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Stereoselective Synthesis of Homogynolide-A, A Bakkane from *Homogyne alpina*

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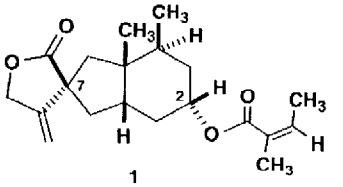
Abstract Homogynolide-A, an antifeedant sesquiterpene, has been stereoselectively prepared from benzoquinone

The bakkanes, a class of naturally occurring spiro β-methylene-γ-butyrolactones, have been isolated from several genera of the *Senecioneae* tribe (Compositae) [1] The antifeedant effect of several of these novel hydrindanes on stored grain and seed pests is noteworthy homogynolides A and B and bakkenolide-A, for example, show moderate to excellent protectant activity against beetle adults (*Sitophilus granarius, Tribolium confusum*) and larvae (*Trogoderma granarium, Tribolium confusum*) [2]

In view of the dearth of synthetic activity in this area, we began a few years ago a study of possible approaches to the bakkanes, which culminated in the first syntheses of (+)-bakkenolide-A[3] and (±)-homogynolide-B [4] In this communication, we wish to record the first preparation of homogynolide-A (**1**) [5] This racemic synthesis, which required a number of modifications of our basic bakkane approach, permits good to excellent stereocontrol at all 5 stereogenic centers [6]



Homogynolide-A

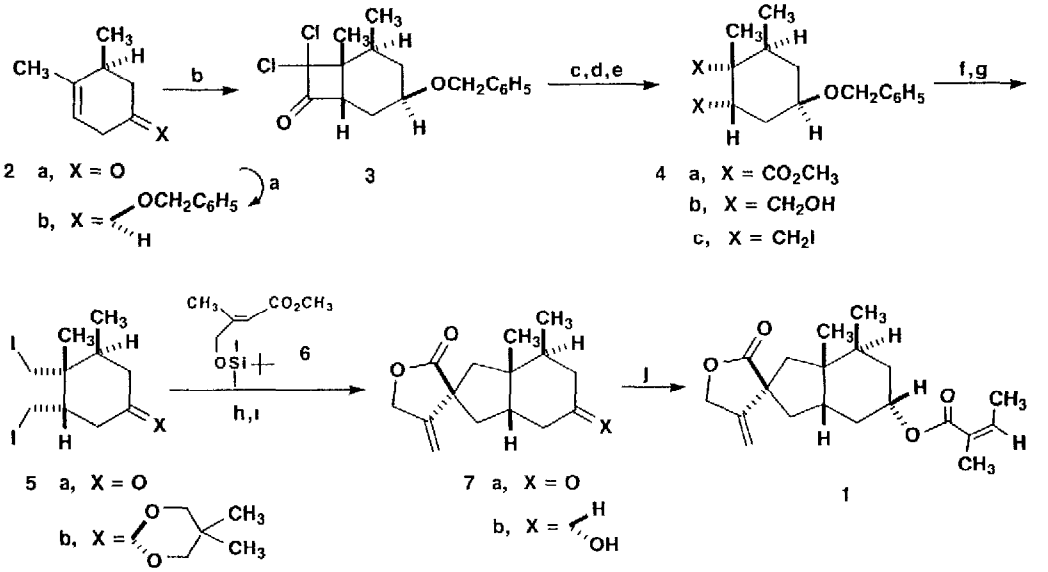
1

4,5-Dimethyl-3-cyclohexenone (**2a**), easily prepared from benzoquinone,[7] was stereoselectively (≥98 2) converted with lithium aluminum hydride to the cis alcohol, which could be benzylated under standard conditions to give **2b** (97% overall) The reaction of **2b** with dichloroketene, using the Hassner protocol,[8] produced with excellent face selectivity (≥95 5) the desired cycloadduct **3** In that large material loss attended chromatographic purification of this non-crystalline substance, it was immediately subjected to enol acetate formation, and then ozonolytic cleavage and in situ esterification[4] to afford the stereochemically homogeneous diester **4a** in 44% overall yield from **2 b** (81%/step) Hydride reduction of this diester gave diol **4b**, which could be cleanly converted to diiodide **4c** via the corresponding ditriflate (54% overall) Numerous other potential methods for accomplishing this problematical conversion failed entirely due to competing elimination and/or tetrahydrofuran formation

As preliminary studies had indicated that a C-2 (bakkane numbering) acetal would provide the best C-7 nat-epi stereochemical ratio in the upcoming cycloalkylation reaction, the benzyl ether of **4c** was cleaved with TMSI and the resulting alcohol (mp 113-114°C) was oxidized to give **5 a** (mp 105-106°C), which was acetal-protected to provide **5 b** (mp 87-88°C) in 73% overall yield [9] This adjustment concomitantly served toward the introduction of the required configuration at C-2 (see below)

Cycloalkylation and double deprotection-lactonization[4] generated in 50% yield an easily separated, ca 3 1 favorable mixture of C-7 epimeric ketones, the major of which (**7a**[10]) on hydride reduction produced highly stereoselectively (≥95 5) in 83% yield alcohol **7b** [10] Esterification of this alcohol could be effected with angelic acid, without detectable *Z*→*E* isomerization, by using a slight modification of Yamaguchi's procedure[11] to give in 70% yield homogynolide-A, whose identity was confirmed through spectroscopic comparison

In summary, racemic homogynolide-A has been obtained from ketone **2 a** in 16 steps with an overall yield of 4% Additional work in the bakkane area is in progress



[a] $LiAlH_4$, THF, -78°C, NaH, $C_6H_5CH_2Cl$, $(C_4H_9)_4NI$(cat), THF, reflux [b] CCl_3COCl, $POCl_3$, Zn-Cu, ether, reflux [c] $(CH_3)_2CuLi$, ether, -50°C, then $(CH_3CO)_2O$, -50→20°C, O_3, CH_2Cl_2-CH_3OH, -78°C, then CH_3SCH_3, -78→20°C, aq NaOH, CH_3I, HMPA, 20°C [d] $LiAlH_4$, THF, 20°C [e] $(CF_3SO_2)_2O$, 2,6-di-*t*-butylpyridine, CH_2Cl_2, -30°C, $(C_4H_9)_4NI$, $C_6H_5CH_3$, 20 °C [f] TMSI, CH_2Cl_2, 20°C, PCC, CH_2Cl_2, 20°C [g] $(CH_3)_2C(CH_2OH)_2$, BF_3·$O(C_2H_5)_2$, CH_2Cl_2, 0°C [h] **6**, $(TMS)_2NLi$ (2x), DME-THF-HMPA (3 2 1), -58°C, aq HF CH_3CN, 20°C, separation [i] $LiAl(Ot\text{-}C_4H_9)_3H$, THF, 0°C [j] Angelic acid, $Cl_3C_6H_2COCl$, $(C_2H_5)_3N$, THF, 20°C, filtration, evaporation, addition of **7b** in $C_6H_5CH_3$, 60°C

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Notes and References

1 See Fischer, N H , Olivier, E J , Fischer, H D In *Progress in the Chemistry of Organic Natural Products* Herz W , Grisebach, H Kirby, G W Eds , Springer-Verlag New York 1979 Vol 38, Chapter 2, and references cited therein

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3 Greene, A E , Coelho, F Deprés, J -P Brocksom, T J *Tetrahedron Lett* **1988**, 29 5661-5662 For syntheses of (±)-bakkenolide-A, see references cited therein

4 Coelho, F , Depres J -P , Brocksom, T J , Greene, A E *Tetrahedron Lett*, **1989**, *30*, 565-566

5 Harmatha, J Samek, Z , Synackova, M , Novotny L Herout, V , Sorm, F *Collect Czech Chem Commun* **1976**, *41*, 2047-2058 Jakupovic, J , Grenz M Bohlmann, F *Planta Med* **1989** *55* 571-572

6 The structural resemblance of homogynolide-A with homogynolide-B belies the differences encountered in their syntheses These differences will be discussed in the full paper on our bakkane work

7 Benzoquinone was transformed to 4 hydroxy-4 5-dimethyl 2 cyclohexenone (see Solomon M Jamison, W C L , McCormick M Liotta, D Cherry, D A Mills J E Shah, R D , Rodgers J D , Maryanoff C A *J Am Chem Soc* **1988**, *110* 3702-3704), which was converted to **2a** with zinc in acetic acid We thank Prof Liotta for providing experimental details for the first part of this transformation

8 Krepski, L R , Hassner, A *J Org Chem* **1978**, *43*, 2879-2882

9 The acetal of **2a** undergoes dichloroketene cycloaddition on the β-face and, therefore cannot be used at the outset to obtain **5b**

10 This material provided NMR data in excellent agreement with the literature values for the natural product-derived compound

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