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A General Approach Toward Bakkanes: Short Synthesis of (±)-Bakkenolide-A (Fukinanolide)†

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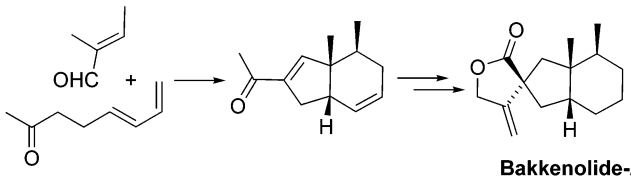
ABSTRACT



Bakkenolide-A

An efficient, general, and fully stereocontrolled approach to the family of bakkanes is disclosed. This route highlights a highly diastereoselective Diels–Alder/aldol sequence to furnish the common hydrindane precursor for the synthesis of bakkanes. The projected common intermediate was transformed to the (±)-bakkenolide-A in a short sequence.

Bakkanes are sesquiterpenoids possessing a *cis*-hydrindane skeleton decorated with two quaternary centers and usually a β-methylene-γ-butyrolactone moiety (Figure 1). Aproximately 50 bakkanes have been isolated from plants to date, and they are believed to derive biogenetically from eremophilanes.[1] Varied biological properties have been attributed to the members of this family, which includes selective cytotoxicity,[2] antifeedant effects,[3] and inhibition of platelet aggregation.[4] The interesting biological activity and structural features present in bakkanes have kept the synthetic community busy since the first successful synthesis of bakkenolide-A (**1**) in 1973 by Evans and Sims.[5]

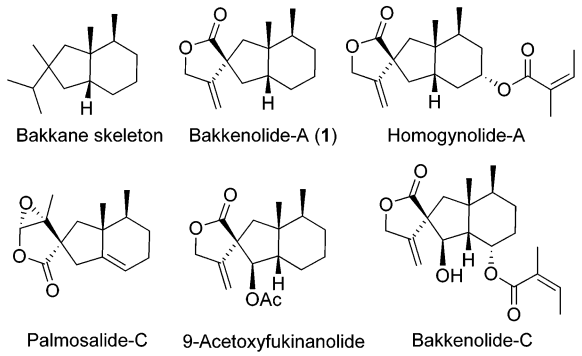


Figure 1. Selected members of the bakkane family.

Disclosed herein is a general approach to the family of bakkanes via the common intermediate obtained from a Diels−Alder/aldol sequence and a short synthesis of bakkenolide-A (**1**), the most prominent member of this class of compounds. Bakkenolide-A (**1**), also known as fukinanolide, was isolated from the wild butterbur *Petasites japonicus*,

† Dedicated to Professor Goverdhan Mehta.

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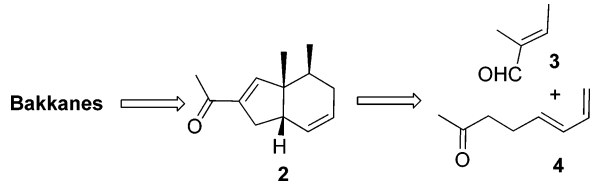
showed cytotoxicity toward several carcinoma cell lines, and is an effective insect antifeedant.[6]

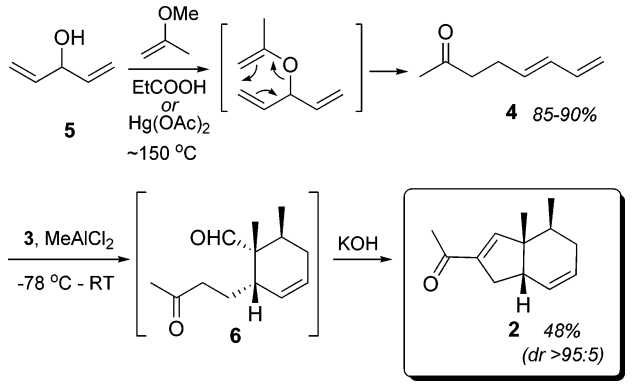
Retrosynthetically, most of the bakkanes could be assembled from the functionalized hydrindane precursor **2** with chemically differentiated olefins. Compound **2** can be visualized from the Diels−Alder/aldol sequence of tiglic aldehyde **3** and diene **4** (Scheme 1).

Scheme 1



The diene **4**[7] was synthesized in high yield from a commercially available divinyl carbinol **5** and methoxy propene in the presence of propionic acid or mercuric acetate in one step via Claisen rearrangement[8] (Scheme 2). Reaction

Scheme 2

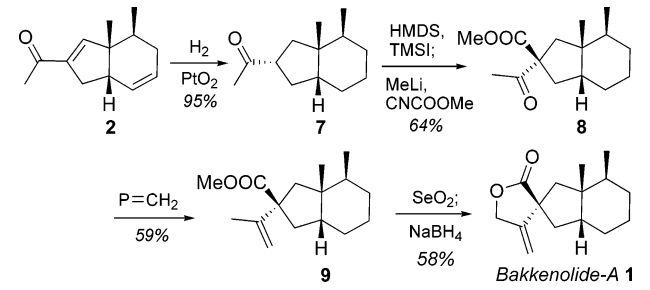


of the diene **4** with tiglic aldehyde **3** in the presence of a Lewis acid followed by base treatment furnished enone **2**[9] in a highly diastereoselective fashion. This transformation established the requisite stereochemistry of three contiguous stereogenic centers of the bakkane family of natural products.

The Lewis acid mediated intermolecular Diels−Alder reaction[10,11] produces the *endo*-adduct **6**[12] having the aldol partners (i.e., aldehyde and ketone) in close proximity, allowing for subsequent intramolecular aldol reaction to give **2**. The diastereo- and regioselectivity can be explained on the basis of secondary orbital interactions and atomic coefficient preferences, respectively.[13] The functionally embellished *cis*-hydrindane **2** is an ideal intermediate for the construction of most of the bakkane family members as it possesses chemically differentiated olefins for the selective functionalization of either ring.

The efficiency of this approach toward the bakkanes was readily demonstrated by a rapid construction of bakkenolide-A (**1**) from the common hydrindane precursor **2**. Toward that goal, both double bonds in **2** were hydrogenated to give a saturated ketone **7** in a highly stereoselective manner (>9:1). The stereochemistry shown in compound **7** is based on the assumption that the hydrogenation occurred from the convex face of the enone **2**. For the construction of the spirolactone of **1**, a quaternary methoxycarbonyl group was introduced stereoselectively on the five-membered ring with Mander's reagent[14] via a thermodynamically stable silyl enol ether.[15,5k] Once again, the shape of the molecule controlled the reagent approach from the convex face to give highly selective reaction. Wittig olefination on keto-ester **8** resulted in Hayashi's intermediate **9**[5l] in 59% yield (Scheme 3).

Scheme 3



Finally, the intermediate **9** was converted to the bakkenolide-A (**1**), by treatment with SeO_2 followed by $NaBH_4$ reduction of the aldehyde that resulted from overoxidation. This conversion was carried out in a one-pot sequence by modi-

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(9) Stereochemistry was assigned on the basis of literature precedence; see: refs 10, 11, and 13.

(10) For the synthesis of eremophilanes using similar Diels−Alder reaction, see: Reddy, D. S.; Kozmin, S. A. *J. Org. Chem.* **2004**, *69*, 4860−4862.

fying the reported procedure.[5l] All spectral data (IR, ^{1}H and ^{13}C NMR) were found to be identical to those reported by Back et al.[5j] The overall yield of **1** was 9% for eight steps starting from commercially available divinyl carbinol **5**.

In short, this letter reports a general approach to the family of bakkanes via a functionalized common intermediate, using a Diels−Alder/aldol sequence as the key step. The potency of this approach was demonstrated by a short synthesis of bakkenolide-A in eight steps. Synthesis of other bakkanes and adaptation to an asymmetric version will be the subject of future directions of this laboratory work.

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Supporting Information Available: Detailed descriptions of experimental procedures and ^{1}H, and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Compound **6** could not be isolated in pure form, and the crude reaction mixture was subjected to the next step as such.

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