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SYNTHESIS OF CHIRAL CYCLOPENTENOIDS

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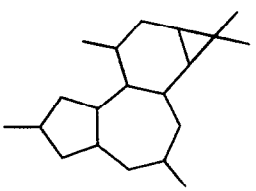
Abstract: A synthetic route has been developed from (-)-citronellal to methylcyclopentenoids which retain the chiral center. These cyclopentenoids should be valuable intermediates in the syntheses of several diterpenoids.

A large number of diterpenoids,[1] including those with the tigliane(1),[2] lathyrane(2),[3] and jatrophane(3)[4] skeletons, have a methylated cyclopentane ring as a common feature. In many cases, if the methyl group is attached to a chiral carbon this asymmetric center is remote from other functionality. Thus, stereochemical control of this center at an early stage is essential in syntheses directed towards optically active natural products. The ideal synthetic intermediate should be readily available in optically active form, and contain substituents that would allow elaboration of a single enantiomer into diterpenoids of either absolute configuration.[5]



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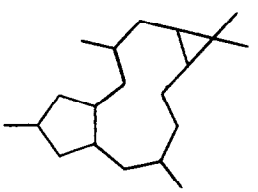

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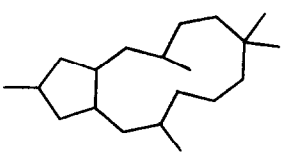

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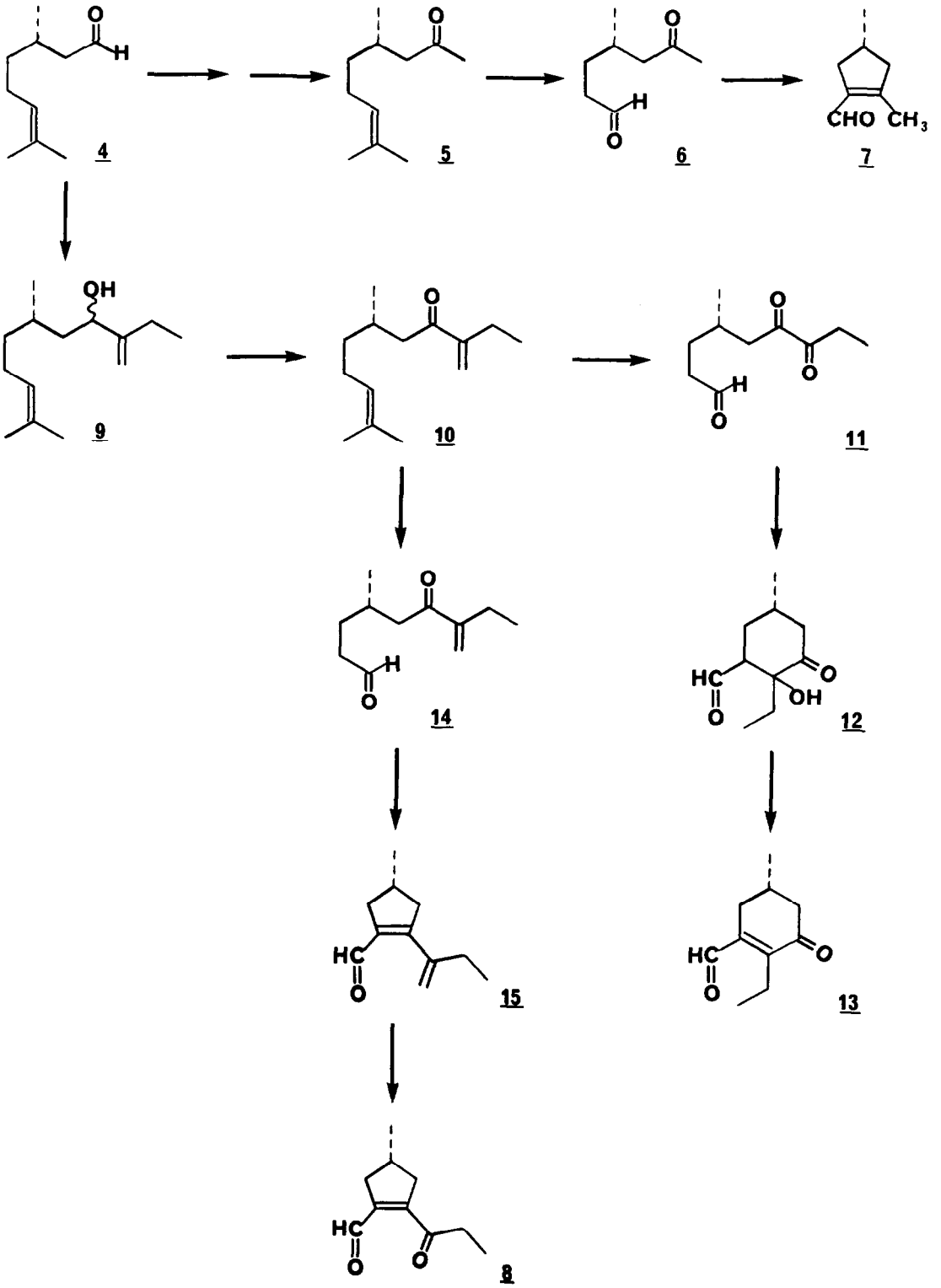
Our synthetic plan originated with the observation that optically active cyclopentenoids could be derived in principle from readily available (-)-citronellal(4), through a series of manipulations remote from the asymmetric center. To test this hypothesis we prepared 4,8-dimethylnon-7-en-2-one(5),[6] which upon reaction with ozone (CH_2Cl_2, -78°; then H_2, Pd/C) affords the ketoaldehyde 6.[7] When compound 6 is treated with catalytic amounts of piperidine and acetic acid (benzene, reflux with Dean-Stark trap), a regiospecific condensation[8] is achieved to produce the cyclopentene aldehyde 7 in good yield. More elaborate analogues could be prepared from the cyclopentene 7 by functionalization of the vinylic methyl group, but it would require a fairly lengthy sequence to prepare our immediate objective, the ketoaldehyde 8, from compound 7. Instead, we chose to attempt the synthesis of compound 8 via cyclization of an intermediate bearing a propionyl group, or a protected propionyl equivalent.


O
H
4
5
6
CHO CH3
7
OH
9
10
11
14
HC
O
OH
12
13
15
8

The desired acyclic intermediate 10 is easily obtained. Reaction of citronellal with the Grignard reagent derived from 2-bromo-1-butene[9] gives a mixture of diastereomeric allylic alcohols(9, 95% yield). Upon treatment with pyridinium chlorochromate,[10] these alcohols are readily oxidized to afford the dienone 10 (71%). The shortest conceivable route from the dienone 10 to the desired cyclopentene 8 would require oxidative cleavage of both double bonds followed by cyclization to the five-membered ring, rather than the six-membered ring, product. The oxidative cleavage is readily brought about by reaction with ozone (CH_2Cl_2, -78°; then dimethyl sulfide), but treatment of the resulting diketoaldehyde 11 with piperidine/acetic acid gave a complex mixture. The products isolated from this mixture were those in which cyclization had occurred but dehydration of the aldol intermediates(12) had not. Subsequent dehydration of the mixture (p-toluenesulfonic acid, benzene, reflux) gave a major product assigned structure 13. This assignment was indicated by the ^{13}C NMR spectrum (especially methyl resonances of 16.7 and 15.8 ppm), which was significantly different from our predictions for the desired five-membered ring structure bearing a propionyl group.[11]

Conversion of the dienone 10 to the desired cyclopentenoid 8 is best accomplished by sequential cleavage of the double bonds. The first cleavage, of the non-conjugated double bond, can be achieved in two ways. Selective epoxidation is obtained upon treatment of compound 10 with m-chloroperoxybenzoic acid (CH_2Cl_2/aq $NaHCO_3$, room temperature),[12] and the resulting diastereomeric epoxides can be cleaved by reaction with periodic acid.[13] However, the ketoaldehyde 14 appears to be unstable under these conditions; yields were low and variable. In contrast, treatment of compound 10 with one equivalent of ozone results in near quantitative conversion to the ketoaldehyde 14. Cyclization of this ketoaldehyde proceeds as expected to afford the dienal 15 (~60% after purification by column chromatography), but ozonolysis of this dienal to afford the desired product 8 did not, at first, appear promising. However, after a series of experiments with alternative oxidants (including $OsO_4/NaIO_4$, MCPBA, H_2O_2/OH^-, etc.) failed to produce useful results, we returned again to use of ozone. We discovered that standard solutions of ozone in CH_2Cl_2 (Rubin ozonolysis[14]) could be used to effect the desired transformation. Thus the ketoaldehyde 8[15] is now available via a five step sequence from (-)-citronellal.

This work suggests that a variety of 1,2-substituted-4-methylcyclopentenes can be prepared in optically active form. As a synthetic intermediate, compound 8 has the special advantage that the single enantiomer we have prepared[15] could lead to either absolute configuration at the chiral methine of these diterpenoids via selective reactions at the aldehyde and ketone groups. Given the growing interest in synthesis of lathyrane[16] and jatrophane[17] diterpenoids, this approach should prove very useful.[18]

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15. ^{1}H NMR ($CDCl_3$) δ 1.10 (3, d, J = 6 Hz), δ 1.12 (3, t, J = 6 Hz), 2.3-2.9 (7, m), 10.12 (1, s); ^{13}C NMR ($CDCl_3$) δ 201.3(s), 190.5(d), 153.4(s), 147.3 (s), 43.6(t), 38.8(t), 35.7(t), 30.8(d), 21.0(q), 7.4(q); EI MS (70 eV) 166 (M^+, 77), 151(97), 137(61), 109(100), 96(49), 81(74), 79(65); High resolution mass spectrum. Calcd. for $C_{10}H_{14}O_2$: 166.0994; Found: 166.0992. Starting with citronellal of $[\alpha]_D = -6.5^{o}$ (ca. 60% ee, Aldrich) we obtained compound 8 with $[\alpha]_D = +1.2^{o}$.

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