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A SYNTHETIC APPROACH TOWARDS THE CLERODANE DITERPENOIDS, A VERSATILE SYNTHON

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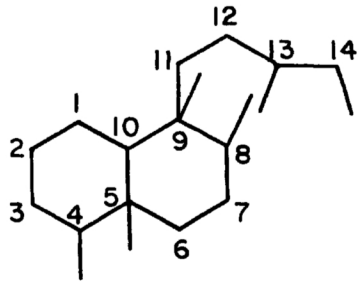
A potential synthetic route to the trans-clerodane diterpenes is described. Two key features involved in the synthesis are a unique acid-catalyzed Michael addition-cyclization sequence developed by G. Saucy, and an opening of the cyclic hemiketal intermediate 10 by thioketalization. A known steroidal synthetic intermediate 7 prepared in a series of reactions from 4 confirmed the trans-decalin structure of our intermediates.

From the roots of Solidago species a number of new diterpenes belonging to the clerodane class have been isolated in recent years[1]. This class of diterpene has the basic skeleton 1 derived from labdane through a backbone rearrangement with sequential hydride and methyl shifts. Clerodanes with cis-decalin structure have also been found in the same species[2] and the Scrophulariaceous plants[3]. Most of these diterpenes are further noted as carrying a furan ring. In continuing our general program aimed at the total synthesis of higher terpenes we bacame interested in some of these diterpenes because of the varying nature of the side chain structure with similar or identical bicyclic skeletons. For this purpose, it would be highly desirable that these natural products be synthesized from a common intermediate. Here we wish to disclose a convenient route to such an intermediate that can serve as a synthon for a variety of clerodanes (e.g. kolavelool 13,[4] junceic acid 14[5] and solidagolactone 15[6]). Unlike conventional approaches in this kind of synthesis in which the side chain portions in the diterpenes would be introduced onto decalones by alkylation, ours takes advantage of the unique cleavage of the cyclic hemiketal (10 → 11) by thioketalization[7]. Accordingly, a four carbon unit with a hydroxy group is revealed for a side chain as well as a thioketal group on the decalin portion, both of which are necessary for further manipulations.

The key substance 4[8] was prepared by the method patterned after G. Saucy's stereoid total syntheses[9]. The starting material was the hydroxy α,β-unsaturated ketone 2 which was itself available by the controlled Grignard reaction of 5-methyl-5-pentanolide[10] with vinyl bromide at -70°C (ca. 50% yield). According to the published procedure, 2 was condensed with 2-methyl-1,3-cyclohexadione in a boiling mixture of acetic acid and toluene (1:3) (the yield was always relatively low, 40-%). Hydrogenation of 3 to 4 on 10% Pd/C was quantitative and stereospecific as shown at a later stage. In order to ensure the expected trans-stereochemistry at the A,B ring junction, we transformed 4 into the α,β-unsaturated ketone already known 7[11] through the following Saucy's procedures; a) Hydration with dilute sulfuric acid (1N) in acetone (4 → 5) b) Jones' oxidation (5 → 6) and c) Cyclization by refluxing either in benzene with p-TsOH or in alcoholic KOH (6 → 7). The overall yield from these operations was 31%. In the event, 7 was

obtained as yellow crystalline form[12] (the total yield: 8% from 2), mp 120-122°C: IR(KBr) 1712, 1668 cm^{-1}; UV max 240 nm (ε 2.61 x 10^4). With the trans-A,B ring structure in hand, some preliminary studies were undertaken towards our goal. Methyl Grignard reagent added to 5 without difficulty, and the resultant mixture of alcohols 8 was dehydrated to 9 upon refluxing with HCl in methanol. Treatment of the alcohols with thionyl chloride in pyridine at 0°C produced a complex mixture from which only trace of 9 was detectable. The crucial cleavage of 9 after the same hydration procedure as above (9 → 10) was achieved by thioketalization, (1,2-ethanedithiol and boron trifluoride etherate) whereby 11 was obtained in 64% yield. This procedure was necessary since both C-8 and C-13 have to be differentially functionalized so as to allow the construction of the rest of the molecules at later stages. Oxidation of 10 with Jones' reagent as described above (5 → 6) would afford a diketone similar to 6 in which C-8 and C-13 are not discriminated. Finally, the hydroxy thioketal 11 was oxidized to 12[13] by Sarret oxidation (chromium trioxide in pyridine). Compound 12 appears to be a valuable intermediate in the preparation of various clerodane diterpenes such as 13, 14 and 15 provided the stereospecific introduction of the vicinal dimethyl groups at C-8 and C-9 can be solved along with the construction of the various side chains[14]. These transformations are under active study in our laboratory.



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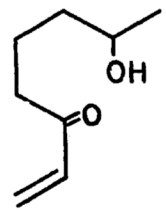

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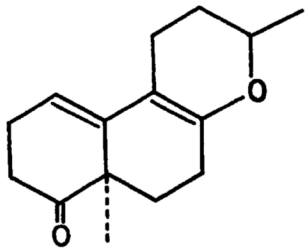

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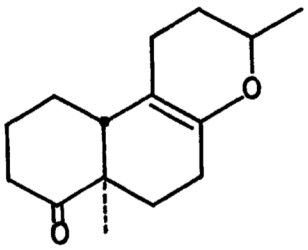

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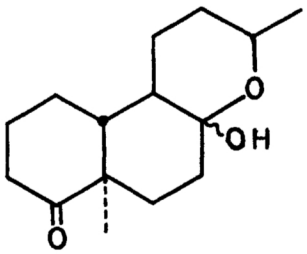

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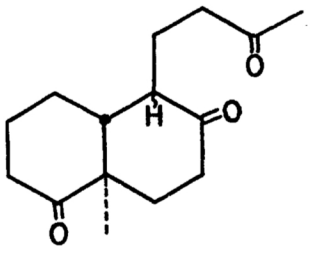

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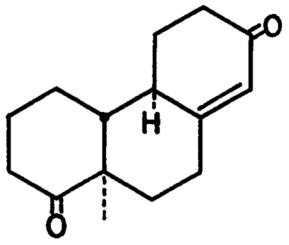

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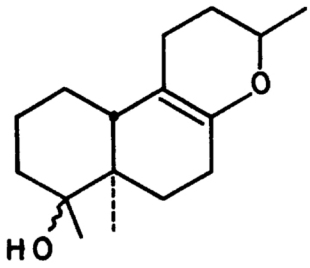

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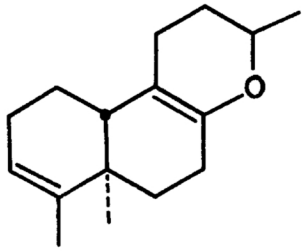

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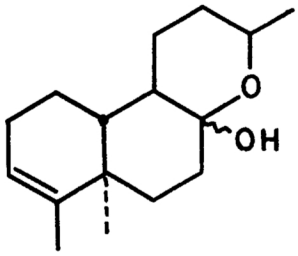

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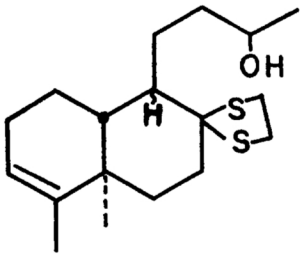

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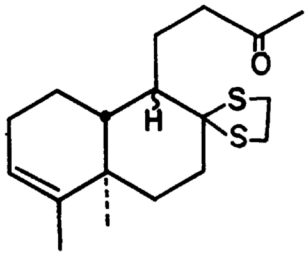

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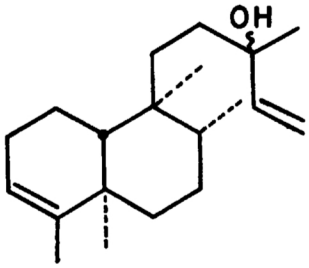

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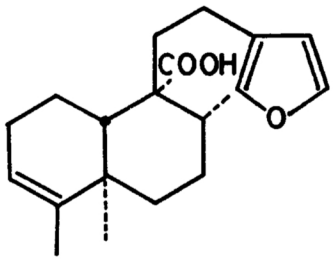

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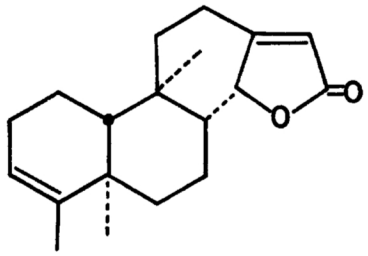

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8) mp 71-73°C; IR(KBr) 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.26 (d, 3H, J = 6 Hz), 3.76 (m, 1H); mass spectrum 234 (M^+); Anal. Calcd for $C_{15}H_{22}O_2$; C, 76.88; H, 9.46. Found: C, 76.87; H, 9.45.

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12) The authentic sample provided by Professor S. Danishefsky confirmed the structure of 7.

13) mp 71-72°C; IR(KBr) 1717 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (s, 3H), 2.14 (s, 3H), 3.23 (s, 4H), 5.20 (s, 1H); Anal. Calcd for $C_{18}H_{28}OS_2$; C, 66.61; H, 8.70; S, 19.76. Found: C, 66.66; H, 8.69; S, 19.73. The yield of this stage was ca. 45% and not optimized.

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