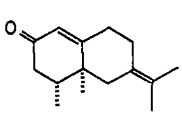
Spirovetivanes from Fulvenes

Summary: Spirovetivanes can be synthesized by adding lithium dimethylcuprate to fulvene **7**, in turn prepared from cyclopentadiene and 5-oxohexanal. No hydroazulene derivatives are formed. Diimide reduction of the diene **9** proceeds with high regiospecificity and the resulting olefin **11** can be transformed to the C_{12} ketone **6**, hinesol **18**, and β-vetivone **2**, all constituents of vetiver oil.

Sir: Commercial vetiver oil [*Vetiveria zizanioides* (L.) Nash] contains the sesquiterpenes α-vetivone (**1**),[1] β-vetivone (**2**),[2] the nor sesquiterpene khusimone (**3**),[3] and minor amounts of the biogenetically related C_{12} compounds **4**,[4] **5**,[4] and **6**.[5] Since the spiroketone **6** appears to play a significant role in the reconstitution of the essential oil[5] we have developed an efficient total synthesis from materials other than β-vetivone (**2**).[6,19]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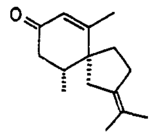
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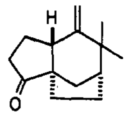
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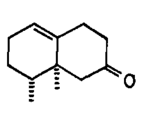
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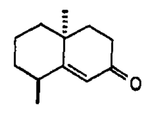
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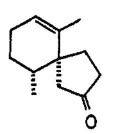
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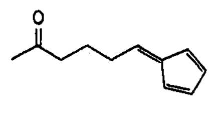
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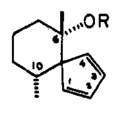
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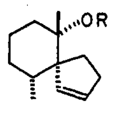
9 R = $COCH_3$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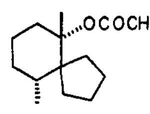
11 R = $COCH_3$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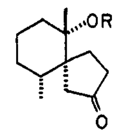
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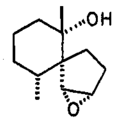
14 R = $COCH_3$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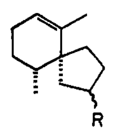
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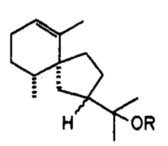
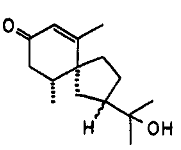
17 R = $COCH_3$


18 R = H

19 R = $COCH_3$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Condensation of 5-oxohexanal[7] with cyclopentadiene in the presence of diethylamine[8] gave fulvene **7** (uv max (C_2H_5OH) 255 nm, ε 1810) in 70% yield. We reasoned that lithium dimethylcuprate[9] should add to this fulvene to produce the derived lithium cyclopentadienide which should combine with the carbonyl group to form a cyclohexanol in preference to a cycloheptanol. In practice the reaction, when performed in ether solution at −20 °C, produced a single carbinol **8** (80–90%). Efforts to regioselectively reduce one of the two double bonds in **8** or **9** [prepared with CH_3COCl in $C_6H_5N(CH_3)_2$ at 50 °C for 6 h in 78% yield] over a variety of catalysts failed. Similarly, monoepoxides prepared by different methods turned out to be mixtures. Surprisingly, reduction with diimide[10] (hydrazine, 30% hydrogen peroxide, ethanol, 20 °C, 3 days) yielded a single dihydro compound, **11**, mp 35–37 °C (57% after recrystallization) and 5–10% liquid tetrahydroacetate **12**. Dehydration of the alcohols **8**, **10**, and **13** under kinetically controlled conditions afforded mostly exocyclic olefins demanding the presence of an equatorial hydroxy group.[11] The methyl group at C-10 is equatorial also because the chemical shift of its protons depends on the presence or absence of double bonds in the cyclopentane ring (δ 0.78 in **9**, 0.77 in **11**, and 0.87 in **12**), while the singlet caused by the axial C-6 methyl group does not (δ 1.53). Preferential reduction of the syn double bond in the reduction of 7-acetoxynorbornadiene has been attributed to an interaction of diimide and acetoxy group.[12] The much more subtle effect causing the rate enhancement in the reduction of only one of the two double bonds in the diene **9** will only find an explanation after the acetoxy–diimide interaction has been specified in precise structural terms.[13]

Transformation of the olefins **10** and **11** to the ketone **6** was accomplished in two ways. Treatment of the acetate **11** with diborane followed by oxidation with sodium dichromate[14] gave the acetoxy ketone **14**. Pyrolysis at 450 °C, followed by equilibration of endo and exocyclic olefins with *p*-toluenesulfonic acid in boiling benzene, yielded the more stable endocyclic olefin **6** [ir ($CHCl_3$) 1740 cm^{-1}] containing <10% exocyclic isomer (35% from **11**). Spectral and chromatographic properties of racemic ketone **6** agreed with those of optically active material.[15] In an alternate synthesis acetate **11** was hydrolyzed to the alcohol **10** (sodium hydroxide, ethanol, reflux) (95%) which on epoxidation with peracetic acid gave the epoxide **15** (95%) assumed to have the α configuration. Butyllithium in ether at room temperature caused isomerization to the ketone **13** (72%) which was dehydrated to olefin **6** in refluxing benzene containing *p*-toluenesulfonic acid (90%).

To complete syntheses of the C_{15} spirovetivanes, ketone **6** was converted to a mixture of epimeric nitriles **16** in 75% yield with the aid of *p*-toluenesulfonyl isocyanide.[16] Condensation with methylmagnesium bromide provided the methyl ketones **17** (80%) which on treatment with methyllithium gave a 3:2 mixture of epimeric carbinols **18** (90%). Infrared and proton magnetic resonance spectra of the acetate **19** derived from the major epimer with α-oriented hydroxypropyl group were identical with those of authentic hinesol acetate (**19**).[17] Oxidation of the mixture of diastereomeric alcohols **18** with chromium trioxide–pyridine[18] afforded a crystalline mixture of epimeric α,β-unsaturated ketones **20**, mp 114–118 °C (70%). Dehydration with *p*-toluenesulfonic acid in hot benzene furnished racemic β-vetivone (**2**), mp 46–48 °C, identical with natural material.[15] If the dehydration is monitored properly by thin layer chromatography the yield of pure β-vetivone (**2**) is 80%.

Acknowledgment. We are indebted to Firmenich SA, Geneva, for generous financial support.

References and Notes

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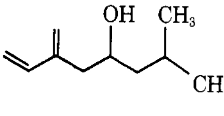
Terpene Synthesis via Pentadienyl Anions

Summary: The introduction of the terminal isoprenoid 1,3-diene unit using pentadienyllithiums is illustrated by the synthesis of monoterpenes from Ho-leaf oil and *Ledum palustre* oil.

Sir: The formation of terpenes by head-to-tail linking of isoprene units has long been an objective of organic synthesis.[1] Although 1,5-dienes are more common among acyclic terpenes,[2] terpenoids with terminal isoprene residues present as 1,3-dienes of three types occur in nature. For example, tagetol[3] (1) is a sex attractant of *Ips confusus*, compound 2[4] is a volatile constituent of *Ledum palustre* essential oil, and hotrienol[5] (3) is a component of Japanese Ho-leaf oil.



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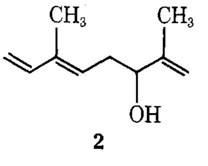

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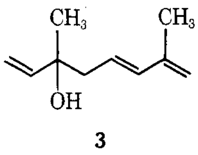

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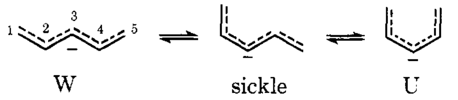
We have recently reported[6] a general method for the introduction of terminal isoprenoid 1,3-dienes of type 1. We now report a convenient method for the stereoselective production of isoprenoid (E)-1,3-dienes of the two remaining types.

Pentadienyl anions have been studied for some time,[7] particularly with regard to the conformations in eq 1. The three planar conformations, W, sickle, an U have been used to rationalize the sites of protonation in various derivatives. In general the W conformer protonates at C-1 and the U conformer at C-3 (the sickle form is intermediate). A recent ^{13}C NMR determination[8] indicated that 3-methylpentadienyllithium 4 exists almost exclusively as the W form from −80 to +40 °C. Thus protonation of 3-methylpentadienyllithium (4) gives 96% 5 (R = H, 95% E) and 4% 6 (R = H).

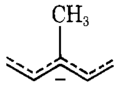


(1)

Table I. Reaction of 4 with Electrophiles at 0 °C

Entry	Electrophile	% 5	% 6
1	H_2O	96[a]	4
2	Adamantanone	75[b]	0
3	Methacrolein	65[b,c]	0
4	$CH_2{=}C(CH_3)(CH_2)_2CHO$	40[b]	60
5	$CH_3(CH_2)_5CHO$	38[b]	48
6	PhCHO	70[b]	30
7	$CH_3(CH_2)_4CH_2I$	38[d]	54
8	$CH_3(CH_2)_4CH_2I$	58[d,e]	34
9	Cyclohexene oxide	28[b]	72

[a] Reference 8. [b] Isolated yields. [c] +9% compound 8. [d] GC yield. [e] With CuBr·SMe$_2$ (−78 °C).



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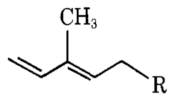

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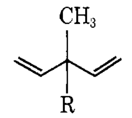

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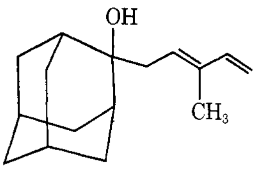

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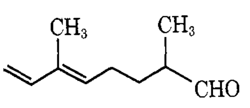
Reaction of anion 4 with adamantanone gave 7[9] (mp 59–61 °C) as the exclusive product (75% yield, >96% E). The pentadienyl anion 4 consequently gives us a convenient method for the introduction of the terminal 1,3-diene of type 2. Reaction of 4 with methacrolein gives the monoterpene 2 in 65% yield. Interestingly, the only other product, isolated in 9% yield, was the conjugate addition product 8 (99% E). Since the uncatalyzed 1,4 addition of an organolithium is rather unusual we felt that the copper catalyzed reaction might be very good. Surprisingly, with 4 and 1 equiv of CuI (THF, −78 °C), compound 8 was formed in only 30% yield and the 1,2 adduct 9 *at the 3 position* was isolated in 25% yield![10] The scope of the reaction of 4 with various electrophiles (Table I) indicates that some exploratory work must be done in order to find optimal conditions for 1,3-diene production.[11]



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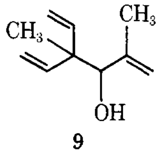

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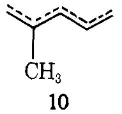
The synthesis of hotrienol 3, the last type of terpenoid 1,3-diene, was achieved using 2-methylpentadienyllithium 10. Compound 10 in contrast to 4 exists as a mixture of con-



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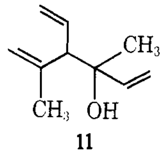

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