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Stereoselective synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomin

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ABSTRACT

A stereoselective approach for the synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomin from L-ascorbic acid has been described. The key steps are highly stereoselective nucleophilic addition reaction on aldehyde **8** and also a single pot transformation of **15** to (+)-(1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomin. The later tandem reaction which involves the hydrogenation of double bond, debenzylation, MOM deprotection and bicyclic ketal formation was carried under Pd/C, H_2 followed by acid treatment.

The 6,8-dioxabicyclo[3.2.1]octane skeleton is a common structural subunit in the pheromones of a variety of bark beetle species. Brevicomin (7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane) **A** was the first of these bicyclic acetals identified from the frass of female western pine beetles.[1] In 1996. Francke et al.[2a] reported the isolation and identification of several new 6,8-dioxabicyclo[3.2.1]octane derivatives such as **B-G** and **1** (Fig. 1) as the components of the head-space volatiles obtained from the male mountain pine beetle, *Dendroctonus ponderosae*. They synthesized the enantiomers and/or racemates of the following compounds: (1*S*,5*R*,7*S*)-**B**, (1*R*,1′*R*,5′*R*,7′*R*)-**D**, (±)-**D**, (±)-**E**, (1*R*,2*R*,5*S*,7*R*)-**F**, (1*R*,2*R*,5*S*,7*S*)-**G** and (±)-**1**. Among these, compound **1** is less abundant and the absolute configuration of **1** was not determined at that time. However, comparative NMR studies showed that **1** could be *exo*-isomer with equatorial OH group in second position.[2a] In 1997, Mori and co-workers[2b] synthesized (1*R*,2*S*,5*S*,7*R*)-**1** employing Sharpless asymmetric dihydroxylation protocol and with this reference, the absolute configuration of **1** is determined as (1*R*,2*S*,5*S*,7*R*).

Brevicomins play a major role in the communication system of the bark beetle species. With the proven importance of single enantiomer compounds in the inhibition of pheromone response, there has been a sustained interest in the synthesis of these pheromones in their enantiomerically pure form.[5] As part of our ongoing research we undertook the synthesis of these hydroxy brevicomins and consequently reported the asymmetric synthesis of (1*R*,1′*R*,5′*R*,7′*R*)-**D** and (1*S*,1′*R*,5′*R*,7′*R*)-**E**[6] and chiron approach for the synthesis of (1*R*,2*R*,5*S*,7*R*)-**F**[7], (1*R*,2*R*,5*S*,7*S*)-**G**[8] and *ent*-**1**.[3a] Now herein we wish to report a highly stereoselective approach for the synthesis of **1**.

In earlier approaches, **1** has been prepared as a mixture of diastereomers utilizing the asymmetric dihydroxylation or the asymmetric aldol reaction and as a racemic mixture utilizing the *m*-CPBA epoxidation.[2,4] The other approaches which used chiral starting material were for the synthesis of unnatural antipode of **1** but not the natural isomer.[3] Therefore a straightforward synthesis for **1** is still to be accomplished. Nevertheless, it is interesting to note that the 2-hydroxy-*exo*-brevicomins have been converted to *exo*-brevicomin **A** by deoxygenation of its free hydroxyl group.[4,2c]

General features of our synthesis of (1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomin **1** are illustrated in the retrosynthetic format in Scheme 1. The key reaction of our synthesis is the tandem hydrogenation of double bond, deprotection of the protecting groups and bicyclic ketal formation of compound **2** to give **1**. Compound **2** can be obtained from alcohol **3** by appropriate protections, deprotections to obtain primary alcohol and then oxidation and Wittig reaction. Whereas, alcohol **3** can be synthesized from appropriately protected aldehyde **4** by stereoselective chelation-controlled nucleophilic addition of ethyl magnesium bromide. Compound **4** can be easily obtained from L-ascorbic acid **5** (Scheme 1).

The synthesis of **1** commenced from **6** which was readily obtained from L-ascorbic acid **5** by following the literature procedure.[9] The secondary hydroxy of **6** was protected as its MOM ether to give compound **7**. The ester functionality in compound **7** was reduced using DIBAL-H in CH_2Cl_2 at −78 °C for 3 h to yield aldehyde **8**. The crude aldehyde **8** on treatment with ethyl magnesium bromide in diethyl ether at −78 °C to rt overnight gave predominantly the *syn* isomer (*syn*/*anti* in 18:1 by ^{1}H NMR) (Scheme 2).

The stereoselectivity of the reaction can be explained by the chelation-controlled addition of the nucleophile as shown in the Figure 2.[10] The two oxygen atoms of methyl oxy methyl group chelated with MgBr and then the nucleophile attacked from less hindered side to give *syn* isomer as major product. These isomers could not be separated at this stage and proceeded further with the mixture.

The hydroxyl functionality in **9** was protected as its MOM ether using MOMCl and DIPEA to give compound **10**. The acetonide in **10** was deprotected selectively using PPTS in MeOH to give diol **11**. The primary hydroxyl in **11** was protected using TBDMSCl and

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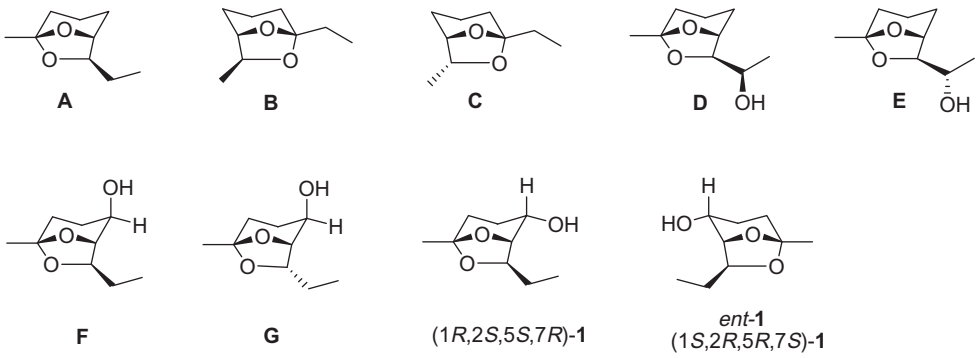
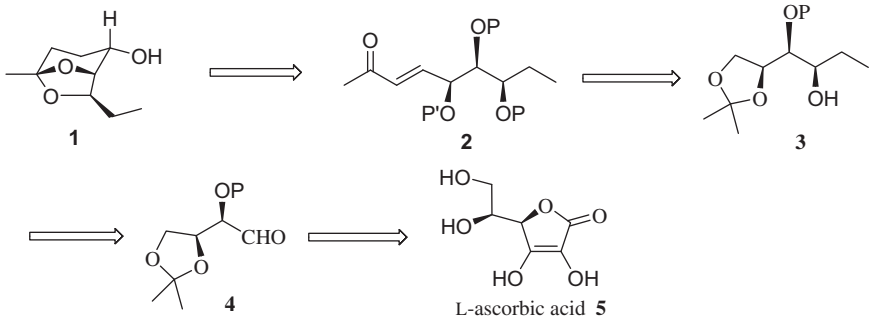
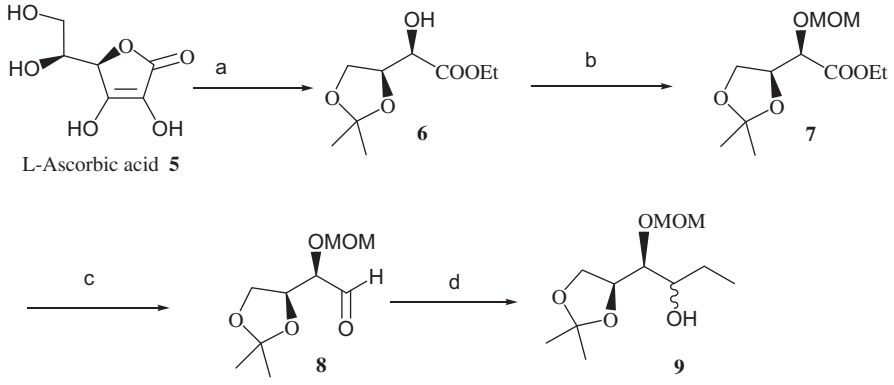


Figure 1. Brevicomins and hydroxy brevicomins.



Scheme 1. Retrosynthesis analysis for compound **1**.



Scheme 2. Reagents and conditions: (a) (i) AcCl, acetone, rt, 3 h; (ii) H_2O_2, K_2CO_3, H_2O, 0 °C to rt, 12 h; (iii) EtBr, ACN, reflux, 24 h, 85% (for three steps); (b) MOMCl, DIPEA, CH_2Cl_2, −15 °C to rt, 12 h, 86%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 3 h; (d) EtMgBr, ether, −78 °C to rt, 12 h, 60% for two steps.

imidazole in CH_2Cl_2 as its TBDMS ether. The major *syn* isomer **12** has been obtained in its pure form at this stage by column chromatography. The secondary hydroxyl in **12** was protected as its benzyl ether using benzyl bromide and NaH in THF to give compound **13**. Compound **13** on treatment with TBAF in THF gave the hydroxyl compound **14**. Compound **14** on Swern oxidation and Wittig reaction gave compound **15**. Compound **15** on hydrogenation with H_2, Pd/C in MeOH in the presence of aq HCl gave inseparable mixture of compounds along with required compound **1**. But, when the compound **15** was subjected to hydrogenation with H_2, Pd/C in MeOH for 25 min initially and then treatment with aq. HCl overnight gave exclusively the target compound **1** in 75% yield (Scheme 3). The spectroscopic data of **1** are in accordance with the reported values.[11] $[\alpha]_D^{25}$ +30.8 (*c* 0.52, $CHCl_3$) lit.[2b] $[\alpha]_D^{20}$ +33.3 (*c* 1.1, $CHCl_3$).

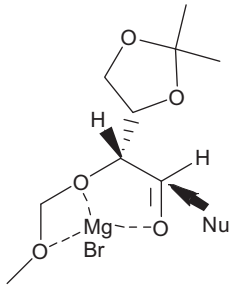
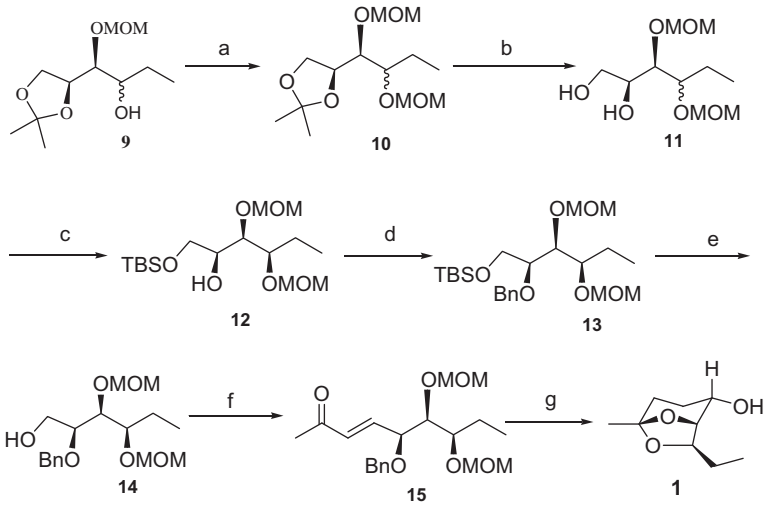


Figure 2. The chelation-controlled addition of nucleophile.

In conclusion we have demonstrated the synthesis of (1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomin in a highly stereoselective fashion starting with chiral pool starting material. The *exo*-



Scheme 3. Reagents and conditions: (a) MOMCl, DIPEA, CH_2Cl_2, −15 °C to rt, 12 h, 88%; (b) PPTS, MeOH, rt, 24 h, 74%; (c) TBSCl, imidazole, CH_2Cl_2, rt, 3 h, 90%; (d) BnBr, THF, 0 °C to rt, 2 h, 77%; (e) TBAF, THF, 0 °C to rt, 2 h, 90%; (f) (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C 2 h; (ii) $PPh_3CHCOCH_3$, toluene, reflux, 5 h, (75% for two steps); (g) H_2, 10% Pd/C, MeOH, 25 min, then aq HCl, rt, 12 h, 75%.

brevicomin **A** is also accessible by this route as its synthesis from **1** is already reported. The key steps are the highly stereoselective chelation-controlled nucleophilic addition on carbonyl and the one-pot double bond reduction, debenzylation, MOM deprotection and bicyclic ketal formation. The single pot reaction helps in minimizing the steps of protections and deprotections which are indispensable in syntheses involving the carbohydrates as starting material.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.011.

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11. Physical data for selected compounds. *(1S,2R/S)-1-((S)-2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-1-(methoxymethoxy) butan-2-ol* (**9**): $[\alpha]_D^{30}$ −53.17 (*c* 2.20, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 3464, 2936, 1459, 1376, 1153, 1035, 919, 759; ESIMS (*m*/*z*): 257 $(M+Na)^+$; ESI-HRMS for $(M+Na)^+$: calcd for ($C_{11}H_{22}O_5Na$) = 257.1364, found = 257.1375; *NMR data for major syn isomer of* **9**: ^1H NMR (500 MHz, $CDCl_3$) δ: 0.99 (t, *J* = 7.2 Hz, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.53–1.63 (m, 2H), 2.38 (br s, 1H). 3.41–3.50 (m, 2H), 3.43 (s, 3H) 3.80 (dd, *J* = 7.2, 8.2 Hz, 1H), 4.06 (dd, *J* = 6.7 Hz, 8.2 Hz, 1H), 4.36 (ddd, *J* = 6.2, 6.7, 7.2 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.90 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.1, 25.3, 26.4, 27.0, 56.1, 66.0, 73.1, 76.8, 80.1, 97.5, 109.2. *(2S,3R,4R)-1-(tert-Butyldimethylsilyloxy)-3,4-bis(methoxymethoxy)hexan-2-ol* (**12**): $[\alpha]_D^{25}$ = 11.04 (*c* 0.96, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 3462, 2935, 1400, 1254, 1104, 1034, 840; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.07 (s, 6H), 0.90 (s, 9H), 0.95 (t, *J* = 7.4 Hz, 3H), 1.50–1.80 (m, 2H), 2.52 (d, *J* = 5.7 Hz, 1H), 3.37 (s, 3H), 3.40 (s, 3H), 3.57–3.77 (m, 5H), 4.62, 4.66 (AB-q, *J* = 7.0 Hz, 2H), 4.71, 4.74 (AB-q, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.4, 9.9, 18.2, 23.5, 25.8, 55.9, 56.2, 64.2, 71.2, 78.6, 79.6, 96.5, 98.4. ESIMS (*m*/*z*): 375 $(M+Na)^+$; ESI-HRMS for $(M+Na)^+$: calcd for ($C_{16}H_{36}O_6NaSi$) = 375.2178, found = 375.2171. *(5S,6S,7R,E)-5-(Benzyloxy)-6,7-bis(methoxymethoxy)non-3-en-2-one* (**15**): $[\alpha]_D^{25}$ = 12.55 (*c* 0.8, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 2934, 1677, 1456, 1104, 1032, 919; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.91 (t, *J* = 7.0 Hz, 3H), 1.47–1.57 (m, 1H), 1.61–1.71 (m, 1H), 2.26 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.51–3.56 (m, 1H), 3.63 (dd, *J* = 5.0, 6.0 Hz, 1H), 4.20 (dd, *J* = 5.0, 6.0 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.57–4.60 (m, 2H), 4.62 (d, *J* = 7.0 Hz, 1H). 4.68 (d, *J* = 7.0 Hz, 1H), 4.78 (d, *J* = 7.0 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 6.81 (dd, *J* = 6.0, 15.9 Hz, 1H), 7.21–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.7, 23.6, 27.0, 55.8, 56.1, 71.9, 78.7, 79.3, 79.8, 96.9, 98.2, 127.8, 128.3, 131.5, 137.5, 144.1, 198.1; ESIMS (*m*/*z*): 389 $(M+Na)^+$; ESI-HRMS for $(M+Na)^+$: calcd ($C_{20}H_{30}O_6Na$) = 389.1940, found = 389.1925. *(1R,2S,5S,7R)-2-Hydroxy-exo-brevicomin* (**1**): $[\alpha]_D^{25}$ = 30.77 (*c* 0.52, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 3443, 2922, 1452, 1030; ^1H NMR (400 MHz, C_6D_6) δ: 0.76 (br s, 1H), 0.89 (t, *J* = 7.6 Hz, 3H), 1.43 (s, 3H), 1.28–1.70 (m, 6H), 3.57 (m, 1H), 3.75 (d, 1H, *J* = 3.5 Hz), 4.15 (t, 1H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ: 10.0, 24.3, 27.0, 28.9, 35.4, 66.3, 77.3, 81.0, 106.9; ESIMS (*m*/*z*): 172 (M^+).