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STEREOSELECTIVE TOTAL SYNTHESIS OF (±) EREMOPHILONE

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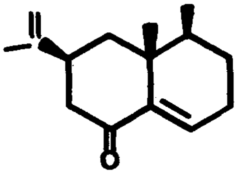
The synthesis of (±) eremophilone 1 , an unusual sesquiterpene[1] which does not follow the isoprene rule,has long been a synthetic challenge because of the problem associated with the *cis* relationship between the three alkyl groups, together with the sensitive cisoid enone function. The latter forces the system either to have the methyl and isopropenyl groups on the cyclohexanone ring 1:3 diaxial or to distort the cyclohexanone ring toward a boat conformation.



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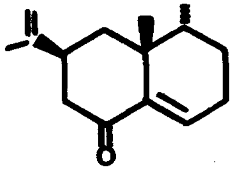

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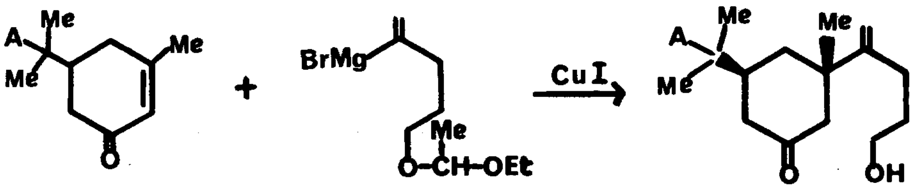
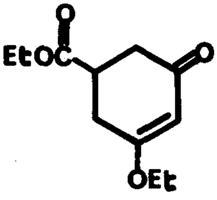
Two syntheses have been reported recently[2]. Of these, one is not stereoselective and the other achieves its goal indirectly *via* a conversion of the previously synthesized isonootkatone. In the stereoselective total synthesis of (±) eremophilone that we describe here, we first establish the proper relationship between the isopropenyl and the angular methyl groups by the established axial conjugate addition of organocopper reagents with 5-alkyl cyclohexenones of type 3. Control of the secondary methyl stereochemistry is then achieved by the reduction of an exocyclic methylene group precursor. This approach, in turn, required protection of the isopropenyl group : the dimethyl carbinol 3c was chosen for this purpose.



3 **4** **5**

a) A=H ; b) A=$\text{O-}\overset{\text{Me}}{\overset{|}{\text{C}}}\text{H-OEt}$; c) A=OH

Synthesis of the starting cyclohexenone 3c :[nmr (CCl_4) δ 1.15 (s,6H), 1.85 (s,3H), 5.65 (s,1H)] was readily achieved in 70 % yield, by reaction of the known enol-ether 6[3] with an excess of methylmagnesium bromide followed by treatment with dilute acid. Protection of the alcohol function by reaction with ethyl-vinyl ether then gave 3b :[bp 115° (0.01 mm) ; 92 % yield ; nmr ($CDCl_3$) δ 1.9 (s,3H), 3.45 (q,2H), 4.85 (q,1H), 5.80 (s,1H)].



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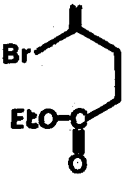

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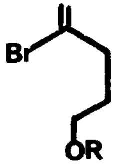
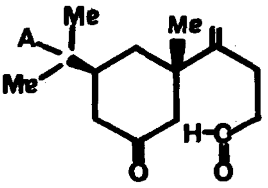


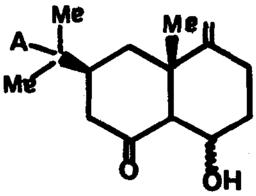
8 a) R=H ; b) R=$\overset{Me}{CH}$-OEt

The following reactions were carried out with 3b, the precursor of eremophilone, and also with 3a[4] which leads to dihydro-eremophilone. Addition of the Grignard reagent 4[5] (2,5 equiv. in tetrahydrofuran, catalytic amount of CuI) leads respectively, after acidic hydrolysis (10 % HCl) to the saturated cyclohexanones 5c :[chromatography on alumina : eluant : benzene/ethyl-acetate: 7/2 ; 80 % yield ; nmr ($CDCl_3$) δ 1.25 (m,9H), 4.85 (s,2H)] and 5a : [bp 190° (0.05 mm) ; nmr ($CDCl_3$) δ 0.9 (d,6H), 1.2 (s,3H), 4.9 (s,2H) as single isomer, the purity of which is established[6] by ^{13}C nmr.]

Collins oxidation of 5b[7] and 5a gave the corresponding aldehydes 9b : Crude, 90 % yield and 9a :[bp 170° (0.1 mm) ; 90 % yield ; nmr ($CDCl_3$) δ 0.9 (d,6H), 1.2 (s,3H) 4.8 (s,1H), 4.85 (s,1H), 9.9 (1H)] which then underwent quantitative internal aldol condensation (MeONa 0.1 N MeOH, 4 h, 0-10°) to produce the substituted decalones 10b and 10a.



9 a) A=H ; b) A=O$\overset{Me}{CH}$-OEt



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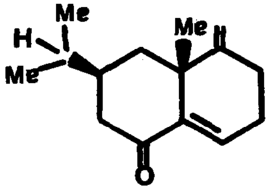

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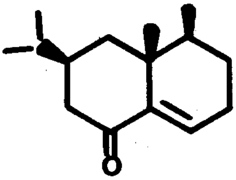
Dehydration of the aldol 10a could be achieved easily by thermal cracking (250°) to produce (80 % yield) enone 11 :[bp 170° (1 mm) ; nmr ($CDCl_3$) δ 4.8 (s,2H), 6.6 (t,1H)] which could be used to test the stereochemical outcome of catalytic hydrogenation of the exocyclic methylene.

We were aware that although this type of reduction can be made regiospecific by use of triphenylphosphine-rhodium chloride catalyst[8], the stereochemical result with flexible systems like 11 cannot be predicted. In fact, the (±) dihydroeremophilone which is obtained quantitatively is a mixture of the two isomers 12 et 13, in the ratio of about one to one[9].



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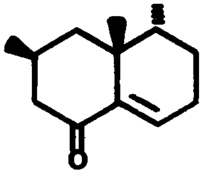

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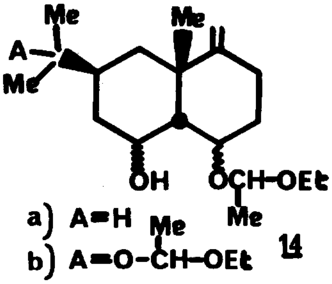

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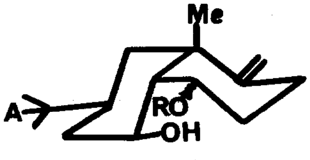
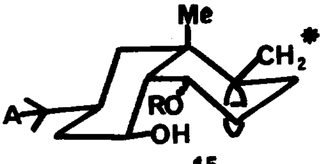
In contrast to catalytic hydrogenation, thermodynamically controlled reduction of the methylene would lead to an equatorial secondary methyl. The proper choice of bicyclic system could then lead to a situation in which the equatorial secondary methyl and the angular methyl are cis.

A system which seems to meet these requirements is easily produced from the aldols 10 by protection of the hydroxyl (ethylvinyl ether) and reduction of the carbonyl ($NaBH_4$, MeOH, 0°) leading in 95 % yield, to the bicyclic structure shown in 14.

Of the two possible conformers corresponding to 14, the more stable appears to be 14-I largely because it avoids the very serious 1,3 diaxial interaction of the alkyl groups in the other conformer. We would, therefore, expect that the product of a thermodynamically controlled reduction of the exocyclic methylene function should be 16.



14-I



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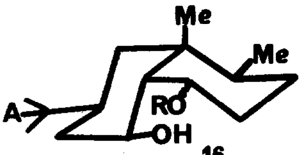

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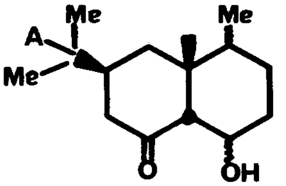
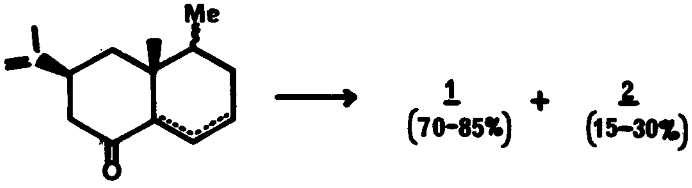
Reduction of the methylene of 14 by lithium in ethylene-diamine[10] should lead to the desired result because one would expect the methyl group to be equatorial[11] at the transition state for protonation of the tertiary carbanion center in 15, in which the star denotes an anion, a radical or a hydrogen. Furthermore, we hoped that the free hydroxyl of 14 (see 15) might utilize its favorable location to transfer a proton intramolecularly. Complete stereospecificity might then be expected.

In fact, chemical reduction of 14 (0.4 M in dioxane) with a large excess of lithium and of ethylene diamine (80 equiv. each) at 10-20° (complete decolorization in 30 min.), followed by Jones oxidation of the free secondary alcohol and liberation of the protected hydroxyl (10 % HCl) gave aldols 17 in 90 % yield from 14.



17 a) A=H ; b) A=OH



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In the dihydroeremophilone series, the aldol 17a could be cleanly dehydrated to (±) dihydroeremophilone in 80 % yield, merely by Kugelrohr distillation at 280°. In the eremophilone series itself, the dehydration of the tertiary carbinol in the side chain to the isopropenyl group together with the aldol dehydration required cracking in the presence of alumina (280°). The instability of eremophilone to these conditions unfortunately markedly reduces the yield[12].

The doubly dehydrated product 18 (25 % yield) was obtained as a mixture of α,β and β,γ[13] isomers. The mixture was quantitatively transformed to the α,β isomer by base-catalyzed epoxidation followed by reduction of the epoxide with chromous ion[8]. The α,β unsaturated ketones thus obtained consisted of 70-85 %[14] of (±) eremophilone 1 , identical (^{1}H and ^{13}C nmr, ir, mass spectrum) with natural eremophilone[15], and of 15-30 % of the isomer 2.

References and Notes :

1) For reviews see : J. Simonsen, D.H.R. Barton "The Terpenes", vol. III, Cambridge University Press, New York, p. 212 (1952) ; D.H.R. Barton, Proc. Chem. Soc. London, 61 (1958) ; A.R. Pinder, Perfumery Essent Oil Record, 59, 280, 645 (1968).

2) F.E. Ziegler and P.A. Wender, Tetrahedron Letters - 449 (1974) ; J.E. Mc Murry, J.H. Musser, M.S. Ahmad, and L.C. Blaszczak, J. Org. Chem. - 40, 1829 (1975).

3) E.E. van Tamelen and G.T. Hildahl, J. Amer. Chem. Soc.- 78, 4405 (1956).

4) E.C. Horning, M.O. Denekas, and R.E. Field, J. Org. Chem., 9, 547 (1944).

5) Synthesis of vinyl bromide 8b :[bp 60° (0.05 mm) ; 93 % yield ; nmr (CCl_4) δ 5.35 (s,1H), 5.55 (s,1H)], leading to the Grignard reagent 4 is achieved by protecting with ethyl-vinyl ether the alcohol 8a : [bp 80° (0.05 mm) 91 % yield] obtained ($LiAlH_4$, ether,-20°) from ester 7 : [bp 60° (0.05 mm) 75 % yield] which was derived via Claisen rearrangement from 2-bromo-2 propen-1-ol.

6) Each carbon atom appears as a singlet in the ^{13}C nmr spectrum ($CDCl_3$)-Varian XL100 for which we thank Miss Convert, Centre de Spectroscopie, Université Pierre et Marie Curie, Paris.

7) 5b is obtained from 5c in 85 % overall yields by regioselective esterification of the primary alcohol with acetic anhydride, protection of the tertiary alcohol with ethyl-vinyl ether, and saponification of the primary acetate. The yields of Collins oxidation of the primary alcohol drops to 35 % if carried out on the diol 5c.

8) M. Brown and L.W. Piszkiewicz - J. Org. Chem. - 32, 2013 (1967).

9) This follows from the integration of the vinyl hydrogen signals in the nmr spectrum after irradiation of the α-methylene : 12, δ 6.66 (s,1H) ; 13 : δ 6.58 (s,1H). We thank Mr Miura of Columbia University for this analysis.

10) L. Reggel, R.A. Friedel, and I. Wender, J. Org. Chem. - 22, 891 (1957).

11) A study in progress in our laboratory has shown that this is, indeed, true of simple systems. See also E.J. Corey and E.W. Cantrall, J. Amer. Chem. Soc. - 81, 1745 (1959).

12) Natural eremophilone itself could only be recovered in 30 % yield after this treatment.

13) β,γ isomer : [ir (neat) 1715,1645,890 cm^{-1} ; nmr (CCl_4) δ 5.6 (m,2H), 4.65 (s,2H)] which also occurs in the oil of Eremophila Mitchelli - L.H. Zalkow and G.L. Chetty, J. Org. Chem. 40, 1833 (1975) can be separated from the α,β isomer by GLC.

14) Assignment made by integration of the vinylic hydrogen (β to the carbonyl) signals in the nmr spectrum (Cameca, 250 MHz) (in benzene D) ; 1 : 6.70 (t,1H) ; 2 : 6.66 (t,1H). We thank Mr Lallemand, Ecole Normale Supérieure (Paris), for this determination.

15) We thank Professor de Mayo (University of Western Ontario) for a sample of natural eremophilone and Professor J.F. Leroy (Muséum d'Histoire Naturelle, Paris) for a sample of the oil of Eremophila Mitchelli.