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AN APPROACH TO THE STEREOCONTROLLED CREATION OF AN ACYCLIC SIDE CHAIN OF SOME NATURAL PRODUCTS

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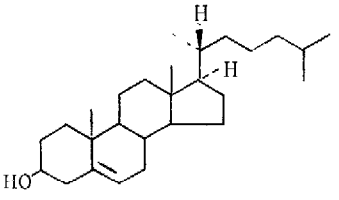
The acyclic C_7 side chain of steroids 1, Vitamin D metabolites 2, ophiobolin 3, etc. require the development of methods for the selective control of the stereochemistry of the acyclic carbon bearing methyl relative to ring



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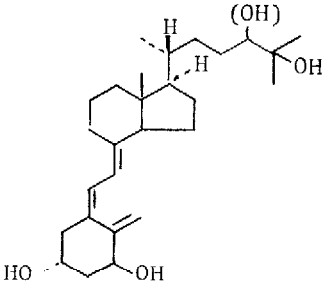

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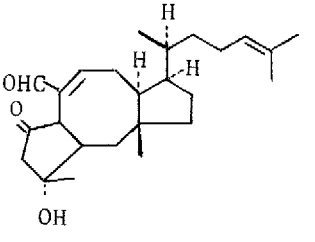

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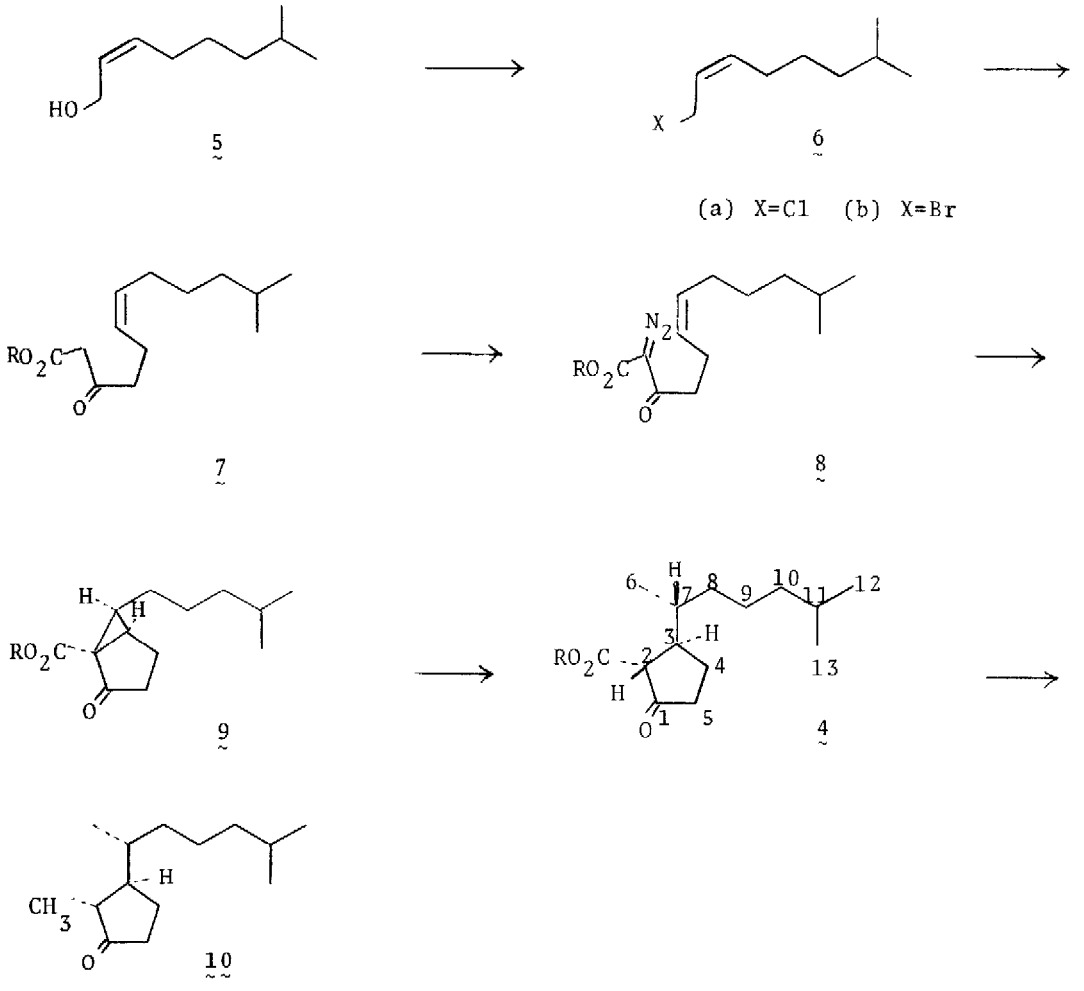
geometry.[1] We wish to report an approach to this problem based upon the opening of a cyclopropane ring with an organocopper reagent.[2,3] The target compound 4 can be envisioned as an intermediate in the total synthesis of the above types of compound.

The scheme outlines the approach. 7-Methyloct-Z-2-en-1-ol (5), available from Z-2-buten-1,4-diol as previously described,[4] was converted to the chloride 6a[5a] [NCS,[6] $(CH_3)_2S$, CH_2Cl_2, 0°, bp 90° @ 11 mm, 76%] or preferably the bromide[5b] 6b [PBr_3, CaH_2,[7] ether, 0°, bp 54-7° @ 1.4 mm, 80%]. Alkylation of the dianion of methyl acetoacetate generated in the usual way[8] [alkylation, 25°, bp 109° @ 0.1 mm, 71%] gave the unsaturated ketoester 7[5a] [IR 1752, 1726, 1659, 1640 cm^{-1}; NMR δ 5.16-6.48, m, 2H; 1.0-1.7, m, 5H; 0.90, d, J=7, 6H]. The corresponding t-butyl ester was also easily prepared in an identical fashion

utilizing t-butyl acetoacetate. Diazo transfer[9] [TsN_3, CH_3CN, $(C_2H_5)_3N$, 25°] was monitored by the appearanee of strong IR bands at 2140, 1720, and 1657 cm^{-1}

Scheme. Synthetic Approach to 4.



and the crude product 8 subjected directly to intramolecular cyclization[10] [Cu-bronze powder, $PhCH_3$, reflux, 73-80%] to give the desired cyclopropane 9[5a] [IR 1740 cm^{-1}, NMR δ 3.68, s, 3H; 1.75-2.6, m, 6H; 1.1-1.65, m, 7H; 0.88, d, J=7 Hz, 6H]. It is interesting to note that 9 behaves as if it is exceptionally polar on tlc.

The key reaction employs the ring cleavage of the cyclopropane with cuprates.[2,3] Indeed, treatment of 9 with lithium dimethylcuprate [0°, ether, 86%]

gave the desired 4[5a] [IR 1764, 1736, 1660, 1612 cm^{-1}; NMR δ 3.64, s, 3H; 2.76 d, J = 11 Hz, 1H; 1.0-2.6, m, 4H; 1.0-1.8, m, 9H; 0.88, d, J = 7 Hz, 9H] which was homogeneous by spectral and chromatographic criteria. The E stereochemistry of the ring is suggested by the 11 Hz coupling constant between the H on C(2) and C(3) and by thermodynamics. The stereochemistry of C(7) relative to the ring junctio follows from the cis stereochemistry of the olefin and the known inversion of the con figuration in the cuprate ring opening.[2c,3] The compound was further characterized by methylation, hydrolysis, and decarboxylation of 4 (R = $CO_2C_4H_9t$) to give 10.[5a] This approach should be applicable to either stereochemistry at C(7) since the E olefin should give the opposite configuration.

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