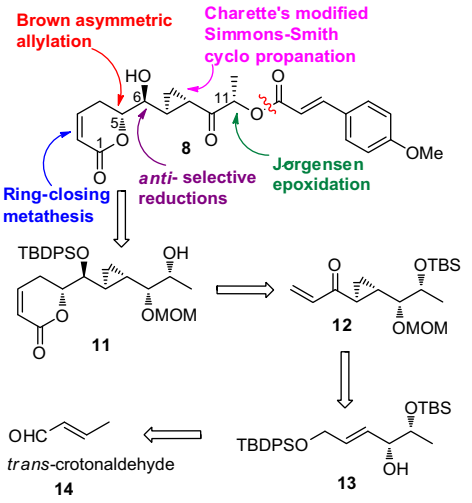
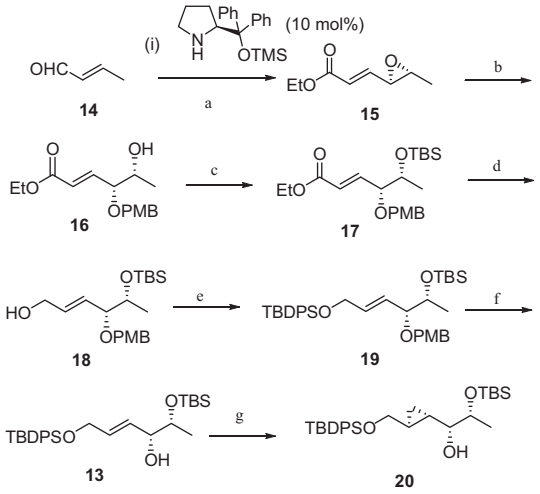


Scheme 1. Retrosynthesis of brevipolide H (**8**).



Scheme 2. Reagents and conditions: (a) (i), H_2O_2 (1.3 equiv), CH_2Cl_2, rt, 24 h, PPh_3 = $CHCO_2Et$, CH_2Cl_2, 2 h, 78% (over two steps); (b) PMBOH, $Pd(PPh_3)_4$, $(PhO)_3B$, THF, 0 °C to rt, 3 h, 96%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 30 min, 95%; (d) DIBAL-H, CH_2Cl_2, −78 °C to 0 °C, 2 h, 95%; (e) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 1 h, 98%; (f) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C to rt, 2 h, 86%; (g) Et_2Zn, CH_2I_2, CH_2Cl_2, −78 °C to 0 °C, 4 h, 97%.

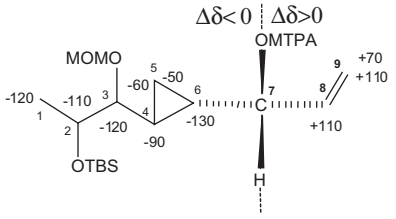


Figure 2. $(\Delta\delta = \delta_S - \delta_R) \times 10^3$ for (*S*) and (*R*)-MTPA ester of compound **23**.

The attractive structural features and the versatile biological profiles showing significant activity prompted us to initiate the synthesis of brevipolide H (**8**).

As a part of our work, the synthesis of novel biologically active compounds,[4] we have ventured into the total synthesis of pharmacological active cyclopropane containing natural products.

Very recently, Hou and co-workers reported the total synthesis of *ent*-brevipolide H and Kumaraswamy et al. reported the studies toward diastereoselective synthesis of derivative of 11′-*epi*-brevipolide H.[5] Herein, we report a diastereoselective synthesis of C_1–C_{12} fragment of brevipolide H. According to our retrosynthetic analysis of brevipolide H (**8**) as illustrated in Scheme 1, the lactone **11** could be achieved through ring-closing metathesis reaction of corresponding diolefinic ester. Fragment **12** could be obtained by Charette's modified Simmons–Smith cyclopropanation from olefin fragment **13**, which in turn could be derived from commercially available achiral starting material *trans*-crotonaldehyde **14**.

The synthesis of lactone fragment **11** began with commercially available *trans*-crotonaldehyde **14**. Following Jørgensen's chiral epoxidation[6] protocol aldehyde **14** was enantioselectively epoxidized by using (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether as the chiral catalyst to afford chiral epoxide followed by two carbon homologation using stable Wittig ylide to form α,β-unsaturated epoxy ester **15** in 78% yield over two steps with dr 95:5 (by ^{1}H NMR analysis) and with 93:7 enantiomeric ratio (by HPLC). Palladium(0) catalyzed regioselective opening of the resulting epoxide compound **15** by *p*-methoxy benzyl alcohol afforded secondary homoallylic alcohol **16** in 96% yield.[7] The secondary alcohol **16** was protected as its TBS ether using *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine as base in CH_2Cl_2 to obtain the compound **17** in 95% yield. The α,β-unsaturated ester **17** was converted to primary alcohol **18** using diisobutylaluminium hydride in CH_2Cl_2 at −78 °C in 95% yield. The protection of primary alcohol **18** with *tert*-butylchlorodiphenylsilane resulted in TBDPS protected product **19** in 98% yield. At this stage, we performed Simmons–Smith cyclopropanation reaction but the reaction was unsuccessful. PMB-ether group in compound **19** was oxidatively cleaved by using DDQ in CH_2Cl_2: pH 7 buffer solution (9:1) to obtain secondary alcohol **13** in 86% yield.[8] Following Charette's modified[9] Simmons–Smith cyclopropanation, treatment of allylic alcohol **13** with Et_2Zn and CH_2I_2 in CH_2Cl_2 at −78 °C afforded cyclopropyl alcohol **20** as a major diastereomer (de. 99% by HPLC) in 97% yield (Scheme 2).

Secondary alcohol **20** was protected as its MOM ether using MOM-Cl and DIPEA as a base to furnish compound **21** in 96% yield. Selective deprotection of 1° TBDPS ether in the presence of 2° TBS ether with NH_4F[10] in methanol at 0 °C afforded primary alcohol **22** in 92% yield, which was then oxidized to aldehyde using Dess–Martin periodinane[11] in CH_2Cl_2 with 95% yield. The resulting aldehyde was then subjected to vinyl magnesium bromide in THF at −78 °C to afford the diastereomers **23** and **24** (dr 2:3) in 90% yield, which was easily separated by column chromatography.

Stereochemical assignment at the newly created hydroxy bearing center was confirmed by the modified Mosher's method.[12] Thus, esterification of the isomer **23** with both (*S*)- and (*R*)-methoxy-α (trifluoromethyl)phenylacetic acid (MTPA) showed positive chemical shift difference $[(\Delta\delta = \delta_S - \delta_R) \times 10^3]$ for protons on C_8 through C_9 (Fig. 2), while protons on C_1 through C_6 showed negative chemical shift differences, which is the indicative of C_7 bearing an *R*-configuration. Therefore, the absolute configuration of C_7 was assigned as *R*.

Inversion of C_7 center of isomer **24** under Mitsunobu conditions[13] gave desired isomer **23** in low yield. To improve the yield and selectivity of required isomer, the two diastereomers were treated with Dess–Martin periodinane[11] in CH_2Cl_2 to afford the α,β-unsaturated ketone **12** in 93% yield (Scheme 3). Diastereoselective reduction of cyclopropyl enone **12** was screened under various reducing agents and conditions (depicted in Table 1). Among the selected reagents, lithium tri-*tert*-butoxyaluminumhydride[14] in ethanol −78 °C gave the desired *anti* alcohol **23** in 94% yield as a single isomer.