The First Entry to Complex Bakkanes: A Highly Effective Retroaldol–Aldol-Based Approach to (−)-Bakkenolides III, B, C, and H**

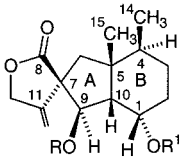
Olivier Hamelin, Yanyun Wang, Jean-Pierre Deprés,* and Andrew E. Greene

Dedicated to Prof. Jean Lhomme on the occasion of his retirement

Since the first members were isolated and elucidated in the late 1960s, the bakkanes have rapidly increased in number, particularly recently, so as to count now approximately 50.[1] These hydrindane sesquiterpenes of both terrestrial and marine origin, characterized by their novel spiro γ-butyrolactone function and significant biological effects,[1m,n, 2] have become popular synthetic targets. To date bakkenolide A, homogynolides A and B, palmosalide C, and 9-acetoxyfukinanolide have been prepared, most more than once.[3]

The nonfunctionalized and monofunctionalized bakkenolides, however, are each oxygenated singly and taken together comprise only a relatively minor number of the known bakkanes. Much more representative (ca. 80%) of this class are the densely functionalized and stereochemically challenging C1,C9-dioxygenated bakkenolides (**I**, R, $R^1 = H$, acyl). These compounds, which have significant inhibitory activity toward Hep G2, Hep G2,2,15, and P-388 tumor cell lines,[1n] as well as PAF, arachidonic acid, and collagen-induced platelet aggregation,[1m] have been isolated from *Petasites japonicus* Maxim. and *Petasites formosanus* Kitamura (Compositae).[1b–f, m, n]

Herein we illustrate the first entry to this large group of bakkanes through the preparation of the representative natural bakkenolides III, B, C, and H (**1**–**4**). We note in advance that this highly stereocontrolled and efficient approach allows potentially total access to the group.



I

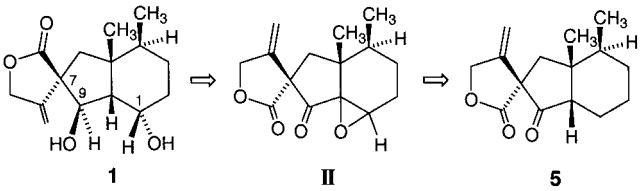
1, R = R^1 = H Bakkenolide III

2, R = H; R^1 = $COC(CH_3)\overset{Z}{=}CH(CH_3)$ Bakkenolide C

3, R = $COCH_3$; R^1 = $COC(CH_3)\overset{Z}{=}CH(CH_3)$ Bakkenolide B

4, R = R^1 = $COCH(CH_3)_2$ Bakkenolide H

With its six stereocenters in the proper configurations and two hydroxyl groups which could be, in principle, easily differentiated, diol **1** (bakkenolide III) appeared to be the ideal late intermediate for accessing the entire range of known C1,C9-difunctionalized bakkenolides (Scheme 1). It seemed this diol might be secured from epoxy ketone **II** through chemoselective reduction, followed by stereochemical adjustments.

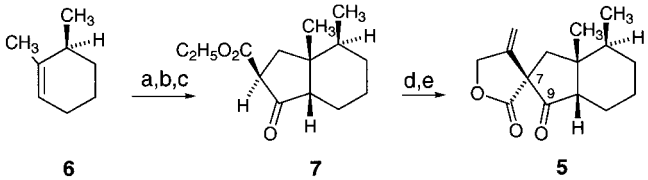


1 **II** **5**

Scheme 1. Retrosynthesis of bakkenolide III (**1**).

Molecular mechanics calculations[4] revealed diol **1** to have the lowest global minimum energy of the four C7,C9 diastereomers, thus it could possibly be reached through a retroaldol–aldol equilibration. Epoxy ketone **II**, in turn, was viewed as arising from keto lactone **5**, an intermediate previously prepared in our laboratory from 1,6-dimethylcyclohexene.[3n, 5]

Keto lactone **5** was synthesized stereoselectively from enantiopure 1,6-dimethylcyclohexene (**6**)[3d] in five steps and 27% overall yield[6] in a manner similar to that used earlier. It was found, however, that ring expansion could be improved by using boron trifluoride as the catalyst and that neutral conditions benefitted the transesterification[7] (Scheme 2).



6 **7** **5**

Scheme 2. Synthesis of keto lactone **5**. a) Ref. [3d, n]; b) Zn, CH_3CO_2H, 70 °C, 1 h (63%, 2 steps); c) $N_2CHCO_2C_2H_5$, $BF_3 \cdot O(C_2H_5)_2$, $(C_2H_5)_2O$, 0 °C, 12 h (72%); d) $HC{\equiv}CCH_2OH$, $C_6H_5CH_3$, reflux, 24 h (87%); e) $Mn(O_2CCH_3)_3$, C_2H_5OH, 20 °C, 2.5 h (68%).

Of the numerous procedures examined for effecting dehydrogenation of this keto lactone to its $\Delta^{1(10)}$ derivative **8a**, phenylselenenylation/oxidation[8] was clearly the most efficacious and under carefully optimized conditions the sensitive enone could be isolated in 77% yield (Scheme 3). Base-catalyzed epoxidations with this derivative invariably resulted in degradation, and so a hydroxyl-directed procedure was next considered. Toward this end, enone **8a** was subjected to a Luche reduction in ethanol,[9] which led cleanly and highly stereoselectively ($\geq$98:2) to the retroaldol-prone allylic alcohol **8b**, in which the hydroxyl group had the desired α orientation.[10] This material was exposed without purification to a $[VO(acac)_2]$-catalyzed epoxidation with *tert*-butyl hydroperoxide (TBHP) in warm toluene[11] to provide selectively the required epoxide **9a**, which was isolated in 57%

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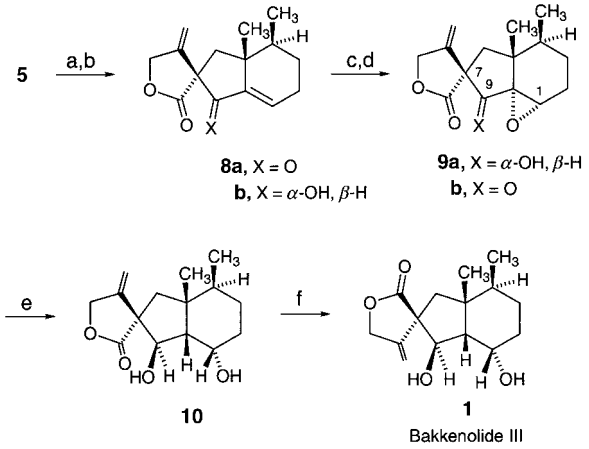
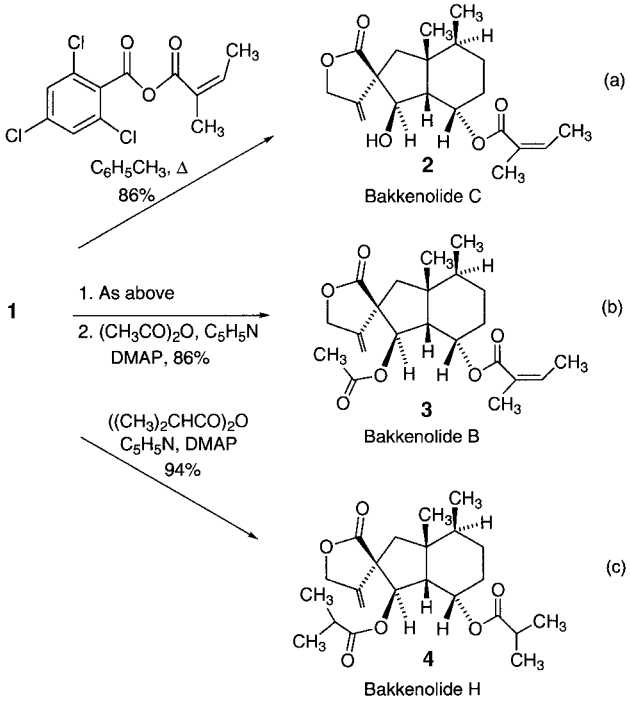


Scheme 3. Synthesis of bakkenolide III (**1**). a) NaHMDS, THF, −65 °C, 4 h; C_6H_5SeBr, −65 → 0 °C, 1 h; H_2O_2, CH_3CO_2H/H_2O, 0 °C, 1.5 h (77 %); b) $NaBH_4$, $CeCl_3$, C_2H_5OH, −30 °C, 1.5 h; c) [$VO(acac)_2$], TBHP, $C_6H_5CH_3$, 50–60 °C, 6 h (57 %, 2 steps); d) $(ClCO)_2$, DMSO, CH_2Cl_2, −60 °C, 15 min; $(C_2H_5)_3N$, −60 → 20 °C, 1 h (83 %); e) SmI_2, THF/H_2O, 20 °C, 0.5 h (83 %); f) $(C_4H_9)_4NF$, THF, 0 °C, 0.5 h (82 %). acac = acetylacetonate; DMSO = dimethyl sulfoxide; HMDS = 1,1,1,3,3,3-hexamethyldisilazide; TBHP = *tert*-butyl hydroperoxide.



Scheme 4. Synthesis of a) bakkenolide C (**2**), b) bakkenolide B (**3**), and c) bakkenolide H (**4**). DMAP = 4-dimethylaminopyridine.

yield (2 steps). Swern oxidation then gave efficiently epoxy ketone **9b** and set the stage for reduction to the C1,C9-diol.

Previous experience had shown SmI_2 to be uniquely effective for the reduction of 7-epi-9-oxo-bakkenolide A (**5**).[3n] It was therefore hoped that this reagent, also known to be able to effect reductive cleavage of α heteroatom substituents in ketone derivatives, used in excess and in a protic medium might produce a chemoselective double reduction of epoxy ketone **9b**.[12] A clean transformation, in fact, resulted when excess reagent in 1 % aqueous THF was used at room temperature for 0.5 h and delivered only the C1α,C9β-diol derivative **10** in 83 % yield. A single-crystal X-ray analysis corroborated these assignments.[13]

The success of the entire venture now hinged on the thermodynamics predicted by molecular modeling studies[4] for the retroaldol–aldol transformation of lactone diol **10**.[14] To our considerable satisfaction, **10** underwent smooth isomerization, in spite of numerous possible alternative pathways, on exposure to tetrabutylammonium fluoride (TBAF) in THF at 0 °C for 0.5 h to provide a single, crystalline lactone diol in high yield. Confirmation that the crucial conversion had in fact occurred as predicted to deliver the key compound, (−)-bakkenolide III (**1**),[1n] was obtained by direct comparison with the hydrolysis product[1b,d,f] of (−)-bakkenolide B and through single-crystal X-ray analysis.[15]

The hydroxyl groups in bakkenolide III are clearly in different steric environments and this was expected to translate into regioselective acylations. Bakkenolide III in the presence of the Yamaguchi mixed anhydride derived from angelic acid and under conditions earlier found to avoid the facile angelic → tiglic isomerization[16] formed (−)-bakkenolide C (**2**)[1d] in 86 % yield without detectable amounts of C9-acylated material or tiglic ester (Scheme 4a). The bakkenolide C so obtained was identical with a sample secured by partial hydrolysis[1b,d,f] of natural bakkenolide B.

In the presence of excess anhydride and 4-dimethylaminopyridine (DMAP), however, C9 acylation could be readily achieved. Thus, (−)-bakkenolide B (**3**)[1b,d,f,n] could be secured in 86 % yield from (−)-bakkenolide C with excess acetic anhydride in pyridine in the presence of DMAP (Scheme 4b). Likewise, (−)-bakkenolide H (**4**),[1m,n] which shows significant cytotoxic activity in several test systems, could be prepared in 94 % yield from bakkenolide III by using excess isobutyric anhydride under similar conditions (Scheme 4c).

In summary, enantiopure (−)-bakkenolide III has been efficiently synthesized (> 6 % overall yield, 11 steps) through a highly stereocontrolled approach and used as a platform for accessing representative C1,C9-dioxygenated bakkenolides. This first successful entry to these numerous bioactive compounds relies on a novel SmI_2-promoted chemoselective double reduction of an epoxy ketone to generate the C1 and C9 hydroxyl groups and a thermodynamically governed retroaldol–aldol strategy to install the spiro lactone unit and the C9 hydroxyl group with the proper stereochemistry. Both of these should find additional application.

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[4] Calculations were performed on an IBM RS 6000 workstation running Insight II Discover 98.0 (MSI, San Diego). The structures were energy minimized with the force field cvff.frc. and the minimization algorithm VA09A: diastereomer 7*R*,9*R*: 39.2 kcal mol^{-1}; 7*S*,9*R*: 40.0 kcal mol^{-1}; 7*S*,9*S*: 42.0 kcal mol^{-1}; 7*R*,9*S*: 44.3 kcal mol^{-1}.

[5] Early installation of the C1 hydroxyl group by starting from a 3,4-dimethylcyclohex-2-enol derivative was not attempted because of the anticipated difficulties in the cycloaddition. See: R. Malherbe, G. Rist, D. Bellus, *J. Org. Chem.* **1983**, *48*, 860 – 869; E. Vedejs, R. A. Buchanan, *J. Org. Chem.* **1984**, *49*, 1840 – 1841, and references therein.

[6] Yields are for purified, chromatographically homogeneous substances. The NMR, IR, and mass spectra are in full accord with the proposed structures and satisfactory combustion analyses and/or high resolution mass spectral data have been obtained for all new compounds. **5**: m.p. 71 – 71.5 °C (diethyl ether/hexane); $[\alpha]_D^{20} = +426$ ($c = 1.2$ in $CHCl_3$). **7**: $[\alpha]_D^{20} = +62.9$ ($c = 1.8$ in $CHCl_3$). **8a**: m.p. 145 – 146 °C (ethyl acetate/hexane); $[\alpha]_D^{20} = -1.1$ ($c = 2.5$ in $CHCl_3$). **8b**: m.p. 145 – 146 °C (diethyl ether/hexane); $[\alpha]_D^{20} = +50.1$ ($c = 1.6$ in $CHCl_3$). **9a**: $[\alpha]_D^{20} = +32.0$ ($c = 4.1$ in $CHCl_3$). **9b**: m.p. 166.5 – 167 °C (chloroform/hexane); $[\alpha]_D^{20} = -91.2$ ($c = 1.3$ in $CHCl_3$). **10**: m.p. 131 – 131.5 °C (dichloromethane/hexane); $[\alpha]_D^{20} = +100.0$ ($c = 1.4$ in $CHCl_3$). **1**: m.p. 177 – 178 °C (dichloromethane/hexane); $[\alpha]_D^{20} = -71.7$ ($c = 1.0$ in $CHCl_3$), $[\alpha]_D^{22} = -79.7$ ($c = 1.0$ in CH_3OH). **2**: m.p. 165 – 165.5 °C (dichloromethane); $[\alpha]_D^{20} = -76.2$ ($c = 0.8$ in $CHCl_3$), $[\alpha]_D^{22} = -156.1$ ($c = 0.7$ in CH_3OH). **3**: m.p. 101.5 – 102 °C; $[\alpha]_D^{22} = -118.1$ ($c = 0.8$ in $CHCl_3$), $[\alpha]_D^{22} = -149.3$ ($c = 1.1$ in CH_3OH). **4**: m.p. 130 – 130.5 °C (diethyl ether/hexane); $[\alpha]_D^{20} = -105.6$ ($c = 1.0$ in $CHCl_3$), $[\alpha]_D^{22} = -124.5$ ($c = 1.1$ in CH_3OH).

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[8] For a review, see H. J. Reich, S. Wollowitz, *Org. React.* **1993**, *44*, 1 – 296.

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[10] This stereochemical assignment was initially based on literature precedent[3b, i] for an A-ring β-face approach in bakkane derivatives and was later confirmed indirectly by X-ray diffraction analysis of diol **10**. NOSEY experiments on **8b** proved inconclusive.

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[12] For a review, see G. A. Molander, *Org. React.* **1994**, *46*, 211 – 367. This type of double reduction with SmI_2 is apparently unprecedented; however, the less chemoselective Li-NH_3-NH_4Cl system has been used for this purpose. See: A. A. Devreese, M. Demuynck, P. J. De Clercq, M. Vandewalle, *Tetrahedron* **1983**, *39*, 3039 – 3048; C. S. Swindell, S. J. deSolms, *Tetrahedron Lett.* **1984**, *25*, 3801 – 3804. The *cis* ring fusion was anticipated based on precedent;[3b,i] the C9β isomer was expected to result since SmI_2 is known to deliver in general the more stable isomer ($\Delta E_{9\beta\text{-}9\alpha} = -2.0$ kcal mol^{-1}[4]). The configuration at C9 in **10**, however, is irrelevant in that it too is subjected to equilibration in the retroaldol – aldol reaction.

[13] Crystal data for (±)-**10** (from parallel studies):[17] $C_{15}H_{22}O_4$, tetragonal, $I4_1/a$, $a = 20.220(7)$, $c = 13.427(7)$ Å, $V = 5490(3)$ Å^3, $Z = 16$, $\rho_{calcd} = 1.289$ Mg m^{-3}, $F(000) = 2304$, $\theta = 2.0 - 30°$, 5466 measured reflections, 5274 (R(int) = 0.017) independent reflections, $R(F)$ ($F > 2\sigma(F)$) = 0.0487, wR (all data) = 0.0512, GOF = 1.965.

[14] See: J. D. White, N. S. Cutshall, T.-S. Kim, H. Shin, *J. Am. Chem. Soc.* **1995**, *117*, 9780 – 9781 and ref. [3n)].

[15] Crystal data for (±)-**1** (from parallel studies):[17] $C_{15}H_{22}O_4$, monoclinic, $P2_1/c$, $a = 13.261(3)$, $b = 7.267(6)$, $c = 15.454(5)$ Å, $\beta = 110.36(2)°$, $V = 1396(1)$ Å^3, $Z = 14$, $\rho_{calcd} = 1.267$ Mg m^{-3}, $F(000) = 576$, $\theta = 2.50 - 30°$, 4449 measured reflections, 4305 (R(int) = 0.011) independent reflections, $R(F)$ ($F > 1\sigma(F)$) = 0.0452, wR (all data) = 0.0584, GOF = 2.011.

[16] B. Hartmann, A. Kanazawa, J.-P. Deprés, A. E. Greene, *Tetrahedron Lett.* **1991**, *32*, 5077 – 5081.

[17] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-147277 (±-**1**) and -147278 (±-**10**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

A Tandem Sulfur Transfer/Reduction/Michael Addition Mediated by Benzyltriethylammonium Tetrathiomolybdate**

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Disulfides and sulfur containing organic compounds are important functional groups widely present in nature and have commercial significance.[1] Therefore, the synthesis of disulfides, sulfides, and ω-thioketones is not only attractive but also finds numerous applications.[2] Studies directed

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