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The Stereospecific Generation of the *cis*-Vicinal Methyls in Eremophilane and Valencane Sesquiterpenes: The Total Synthesis of (±) Eremophilone and (±) 7-Epieremophilone.

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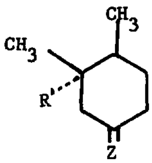
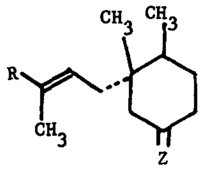
Eremophilone (8b) is a representative of a class of non-isoprenoid sesquiterpenes first isolated by Simonsen from the wood oil of *Eremophila Mitchelli* and characterized by a *cis* arrangement of peripheral alkyl functionality about a 1-octalone framework.[1]

Although a number of techniques have been reported[2] for the establishment of the required *cis*-methyl functionality by variations on the Robinson annelation theme, the sequences are at best stereoselective. While non-annelative methods have specifically provided the *cis*-dimethyl groups, the aforementioned methods[2,3] would entail a carbonyl transposition (2-octalone → 1-octalone) when applied to eremophilone. A partial solution to both of these problems has been provided in a polyene cyclization route to tetrahydroeremophilone.[4] We wish to report the total synthesis of eremophilone and its 7-epimer, by a route which stereospecifically introduces the dimethyl groups and avoids complex carbonyl transpositions.

Treatment of 3,4 dimethyl cyclohex-2-en-1-one[5] with lithium divinyl cuprate-tri-n-butylphosphine complex (ether, -78°)[6] provided the vinyl ketone in > 95% yield free of its diastereomer.[7] The stereocontrol follows from axial addition[8] (chair-like transition state) of the cuprate reagent with the C-4 methyl group in the favorable axial orientation ($A^{1,2}$ interaction).[9] Although metal-ammonia reductions and cuprate additions to enones are considered to proceed by similar mechanistic pathways,[10] the geometry of the transition states are distinctly different, since 3,4 dimethyl cyclohex-2-en-1-one upon metal-ammonia reduction provides an 84/16 trans/cis, (no appreciable $A^{1,2}$ interaction) mixture of 3,4 dimethyl cyclohexanone.[11] The carbonyl of 1a was protected as its ethylene glycol ketal (1b) which was subsequently subjected to hydroboration (Sia_2BH; alkaline H_2O_2)[12], providing the primary alcohol 1c (δ 3.78, t, $-C\underline{H}_2OH$). Oxidation of the alcohol ($CrO_3 \cdot 2$ pyr, CH_2Cl_2, 0°)[13] afforded the ketal aldehyde 1d (1725 cm^{-1}; δ 9.95 (t, 4 Hz, $-C\underline{H}O$)) in 80% yield (65% from 3,4 dimethyl cyclohex-2-en-1-one).[14]



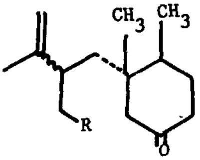


$K=-OCH_2CH_2O-$

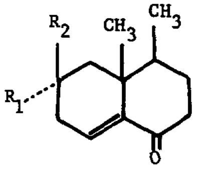
1 a) $R=-CH=CH_2$, $Z=O$
  b) $R=-CH=CH_2$, $Z=K$
  c) $R=-CH_2CH_2OH$, $Z=K$
  d) $R=CH_2CHO$, $Z=K$

2 a) $R=CO_2CH_3$, $Z=K$
  b) $R=CH_2OH$, $Z=K$
  c) $R=CH_2OCH=CH_2$, $Z=K$

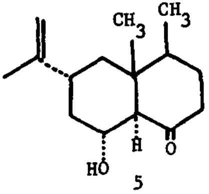
The ketal aldehyde was smoothly converted to the unsaturated ester 2a ($(C_6H_5)_3PCCH_3CO_2CH_3$, benzene, reflux 24 hrs., (E/Z = 14/1)) in 94% yield. Subsequent reduction with lithium aluminum hydride (inverse addition) provided the allylic alcohol 2b (95% yield). Mercuric acetate catalyzed exchange[15] of the allylic alcohol with butyl vinyl ether afforded enol ether 2c, which upon pyrolysis (175°, 10 min, N_2) and subsequent hydrolysis (80% aq HOAc, room temperature, 18 hrs) yielded ketoaldehyde 3a (1715 and 1725 cm^{-1}) as a ~55/45[16] mixture of diastereomers at the pro-C-7-center.[17]



3 a) $R=CHO$
  b) $R=CO_2CH_3$



4 a) $R_1=i\text{-}C_3H_5$, $R_2=H$
  b) $R_1=H$, $R_2=i\text{-}C_3H_5$



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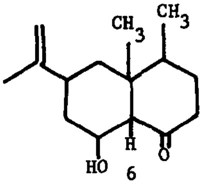

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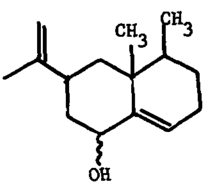

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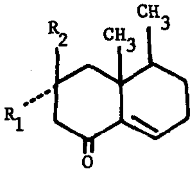

8 a) $R_1=i\text{-}C_3H_5$, $R_2=H$
  b) $R_1=H$, $R_2=i\text{-}C_3H_5$

Aldolization in aqueous methanolic sodium hydroxide produced enone 4a (1690 cm^{-1}, δ 6.67 (1H, dd, J = 3 and 5 Hz), $\sim$5% yield) and a mixture of β-hydroxyketones 5 and 6 (1710 cm^{-1}, 65% yield)[18] upon chromatography. Fractional crystallization of the mixture from hexane provided pure 6, which was pyrolyzed (250-270°, 10 min, N_2) to afford enone 4b. Inversion of the enone functionality was realized upon implementation of the Wharton reaction.[19] Thus, sequential treatment of enone 4b with alkaline hydrogen peroxide (α,β epoxy-ketone), hydrazine hydrate in methanolic acetic acid (7), and Collin's oxidation[13] provided (±) eremophilone identical by solution infrared and nuclear magnetic resonance spectroscopy with a sample from natural sources.[20]

In a similar fashion, enone 4a was transformed into 7-epieremophilone 8a (1690 cm^{-1}; δ 6.32 (1H, t, J = 3Hz)) which displayed similar but distinctly different infrared and nuclear magnetic resonance spectra from eremophilone.[21]

References

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16. The ratio could be determined by integration of the methyl region of the nmr spectrum of the corresponding ketoester 3b derived by Jones oxidation and diazomethane esterification.

17. There is essentially no influence by the assymetry at C-5 over the developing asymmetric center, pro-C-7. Preliminary results in a related system containing asymmetry at the pro C-6 center, indicate that the correct configuration can be generated with high selectivity at the isopropenyl carbon.

18. The stereochemical assignment of 5 is tentatively based upon the most stable configuration expected from the reversible aldol reaction. The stereochemistry of 6 is revealed in its nmr spectrum.

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20. We express our gratitude to Professor A.R. Pinder for a sample of natural eremophilone and Professor R.M. Coates for copies of the ir and nmr spectra.

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