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Enantiospecific Total Synthesis of (–)-Bakkenolide III and Formal Total Synthesis of (–)-Bakkenolides B, C, H, L, V, and X

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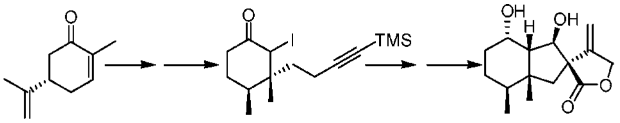
ABSTRACT



(-)-bakkenolide III

A concise enantiospecific synthesis of (–)-bakkenolide III was accomplished from (*S*)-(+)-carvone. The key step involved radical cyclization of an iodoketone intermediate which afforded the *cis*-hydrindanone skeleton. Further synthetic transformations generated bakkenolide III, which also constitutes the formal total synthesis of (–)-bakkenolides, B, C, H, L, V, and X.

The sesquiterpenes represent a vast multitude in the fascinating realm of naturally occurring molecules. Among the salient members of the sesquiterpenes that bear the hydrindane motif are the picrotoxinin, zizzanes, and the bakkanes.[1] The bakkenoids **1a**−**f** and **2a**−**i** (Figure 1) are recognized by the presence of a *cis* fused hydrindane core with an α-spirofused-γ-butyrolactone moiety which is generally accompanied by a *β*-methylene unit.[2]

Ever since the first isolation of bakkenolide A[2a] (**1a**, also known as fukinanolide[2b]) by Abe and co-workers in 1968, over 50 members have been identified so far from both terrestrial and marine sources.[2c] They are biogenetically derived from eremophilanes.[2b,3] The C1, C9 dioxygenated derivatives **2a**−**i** were isolated from *Petasites japonicus* Maxim and *Petasites formosanus* Kitamura (Compositae) primarily by Wu and co-workers.[2b,4] These bakkenolides possess novel biological activities which range from selective cytotoxicity[4b,5] to antifeedant effects.[6] They, in particular,

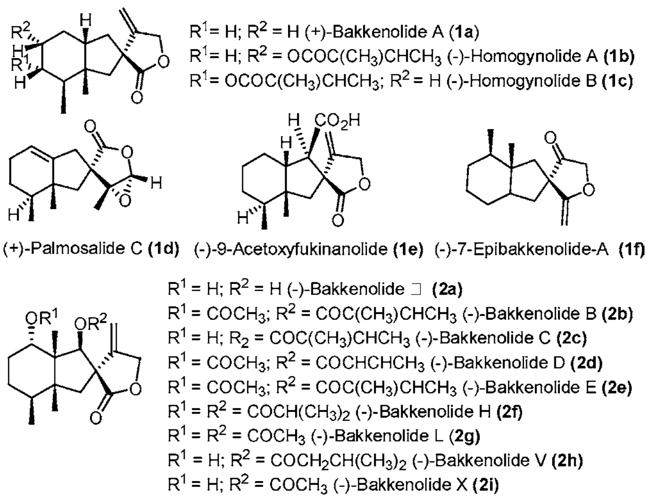


Figure 1. Selected members of bakkanes.

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are known to possess inhibitory activity toward Hep G2, Hep G2,2,15, and P-388 tumor cell lines.[4b]

Additonally, they exhibit inhibitory activities against arachidonic acid and collagen induced platelet aggregation.[6a] Thus the novel structural traits coupled with the biological activities have attracted organic chemists to develop new synthetic routes to these molecules. While the total synthesis of bakkenolide A[7] and the closely related analogues, that is, (−)-homogynolide A[8a−c] (**1b**) and B[8d−f] (**1c**), (+)-palmosalide C[8g] (**1d**), (−)-acetoxyfukinanolide[8h] (**1e**), (−)-7-epibakkenolide-A[8i] (**1f**) (Figure 1) are well documented, synthesis of the C1, C9 dioxygenated analogues bakkenolide III, B, C, D, E, H, L, V, and X (**2a−i**) are hitherto less known. Their total syntheses have been reported only by Deprés et al. via the cycloadditon of dichloroketene with dimethylcyclohexenes.[9] In that report, bakkenolide III is a pivotal intermediate as it was elaborated into a series of bakkenolides such as **2b**, **2c**, and **2f−i**.[9]

Herein, we report the total synthesis of bakkenolide III (**2a**) via the highly efficient α-carbonyl radical cyclization protocol established in our laboratories.[10] We envisaged a highly functionalized hydrindanone core bearing a propargylic ester **3** as a potential precursor to (−)-bakkenolide III (**2a**), which in turn could be obtained from the hydrindanone **4**. Commercially available (*S*)-(+)-carvone (**8**) could give rise to enone **7**. Conjugate addition of the suitable organometallic reagent to **7** followed by trapping the resulting enolate with chlorotrimethyl silane and subsequent iodination could afford iodoketone **6**. Radical cyclization of **6** and further synthetic manipulations could provide **5**. Reduction of compound **5** followed by protection of the alcohol group and ozonolysis could render hydrindanone **4** (Figure 2).

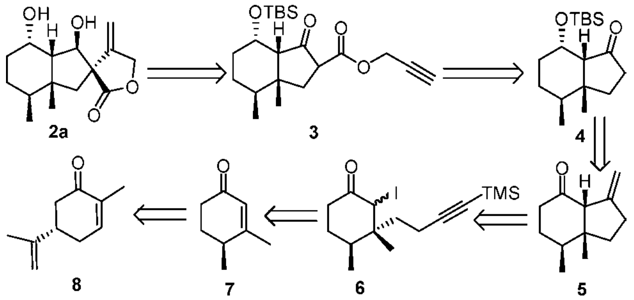

Figure 2. Retrosynthetic analysis of **2a**.

Our synthetic efforts commenced with the reduction of (*S*)-(+)-carvone (**8**) with lithium in liquid ammonia.[11] (2*S*,5*S*)-(−)-*trans*-Dihydrocarvone (**9**) was generated as the major isomer (trans/cis = 10:1). Ozonolysis of **9** in methanol and subsequent treatment with Cu(OAc)$_2$/FeSO$_4$ resulted in enone **10**.[12a] Addition of methyllithium to **10** provided the alcohol **11** ($dr = 1{:}1$), which was smoothly oxidized with PCC to produce **7**[12b] ($[\alpha]^{23}_{D} = -108.2$ c 3.5, CHCl$_3$). CuI-mediated conjugate addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride **12**[10] to **7** ensued by trapping the resulting enolate with chlorotrimethylsilane generated the TMS-enol ether **13**. As **13** was labile to chromatography, it was used immediately without purification. Treatment of **13** with a mixture of NaI and *m*-CPBA resulted in iodoketone **6** as a mixture of diastereomers ($dr = 19{:}1$). The stereochemistry at the newly generated stereocenter C2 is inconsequential with respect to the subsequent transformation and hence was not assigned. The stereochemistry of C3 was assigned with analogy to earlier observations on closely related systems (Scheme 1).[13] The addition of the Grignard reagent **12** presumably occurred from the α-face of **7**.

Exposure of **6** to the photolytic condition in the presence of hexabutylditin effected iodine atom transfer cyclization followed by deiodination with tributyltin hydride/AIBN afforded vinylsilane ketone **14** as a mixture of *E* and *Z* isomers ($E/Z = 3{:}1$). Upon treatment with NaBH$_4$, preferential reduction of the *E* isomer was observed. The steric

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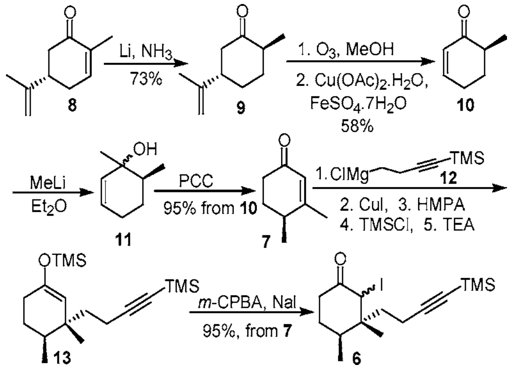
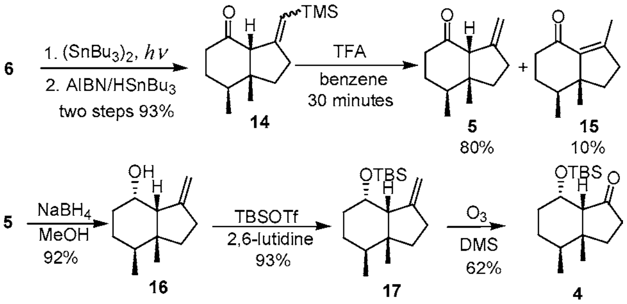
Scheme 1. Synthesis of Iodoketone **6**



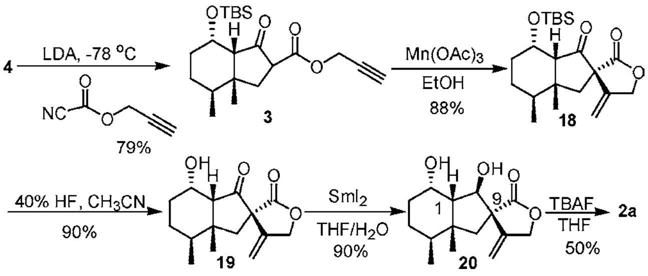
congestion due to trimethylsilyl group in the *Z* isomer presumably prohibited the reduction of the *Z* isomer. Alternatively, the isomeric mixture was treated with trifluoroacetic acid to obtain **5**. However a small amount of enone **15** was also formed as a side product. Attempts of desilylation with trifluoroacetic acid using various solvents gave a mixture of **5** and **15** in varied proportions. Much to our gratification, conducting the reaction in benzene for 30 min at 0 °C considerably minimized the formation of **15**. Stereoselective reduction of **5** with NaBH$_4$ cleanly afforded the alcohol **16** as a single diastereomer. The stereochemistry of **16** was determined by single-crystal X-ray analysis.[14] Treatment of the alcohol **16** with TBS-triflate in presence of 2,6-lutidine gave **17**. Ozonolysis of **17** followed by reductive workup with dimethyl sulfide afforded **4** (Scheme 2).

Scheme 2. Synthesis of Hydrindinone **4**



Deprotonation of **4** with LDA and subsequent treatment with propargyl cyanoformate[15] provided the propargylic ester **3** in good yields. Treatment of **3** with manganese triacetate in ethanol effected radical cyclization to install the spiro framework in **18** according to a modified Deprés procedure[9b] (Scheme 3). Deprotection of the hydroxyl group with 40% HF in acetonitrile generated the hydroxyketone **19**. Samarium(II) iodide reduction of **19** afforded diol **20**. Treatment of **20** with tetrabutylammonium fluoride in THF effected retro-aldol and aldol condensation to give bakkenolide III (**2a**).

Scheme 3. Synthesis of (−)-Bakkenolide III



The spectral data and optical rotation of **2a** are in good agreement with literature data.[9b] Since bakkenolides B, C, H, L, V, and X were prepared from bakkenolide III by Deprés's group, synthesis of bakkenolide III also constitutes the formal total synthesis of bakkenolides B, C, H, L, V, and X.[9b]

In conclusion we have accomplished an enantiospecific total synthesis of (−)-bakkenolide III and the formal synthesis of the other C1,C9 dioxygenated analogues **2b**, **2c**, and **2f−i** by employing α-carbonyl radical cyclization as the key step. Application of this methodology toward the synthesis of other structurally complex natural products are under investigation.

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Supporting Information Available: Full details of experimental procedures, spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] X-ray data for compound **16** will be presented in a full paper.

[15] Propargyl cyanoformate was prepared from propargyl chloroformate. For preparation of propargyl chloroformate see: Fukase, Y.; Fukase, K.; Kusumoto, S. *Tetrahedron Lett.* **1999**, *40*, 1169. For conversion of chloroformate to cyanoformate see: Nii, Y.; Okano, K.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1979**, *20*, 2517.