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Stereoselective Synthesis of (-)-Homogynolide-A

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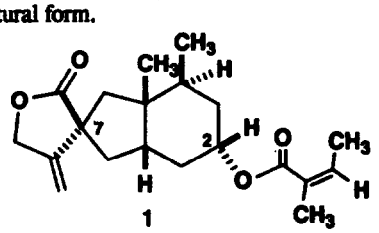
Key words: bakkane, spirolactone, antifeedant, dichloroketene, *Homogyne alpina*

Abstract: (-)-Homogynolide-A, a spiro β-methylene-γ-butyrolactone sesquiterpene from *Homogyne alpina*, has been stereoselectively prepared in natural form from *S*-(+)-carvone.

While approximately 10% of all structurally elucidated natural products are α-methylene-γ-butyrolactones, the number of known, naturally occurring β-methylene-γ-butyrolactones is small.[1] The latter, to date all spiro-fused hydrindane sesquiterpenes of the bakkane family, are however of interest due to their structure and associated biological activity.[2]

Homogynolide-A (1), a bakkane isolated together with homogynolide-B and bakkenolide-A from *Homogyne alpina* (Compositae) and structurally elucidated by spectroscopic methods, displays antifeedant activity against beetle adults and larvae.[2b,3] Recently, we described[4] a total synthesis of (±)-homogynolide-A; in this Letter we disclose a highly stereocontrolled synthesis of (-)-homogynolide-A, the first of any of the functionalized bakkenolides in natural form.

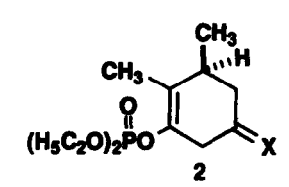


1 (-)-Homogynolide-A

Enantiopure (*S*)-(+)-carvone was subjected to copper-mediated conjugate addition–trapping to produce the enol phosphate **2a** in 86% yield. Selective ozonolysis of **2a** followed by Criegee rearrangement (*p*-$NO_2C_6H_4COCl$; CH_2Cl_2, Δ)[5] then delivered acetate-phosphate **2b** (62% overall), which was subjected to a reduction (Li, CH_3NH_2)–oxidation (H_2CrO_4, ether-water)–reduction ($LiAlH_4$) sequence to give stereoselectively and in good yield the desired alcohol **3**.[6]

The conversion of **3** to (-)-homogynolide-A essentially paralleled our previous approach.[4] Thus, hydroxyl group protection was followed by highly face selective dichloroketene cycloaddition–oxidative cleavage[8,9] to afford efficiently the diester **4a**. Lithium aluminum hydride reduction of the diester produced the corresponding diol, which was best converted to diiodide **4b** via the ditriflate (> 50% overall). Benzyl ether cleavage (TMSI, CH_2Cl_2) to give alcohol **5a** (mp 81-83 °C, $[\alpha]_D^{25}$ +59°)[6] and acetalization of the corresponding ketone (mp 74 °C, $[\alpha]_D^{25}$ +47°), obtained with PCC, afforded the crystalline diiodo acetal **5b** (mp 119-120 °C, $[\alpha]_D^{25}$ +84°) in high yield. As expected,[4] cycloalkylation of lactone synthon **6**[10] with this material generated predominately (ca. 3:1) the required *R* configuration at C-7 and gave after brief exposure to acid 2-ketobakkenolide A (**7a**, $[\alpha]_D^{25}$ -5°).[11] Highly stereoselective (> 95:5) reduction of the C-2 carbonyl with lithium tri-*tert*-butoxyaluminohydride then yielded 2-hydroxybakkenolide-A (**7b**, mp 91-93 °C, $[\alpha]_D^{25}$ -4°; lit.[3a] mp 91-93 °C),[11] which was esterified with angelic acid[12] to give for the first time synthetically derived (-)-homogynolide-A (mp 62-64 °C, $[\alpha]_D^{25}$ -22°, CD $\Delta\varepsilon_{217}$ -2.50; lit.[3a] mp 62-65 °C, CD $\Delta\varepsilon_{220}$ -2.51), whose identity was confirmed by direct spectroscopic comparison with the naturally derived substance.

Work directed toward the preparation of related sesquiterpenes is currently being carried out in our laboratory.



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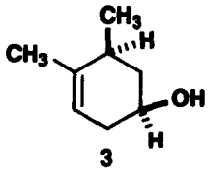

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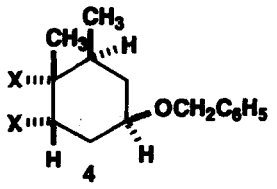

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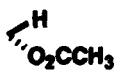
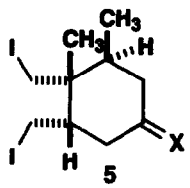
a, X =  ; b, X = 

a, X = CO_2CH_3 ; b, X = CH_2I



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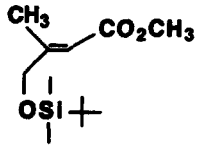

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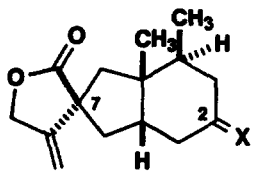

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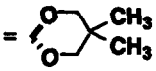
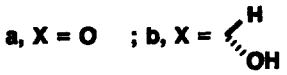
a, X =  ; b, X = 

a, X = O ; b, X = 

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Notes and References.

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6. Analysis of the Mosher ester of 3 revealed the presence of ca. 8% of enantiomeric contamination, which arose from cis conjugate addition. Although pure 3 ($[\alpha]_D^{25}$ +45° (*c* 1.3, $CHCl_3$)) could be obtained by prior separation of cis and trans isomers, it was found that the elimination of the small amount of contaminating material was much more readily achieved by application of the Noe lactol technique[7] to alcohol 5a (93% efficiency).

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

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