Tetrahedron Letters, Vol.30, No.5, pp 565-566, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

DIRECT APPROACH TO THE BAKKANES: A SYNTHESIS OF (±)-HOMOGYNOLIDE-B

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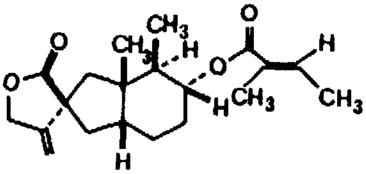
Abstract: A short synthesis of racemic homogynolide-B is described. The key step of the approach, cycloaddition of dichloroketene with the 2,2-dimethyltrimethylene acetal of 2,3-dimethyl-3-cyclohexen-1-one, proceeds with excellent selectivity and in high yield.

The bakkanes, a relatively small group of hydrindane natural products,[1] have to date received only limited attention from synthetic chemists. In fact, merely a few preparations of bakkenolide-A, the structural prototype of the class, have so far been reported.[2] In this Letter we describe the synthesis of homogynolide-B (1), the first synthesis of one of the more highly functionalized bakkanes. Homogynolide-B, isolated from the neutral extracts of the plant Homogyne alpina and structurally and stereochemically elucidated by proton NMR,[3a] has been shown to possess antifeedant activity against certain types of grain and feed pests.[3b]



1

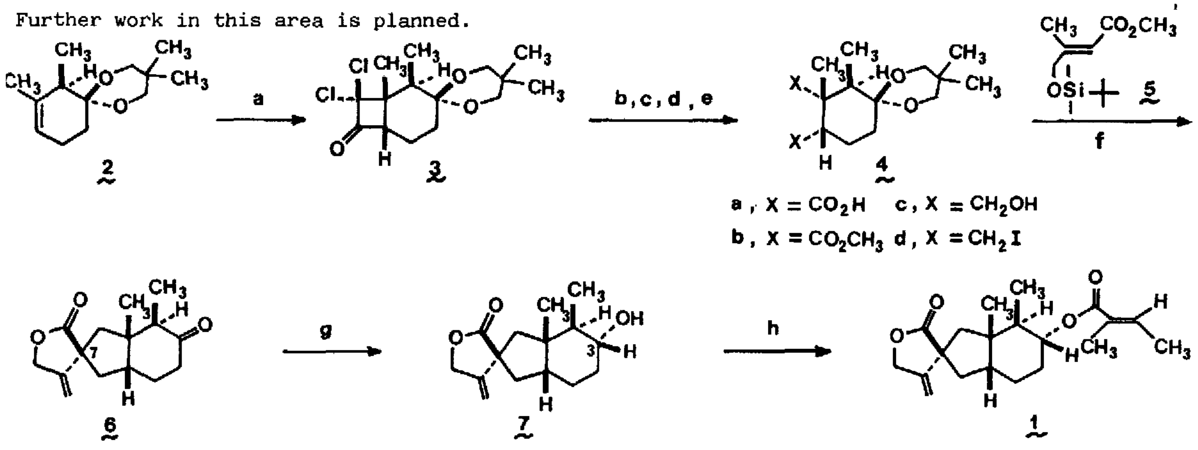
Homogynolide-B

The 2,2-dimethyltrimethylene acetal of 2,3-dimethyl-3-cyclohexen-1-one[4] (2) underwent cycloaddition with in situ generated dichloroketene[5] in a highly regio- and stereoselective manner to provide α,α-dichlorocyclobutanone 3, mp 90-92°C, in 82% yield. The conversion of the cycloadduct to diester **4b** could be achieved in 75% overall yield by sequential treatment[7] with n-butyllithium, acetic anhydride, ozone, and dimethyl sulfide, followed by esterification and chromatographic purification. Lithium aluminum hydride reduction of diester **4b** generated in 89% yield the corresponding diol **4c**, mp 114-116°C, which was converted to diiodide **4d**, mp 126-127°C (dec), by using Corey's phosphite method[8] (41%) followed by reprotection (77%). This procedure for securing the diiodide was the only one of a large number examined that proved effective.

Cycloalkylation of acrylate derivative 5[9] with diiodide **4d** was carried out in THF-HMPA with 2.2 equiv of lithium bis(trimethylsilyl)amide to provide in 70% yield an equimolar mixture of C-7 epimeric hydrindanes, which could be readily separated by silica gel chromatography. The less polar isomer on exposure to aqueous hydrofluoric acid in acetonitrile[9,10] suffered double deprotection and lactonization to give in 73% yield keto lactone **6** (mp 99-102°C), which produced spectroscopic data in excellent accord with the literature values for natural product-derived **6**.[3a]

Reduction of keto lactone **6** with sodium borohydride in 2-propanol afforded in 76% yield an easily separated 2:3 mixture of 3-hydroxybakkenolide-A (mp 105-110°C, δ 3.40 br[11]) and its C-3 epimer (δ 3.84[11]; recycled by PCC oxidation, 80%). 3-Hydroxybakkenolide-A (**7**) was esterified with tiglic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in toluene[12] to provide in 75% yield racemic homogynolide-B, chromatographically and spectroscopically indistinguishable from the natural product.

This synthesis, while serving to confirm the structure and stereochemistry previously assigned to homogynolide-B, demonstrates the flexibility of our approach to the bakkanes. Further work in this area is planned.



^{a}CCl$_3$COCl, POCl$_3$, Zn-Cu, ether, 20°C. ^{b}n-C$_4$H$_9$Li, THF, −78°C, then (CH$_3$CO)$_2$O, −78 → 20°C; O$_3$, CH$_2$Cl$_2$-CH$_3$OH-C$_5$H$_5$N, −78°C, then CH$_3$SCH$_3$, −78 → 20°C. ^{c}aq NaOH, CH$_3$I, HMPA, 20°C. ^{d}LiAlH$_4$, THF, 20°C. ^{e}$\mathrm{C_6H_4{<}^{O}_{O}{>}PCl}$, C$_5H_5$N, ether, 0°C; I$_2$, CH$_2Cl_2$, 20°C; (CH$_3$)$_2$C(CH$_2$OH)$_2$, BF$_3$.O(C$_2H_5$)$_2$, CH$_2Cl_2$, 0°C. ^{f}5, (TMS)$_2$NLi(2x), THF-HMPA(6:1), −78°C; separation; aq HF, CH$_3$CN, 20°C. ^{g}NaBH$_4$, (CH$_3$)$_2$CHOH, 0°C; separation. ^{h}Tiglic acid, DCC, DMAP, C$_6$H$_5$CH$_3$, 65°C.

Acknowledgment. We thank Prof. J. Lhomme and Dr. J.-L. Luche for their interest in our work and Dr. J. Harmatha for comparison samples and spectra. Financial support from the C.N.R.S. (UA 332) and a fellowship award from the C.N.Pq. (to F.C.) are gratefully acknowledged.

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(Received in France 9 December 1988)