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Synthesis of *ent*-Kaurane and Beyerane Diterpenoids via Controlled Fragmentations of Overbred Intermediates**

Emily C. Cherney[†], Dr. Jason C. Green[‡], and Prof. Dr. Phil S. Baran

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Phil S. Baran: pbaran@scripps.edu

Abstract

In the first part of a two-phase pursuit of highly oxidized members of the *ent*-kaurane and beyerane diterpenoid families, steviol was identified as the ideal cyclase phase terminus. Accordingly, a synthesis of steviol has been developed. This synthesis features a polyene cyclization precursor designed to directly yield oxidation on the axial C₁₉ methyl group. Construction of the necessary [3.2.1]bicyclic system found in the *ent*-kaurane skeleton was realized with two overbred intermediates. The resulting [3.2.1]bicyclic system undergoes Wagner–Meerwein rearrangement to yield the beyerane skeleton of isosteviol.

Keywords

total synthesis; diterpenes; *ent*-kaurane; beyerane; overbred intermediates

The *ent*-kauranes present highly varied oxidation patterns (**3**, **4**, Figure 1A), undergo intriguing skeletal rearrangements, and possess antibacterial, antitumor, and anti-malarial activity.¹ These attributes make *ent*-kauranes interesting candidates for two-phase terpene total synthesis.² Steviol (**1**) was chosen as the lowest oxidized logical target due to the known conversion of such structures to beyeranes³ (isosteviol, **2**) and the useful functionality present for an “oxidase phase.” The first total synthesis reported by Mori *et al.* provides steviol (**1**) in 35 steps and 0.013% overall yield.^{4a,b,c} A 19-step synthesis of steviol methyl ester was reported subsequently by Ziegler *et al.*, but it relied on a key step that gave only a 3% yield of the [3.2.1]bicyclic system and 0.015% overall yield.^{4d} An elegant approach to isosteviol (**2**) was reported by Snider *et al.* in 13–18 steps, 0.37–1.2% overall yield.⁵ Conversion of isosteviol (**2**) to steviol (**1**), however, is unknown. In this communication, an efficient synthesis of (±)-steviol (**1**) is presented.

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Correspondence to: Phil S. Baran, pbaran@scripps.edu.

[†]These authors contributed equally.

This work is dedicated to R. W. Hoffmann on the occasion of his 80th birthday.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

In 2009, R. W. Hoffmann formalized the concept of “overbred intermediates” in synthesis design as intermediates having one or more excess C–C bonds that must be subsequently cleaved.⁶ The route to the [3.2.1]bicyclic system of steviol (**1**) relies on the controlled fragmentation of two overbred intermediates. Cyclopropane **5** (Figure 1B) would require preferential cleavage of the C₁₂–C₁₆ bond over the C₁₂–C₁₃ bond. Such a fragmentation would be ambitious because these two bonds appear to be nearly indistinguishable.⁷ Indeed, a similar system fragmented with only modest diastereoselectivity (2:1).^{4c} Cyclobutane **6**, would then arise from a [2+2] photocycloaddition with allene. This strategy should install a very hindered quaternary center with high diastereo-selectivity.⁸ It is known that strained cyclobutanones in similar systems will open upon nucleophilic attack to break the analogous C₁₃–C₁₄ bond.⁹

Tricyclic system **7** presents a challenge when the issues of stereo- and regioselectivity are considered. In particular, the required axial C₁₉ methyl oxidation and *para*-regioselectivity are not adequately addressed by known approaches (Figure 1C). Radical-mediated methods give the undesired *ortho*-methoxy product.¹⁰ C–H activation reactions directed from C₃ preferentially oxidize the C₁₈ methyl group.^{11,12} Cyclizations initiated from a terminal epoxide (i.e. **10**, Scheme 1) provide oxidation on the equatorial C₁₈ methyl group.¹³ Consequentially, a unique cyclization precursor (**8**) was designed with the following considerations: (i) the polycyclization should be Lewis acid-initiated (rather than radically initiated) to give the correct *para*-regioselectivity; (ii) the epoxide should be internal (rather than terminal) to give the required C₁₉ oxidation;¹³ and (iii) the *Z*-stereochemistry of this internal epoxide is imperative to give C₁₉ oxidation.¹⁴

The pursuit of cyclization precursor **8** began from epoxide **9** (see Scheme 1). Elimination to open epoxide **9** followed by vanadium-directed epoxidation gave the *erythro*-product **10** in 68% overall yield (5.3 gram scale). The secondary alcohol in **10** was inverted to give the *threo*-bromide **11** in 81% yield (7.2 gram scale). Nucleophilic addition of benzyloxide to open the epoxide followed by closure of the bromohydrin provided the cyclization precursor **8** (7.1 gram scale). The polycyclization was most efficiently effected by iron trichloride to give tricyclic system **12** (1.1 gram scale). Compound **12** was converted to crystalline enone **13** by Birch reduction-deprotection and isomerization. X-ray analysis confirmed the *para*-regiochemistry, the crucial C₁₉ axial methyl group oxidation and the correct stereochemistry at the C₉ methine group.

Next, the neopentyl alcohol was eliminated followed by hydrogenation to furnish compound **7** (2.1 gram scale). Birch reduction and isomerization proceeded to give enone **14** (1.3 gram scale). Allene [2+2] photocycloaddition with **14** formed the hindered C₈ quaternary center in overbred cyclobutane **6** (1.1 gram scale).⁸ This overbred intermediate was enabling because all other attempts to form this quaternary center failed including: copper, indium, and tin mediated 1,4-additions, Sakurai and Keck allylations, as well as intramolecular bond formations via sigmatropic rearrangements. Cyclobutane **6** was transformed to **15** in a one-pot sequence (1.0 gram scale): ozonolysis, selective fragmentation with methanol to give the methyl ester, and finally acid-mediated condensation to forge the [2.2.2]bicyclic system.⁹

Reductive cyclopropanation of **15** would generate an overbred cyclopropanediol (**16**), which could undergo divergent fragmentation pathways: C₁₂–C₁₃ cleavage or C₁₂–C₁₆ cleavage to give **17** or **18** respectively. Mori *et al.* treated a similar system with Zn(Hg) amalgam in 6 M HCl/toluene at 110 °C for 1 hour to get a 2:1 ratio in favor of the analogous desired isomer in 41% yield.^{4c} Treatment of diketone **15** with these conditions for 45 minutes gave *only* the undesired isomer **17** in 26% yield (see Table 1, entry 1). Encouragingly, when the reaction was stopped after 5 minutes, a 2.2:1 ratio in favor of the desired isomer **18** was observed (entry 3). Moreover, the desired product **18** was found to rearrange to the undesired isomer

17 under acidic conditions (see Scheme 2A). It seemed that Mori's conditions were unsuitable due to the high temperatures, which caused the desired kinetic isomer (**18**) to rearrange to the thermodynamic isomer (**17**). Under the reaction conditions, the ketones in products **17** and **18** likely undergo further reduction. Attempts to run this reaction at lower temperature with activated zinc led to decomposition with trace formation of **17** (entry 4).

To overcome these issues, cyclopropane diol **16** was trapped as diacetate **5**.¹⁵ This would allow for fragmentation at low temperatures thereby avoiding isomerization of kinetic product **18** to thermodynamic product **17**. It would also avoid over-reduction. Treatment of **5** with methanolic HCl at 0–6 °C gave a greater than 7:1 ratio of **18**:**17** in 79% and 11% yields respectively (entry 5). Undesired isomer **17** can also be recycled to **15** (Scheme 2B).

With suitable quantities of **18** in hand, installation of the methylene was attempted (see Scheme 1). While the Wittig olefination of a similar substrate has been reported,^{4a,c} this procedure as well as salt-free variations either yielded rearranged material or gave no reaction respectively. A modified Wittig procedure proceeded to give olefin **19**,¹⁶ which was oxidized to give (±)-steviol (**1**) in 17 steps from geranyl acetate.¹⁷ Acid-induced rearrangement of steviol (**1**) provided isosteviol (**2**) (see Scheme 2C). Alternatively, compound **19** could first be rearranged to the beyerane skeleton followed by Jones oxidation to provide isosteviol (**2**) in 17 steps (see Scheme 2D).

To summarize, a synthetic route that offers efficient access to minimally oxidized members of the *ent*-kaurane and beyerane class of terpenes has been developed. This route could feasibly be rendered enantioselective.¹⁸ The challenging axial C19 oxidation and [3.2.1]bicyclic motifs prompted a reevaluation and strategic modification of literature precedent. The first challenge was addressed with a unique polycyclization precursor (**8**) while the second necessitated the use of overbred intermediates (**6** and **5**) and their controlled fragmentations. Such strained intermediates enabled and simplified the overall synthetic route. The completion of this cyclase phase sets the stage for an in-depth study of the oxidation chemistry of these complex terpenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A. Truncated oxidation pyramid for *ent*-kauranes and beyeranes. **B.** Cyclase phase retrosynthetic strategy. **C.** Polycyclization methods for installation of C_{18} or C_{19} methyl group oxidation.

Scheme 1. Total synthesis of (±)-steviol (1)

Reagents and Conditions: (a) LiNEt_2 (3 equiv), THF, 60 °C, 2 h (92%); (b) $\text{VO}(\text{acac})_2$ (0.25 equiv), $t\text{-BuOOH}$ (5 M in decane) (1.6 equiv), benzene, 6 °C, 2 h (74% or 83% BRSM); (c) CBr_4 (3 equiv), PPh_3 (2.9 equiv), $i\text{-Pr}_2\text{NEt}$ (3.3 equiv), CH_2Cl_2 , -10 °C, 12 h (81%); (d) NaOt-Bu (2.4 equiv) benzyl alcohol (solvent), 100 °C, 3 h (92%); (e) FeCl_3 (2 equiv), CH_2Cl_2 , rt, 3 h (52%); (f) Li^0 (50 equiv), NH_3 , THF; $t\text{-BuOH}$, -78 °C to -45 °C, 2 h; 4M HCl in dioxane, rt, 30 min (79%); (g) DEAD (5 equiv), PPh_3 (5 equiv), THF, 70 °C, 5 h (91%); (h) H_2 , Pd/C (10 wt%)(10 mol%), EtOAc , rt, 7 h (93%); (i) allene, CH_2Cl_2 , rt, 450 W Hg-lamp, pyrex, 12 h (82%); (j) O_3 , MeOH , -78 °C, 5 min; Me_2S , rt, 30 min; AcOH : PPA (9:1), 110 °C, 12 h (62%); (k) HCl(g) , Ac_2O (solvent), act. Zn^0 (60 equiv), 0 °C, 45 min; (l) AcCl (3 M in MeOH), 0–6 °C, 12 h (79% **18** and 11% **17**); (m) PPh_3 (6.6 equiv), $\text{RhCl}(\text{PPh}_3)_3$ (5 mol%), THF, $i\text{-PrOH}$; TMSCHN_2 (20 equiv), 48 h (63%); (n) PDC (5 equiv), DMF , rt, 18 h, (92%); (o) NaClO_2 (6 equiv), NaH_2PO_4 (10 equiv), 2-methyl-2-butene (10 equiv), THF/ $t\text{-BuOH}$, 0 °C to rt, 16 h (85%). (DEAD = diethyl azodicarboxylate, PPA = polyphosphoric acid, PDC = pyridinium dichromate, DMF = N,N -dimethylformamide).

A. Instability of desired fragmentation product in acid (and base) **B. Recycling undesired fragmentation product to diketone 15** **C. Conversion of steviol (1) into isosteviol (2)** **D. Conversion of 19 into isosteviol (2)** **Scheme 2.**

Reagents and Conditions: **(a)** 12 M HCl, PhMe, 110 °C, 30 min (79%); **(b)** CAN (3 equiv), MeCN, 0 °C, 10 min; **(c)** PPA, AcOH, 110 °C, 12 h (72% over 2 steps); **(d)** HBr (48% aq.) Et₂O, rt, 15 h (90%); **(e)** HBr (48% aq.) Et₂O, rt, 18 h (87%); **(f)** CrO₃ (10 equiv), acetone, 0 °C to rt, 3 h (81%) (CAN = cerium ammonium nitrate)

Table 1

Attempts at conversion of 15 or 5 to 18

Reaction scheme:
 diketone 15 or cyclopropane 5 $\xrightarrow{\text{conditions}}$ 18: desired + 17: undesired

Entry	Conditions	Yield% 18	Yield % 17	ratio 18:17
1	15, Zn(Hg), 6M HCl, PhMe, 110 °C, 45 min	0%	26%	0:1
2	15, Zn(Hg), 6M HCl, PhMe, 110 °C, 30 min	13%	9%	1.4:1
3	15, Zn(Hg), 6M HCl, PhMe, 110 °C, 5 min	24%	11%	2.2:1
4	15, act. Zn°, HCl in Et ₂ O, 0 °C, 15 m	trace	--	--
5	5, AcCl, MeOH, 0–6 °C, 12 h	79%	11%	7.2:1