Tetrahedron Letters 56 (2015) 1041–1044

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Toward the synthesis of brevipolide H

Debendra K. Mohapatra *, Suresh Kanikarapu, P. Ramesh Naidu, Jhillu S. Yadav

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 5000 007, India

ARTICLE INFO

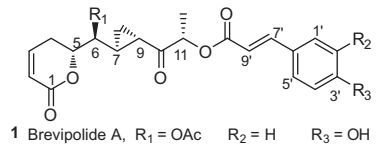
Article history:
Received 18 November 2014
Revised 24 December 2014
Accepted 26 December 2014
Available online 3 January 2015

Keywords:
Jørgensen's asymmetric epoxidation
Palladium-catalyzed regioselective opening of epoxide
Charette's modified Simmons–Smith cyclopropanation
anti-Selective reduction
Brown allylation
Ring-closing metathesis

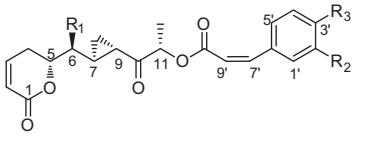
ABSTRACT

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.

* Corresponding author. Tel.: +91 40 27193128; fax: +91 40 27160512.
E-mail address: mohapatra@iict.res.in (D.K. Mohapatra).

http://dx.doi.org/10.1016/j.tetlet.2014.12.125
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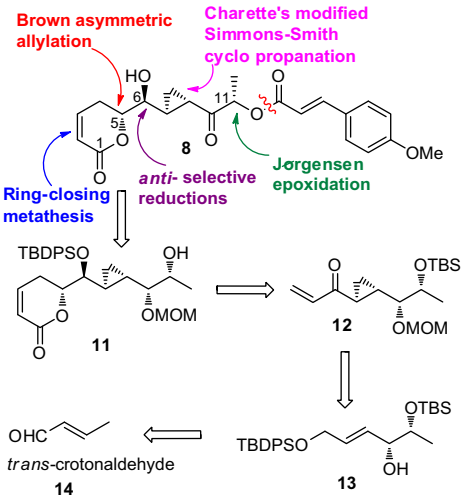
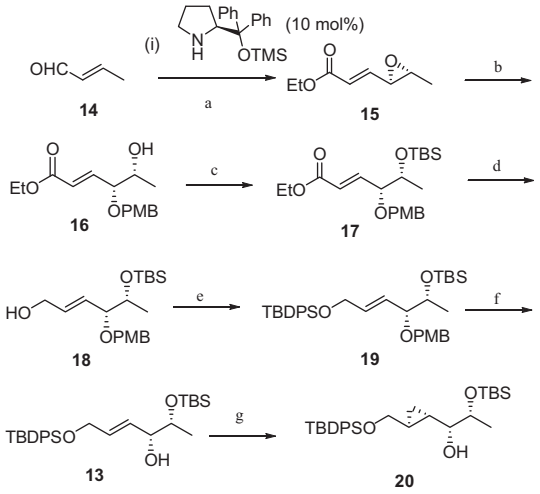


Scheme 1. Retrosynthesis of brevipolide H (**8**).



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%.

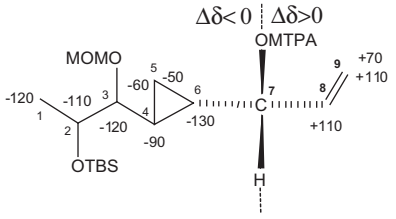


Figure 2. $(\Delta\delta = \delta_S - \delta_R) \times 10^3$ for (*S*) and (*R*)-MTPA ester of compound **23**.

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.

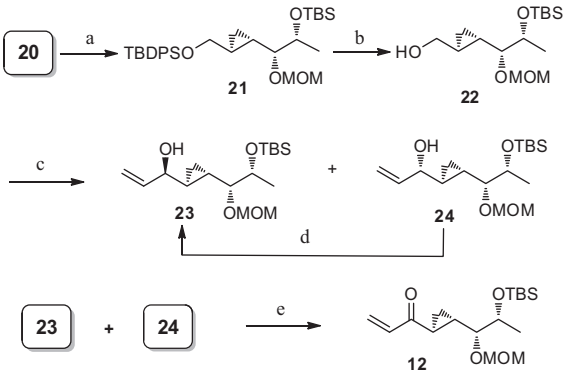
Very recently, Hou and co-workers reported the total synthesis of *ent*-brevipolide H and Kumaraswamy et al. reported the studies toward diastereoselective synthesis of derivative of 11′-*epi*-brevipolide H.[5] Herein, we report a diastereoselective synthesis of C_1–C_{12} fragment of brevipolide H. 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.

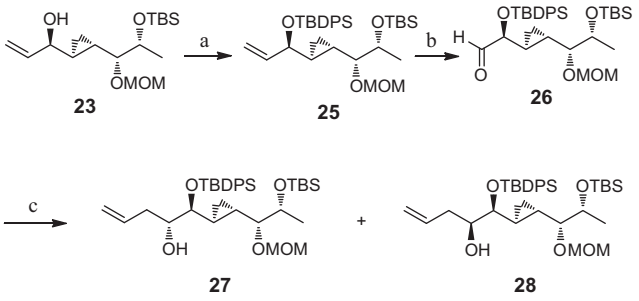


Scheme 3. Reagents and conditions: (a) DIPEA, MOMCl, CH_2Cl_2, 0 °C to rt, 12 h, 96% (b) NH_4F, MeOH, 0 °C to rt, 24 h, 92%; (c) (i) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 2 h, 95%, (ii) vinylmagnesiumbromide, THF, −78 °C to rt, 2 h, 90% (d) (i) TPP, DIAD, AcOH, THF, 0 °C to rt, 12 h, (ii) K_2CO_3, MeOH, rt, 3 h, 50% over two steps; (e) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h, 93%.

Table 1
Hydride reduction of cyclopropyl enone **12**

Sr. no.	Conditions	**23**/**24**[a]	Yield (%)
1	(*R*)-CBS, THF, −25 °C, 12 h	85:15	74
2	DIBAL-H, ether, −78 °C, 1 h	62:38	72
3	$NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 1 h	90:10	87
4	$Zn(BH_4)_2$, ether, −78 °C, 6 h	94:06	82
5	Li(O*t*-Bu_3)AlH, ethanol, −78 °C, 1 h	100:0	94

[a] As per isolated yield.



Scheme 4. Synthesis of homo allylic alcohols **27** and **28**. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 3 h, 92%; (b) OsO_4, 2,6-lutidine, $NaIO_4$, dioxane, H_2O, rt, 4 h, 76%; (c) allyl bromide, Zn dust, aq NH_4Cl, −20 °C, 2 h, 76%.

The allylic alcohol **23** was protected as its TBDPS ether **25** using TBDPSCl and imidazole as base in CH_2Cl_2 at 0 °C in 92% yield. At this stage, Jin's one step dihydroxylation–oxidation protocol[15] followed by Barbier's allylation[16] using allyl bromide in the presence of zinc and aq NH_4Cl in THF at −20 °C furnished diastereomeric homoallylic alcohols **27** and **28** (dr = 2:3) in 76% yield (Scheme 4).

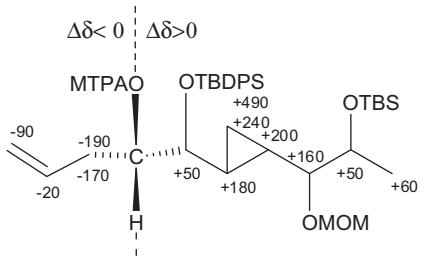
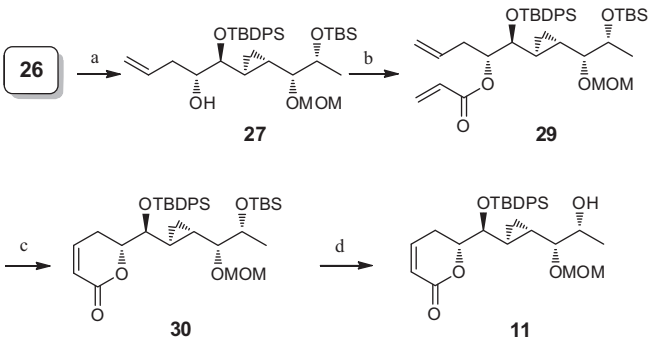


Figure 3. $(\Delta\delta = \delta_S - \delta_R) \times 10^3$ for (*S*) and (*R*)-MTPA ester of compound **28**.



Scheme 5. Synthesis of lactone fragment **11**. Reagents and conditions: (a) (+)-$(Ipc)_2BCl$, allylmagnesium bromide, Et_2O, −90 °C, 4 h, 81%; (b) acryloyl chloride, Et_3N, cat. DMAP, 0 °C to rt, 0 °C, 2 h, 85%; (c) Grubbs 1st generation catalyst, CH_2Cl_2, 5 h, 88%; (d) PPTS, MeOH, 50 °C, 4 h, 81%.

After separation of both the isomers, stereochemistry of the hydroxy center in the major isomer **28** was assigned by modified Mosher's ester method[12] and was found to be unrequired (Fig. 3).

To obtain the required isomer **27** as a major product, Brown's protocol[17] proved useful here. Thus, an allylating reagent allyl-lB(Ipc)$_2$, prepared from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride), reacted with aldehyde **26** in anhydrous ether at −90 °C furnished the desired homo allylic alcohol **27** and **28** in 81% yield with high diastereoselectivity (85:15), in favor of the required isomer **27**. The alcohol **27** was acrylated with acrolyl chloride, Et_3N as base and catalytic amount of DMAP in CH_2Cl_2 at 0 °C to give the acrylated product **29** in 85% yield. Ring-closing metathesis of acryloyl ester **29** was achieved smoothly with 10 mol % of Grubbs 1st generation catalyst under refluxing conditions in CH_2Cl_2 for 5 h to furnish **30** in 88% yield.[18]

Selective desilylation of TBS ether in the presence of TBDPS ether using PPTS[19] in MeOH under refluxing conditions afforded fragment **11**[20] in 81% yield (Scheme 5). To achieve the complete synthesis of brevipolide H, we performed the standard Mitsunobu protocol conditions to couple *p*-methoxy cinnamic acid and alcohol **11**. Unfortunately, the reaction was unable to give the desired inverted product.[13]

In summary, a linear diastereoselective synthesis of C_1–C_{12} fragment of brevipolide H was synthesized in 18 steps with 12.5% overall yield, starting from commercially available *trans*-crotonaldehyde. Efforts to complete the total synthesis of brevipolide H are in progress and will be reported in due course.

Acknowledgments

The authors thank CSIR, New Delhi, India for financial support as part of XII Five Year plan programme under title ORIGIN (CSC-0108). K.S. and P.R.N. thank Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial assistance in the form of fellowships.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.125.

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20. *Spectral data of compound 11:* $[\alpha]_D^{25}$ +32 (*c* 0.3, $CHCl_3$); IR (KBr): 2927, 2855, 1726, 1464, 1385, 1254, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.78–7.73 (m, 4H), 7.49–7.35 (m, 6H), 6.96–6.90 (m, 1H), 6.01 (dd, J = 9.7, 2.5 Hz, 1H), 4.50 (d, J = 6.5 Hz, 1H), 4.46 (dt, J = 11.7, 2.8 Hz, 1H) 4.38 (d, J = 6.5 Hz, 1H), 3.42–3.33 (m, 2H), 3.33 (s, 3H), 2.96–2.86 (m, 1H), 2.76 (dd, J = 6.5, 4.1 Hz, 1H), 2.96–2.86 (m, 2H), 1.02 (s, 9H), 0.99–0.94 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.56–0.49 (m, 1H), 0.30–0.23 (m, 1H), 0.15–0.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 145.2, 136.0, 135.8, 130.0, 129.7, 127.8, 127.6, 121.0, 97.4, 83.8, 80.7, 76.9, 70.0, 55.6, 26.8, 23.6, 19.6, 18.6, 18.1, 16.4, 5.1; HRMS (ESI) *m*/*z*: calcd for $C_{30}H_{41}O_6Si$ $[M+H]^+$.525.2666; found: 525.2676.