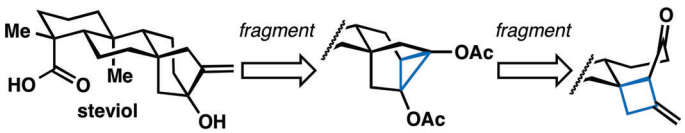
Communications

Total Synthesis

E. C. Cherney, J. C. Green,
P. S. Baran* ——— ■■■■–■■■■

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



[controlled fragmentation of overbred intermediates]

Efficient access to minimally oxidized members of the *ent*-kaurane and beyerane class of terpenes has been achieved by using a polyene cyclization precursor designed to directly yield oxidation at the axial C19-methyl group. Construction of the [3.2.1]bicyclic system found in the *ent*-kaurane skeleton was realized with two overbred intermediates. Wagner–Meerwein rearrangement of the [3.2.1]bicyclic system yields the beyerane skeleton of isosteviol.

Total Synthesis

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

*Emily C. Cherney, Jason C. Green, and Phil S. Baran**

Dedicated to R. W. Hoffmann on the occasion of his 80th birthday

The *ent*-kauranes present highly varied oxidation patterns (**3**, **4**; Figure 1 A), undergo intriguing skeletal rearrangements, and possess antibacterial, antitumor, and antimalarial 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 into beyeranes[3] (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 and Kloek, 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**) into steviol (**1**), however, is unknown. Herein, an efficient synthesis of (±)-steviol (**1**) is presented.

In 2009, 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 1 B) 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 diastereoselectivity.[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 1 C). 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)

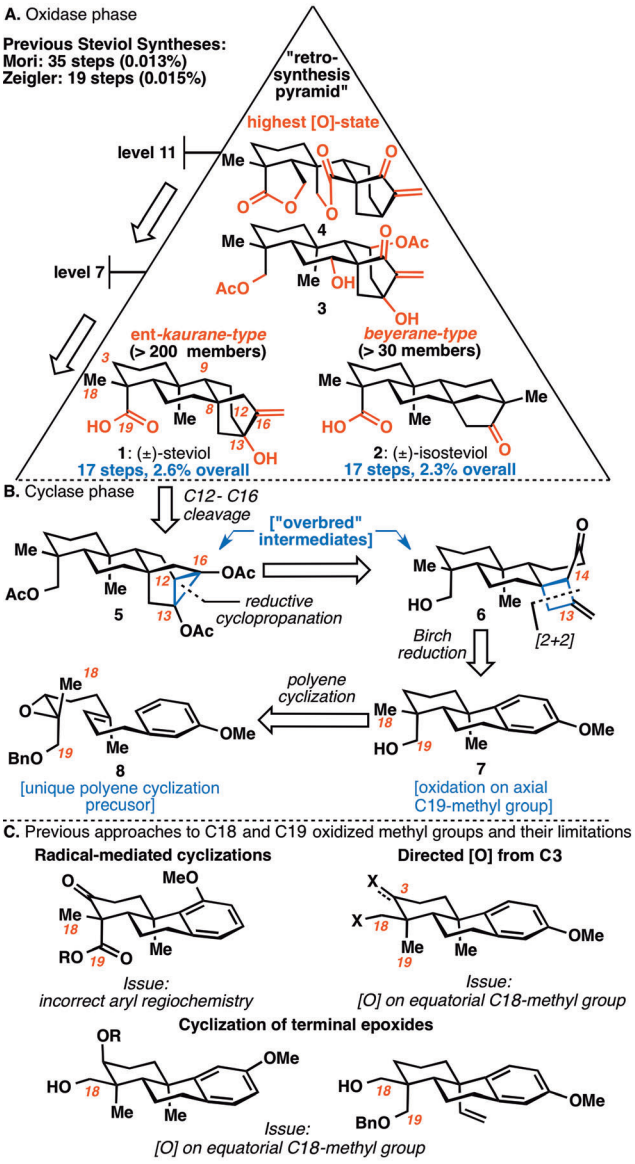

Figure 1. A) Truncated oxidation pyramid for *ent*-kauranes and beyeranes. B) Cyclase-phase retrosynthetic strategy. C) Polycyclization methods for installation of C18 or C19-methyl group oxidation.

[*] E. C. Cherney,[+] Dr. J. C. Green,[+] Prof. Dr. P. S. Baran
Department of Chemistry, The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: pbaran@scripps.edu

[+] These authors contributed equally to this work.

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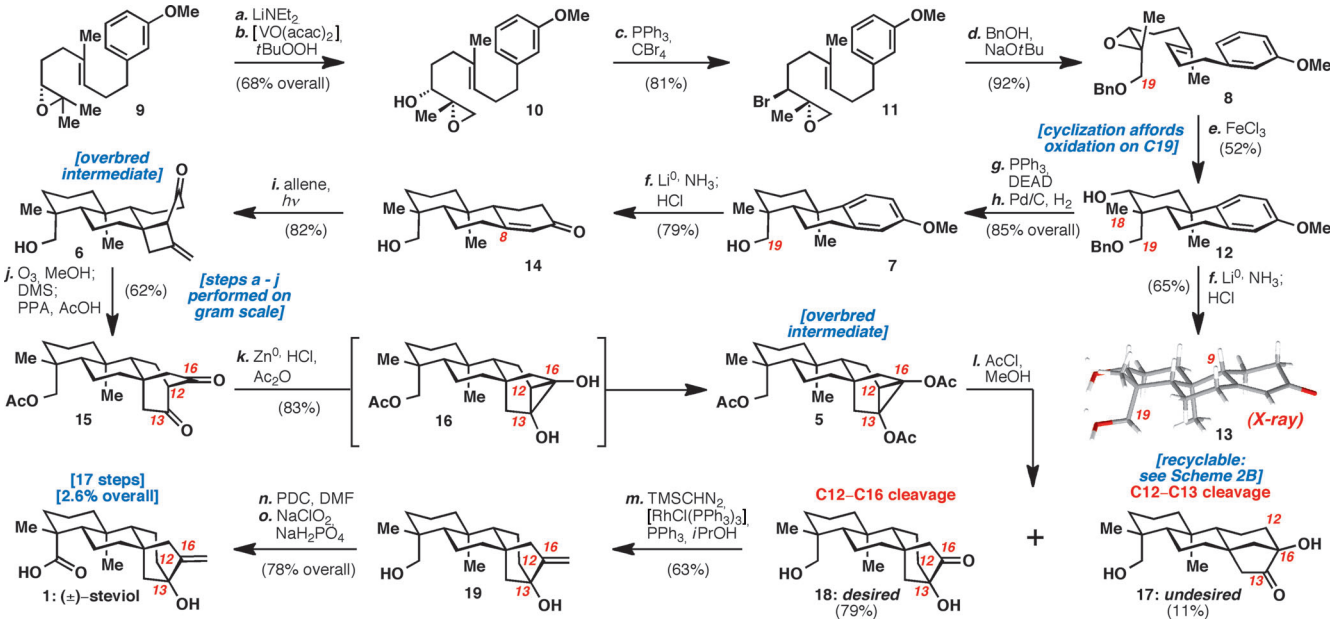


Scheme 1. Total synthesis of (±)-steviol (**1**). Reagents and conditions: a) $LiNEt_2$ (3 equiv), THF, 60 °C, 2 h (92%); b) $[VO(acac)_2]$ (0.25 equiv), *t*BuOOH (5 M in decane) (1.6 equiv), benzene, 6 °C, 2 h (74% or 83% BRSM); c) CBr_4 (3 equiv), PPh_3 (2.9 equiv), *i*Pr_2NEt (3.3 equiv), CH_2Cl_2, −10 °C, 12 h (81%); d) NaO*t*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*BuOH, −78 °C to −45 °C, 2 h; 4 M 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), $[RhCl(PPh_3)_3]$ (5 mol%), THF, *i*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*BuOH, 0 °C to RT, 16 h (85%). acac = acetylacetonate, BRSM = based on recovered starting material, DEAD = diethyl azodicarboxylate, PPA = polyphosphoric acid, PDC = pyridinium dichromate, DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl.

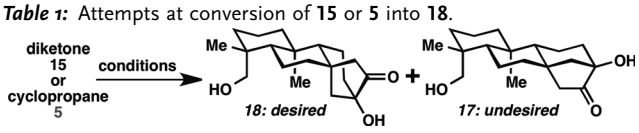
provide oxidation on the equatorial C18-methyl group.[13] Consequentially, a unique cyclization precursor (**8**) was designed with the following considerations: 1) the polycyclization should be Lewis acid initiated (rather than radically initiated) to give the correct *para* regioselectivity; 2) the epoxide should be internal (rather than terminal) to give the required C19 oxidation;[13] and 3) 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 into 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] The formation of this overbred intermediate was strategic 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 through 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 h 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 min gave *only* the undesired isomer **17** in 26% yield (see Table 1, entry 1). Encouragingly, when the reaction was stopped after 5 min, 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 (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

Table 1: Attempts at conversion of **15** or **5** into **18**.



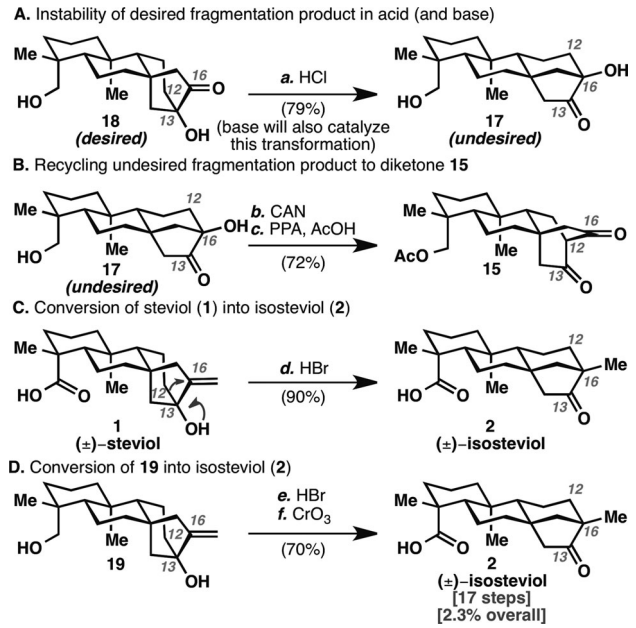
Entry	Conditions	Yield 18	Yield 17	Ratio 18/17
1	**15**, Zn(Hg), 6 M HCl, PhMe, 110 °C, 45 min	0%	26%	0:1
2	**15**, Zn(Hg), 6 M HCl, PhMe, 110 °C, 30 min	13%	9%	1.4:1
3	**15**, Zn(Hg), 6 M HCl, PhMe, 110 °C, 5 min	24%	11%	2.2:1
4	**15**, act. Zn^0, HCl in Et_2O, 0 °C, 15 m	–	trace	–
5	**5**, AcCl, MeOH, 0–6 °C, 12 h	79%	11%	7.2:1

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 **18** and **17** in 79% and 11% yield, respectively (greater than 7:1 ratio; entry 5). Undesired isomer **17** can also be recycled to **15** (Scheme 2B).

With suitable quantities of **18** in hand, installation of the methylene group was attempted (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**; Scheme 2C). Alternatively, compound **19** could first be rearranged to the beyerane skeleton followed by Jones oxidation to provide isosteviol (**2**) in 17 steps (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 conceptually 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.



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) Et_2O, RT, 15 h (90%); e) HBr (48% aq) Et_2O, RT, 18 h (87%); f) CrO_3 (10 equiv), acetone, 0 °C to RT, 3 h (81%). CAN = cerium ammonium nitrate.

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