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A NEW ANNULATION OF CARVONE TO CHIRAL TRANS AND CIS FUSED BICYCLIC KETONES

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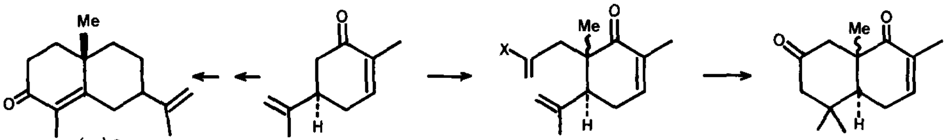
ABSTRACT - Two regiospecific consecutive alkylations of carvone at C_6 followed by acid-catalysed cyclisation afford bicyclic ketones which are potential intermediates for the synthesis of several classes of terpenes. Depending on the sequence of alkylation trans fused ketone 7 or a mixture of 7 and cis fused ketone 13 may be prepared in only three steps, thus constituting a new type of annulation of carvone.

Carvone 1, occurring in both optically active isomers, is an interesting chiron[1] for the synthesis of terpenes. Elaboration of more complex structures has mainly relied on the Robinson annulation of dihydrocarvone (i.e. synthesis of (-) cyperone 2[2]) and subsequent modifications of the resulting enone unit.[3]

A new approach toward optically active terpenes possessing a gem-dimethyl group such as drimanes, labdanes, abietanes, stemodanes and almost all triterpenes is now proposed based on a Lansbury type cyclisation[4] of an haloolefin A prepared by regiospecific alkylation of carvone 1.



(-)2 (-)1 A X=Cl,Br B

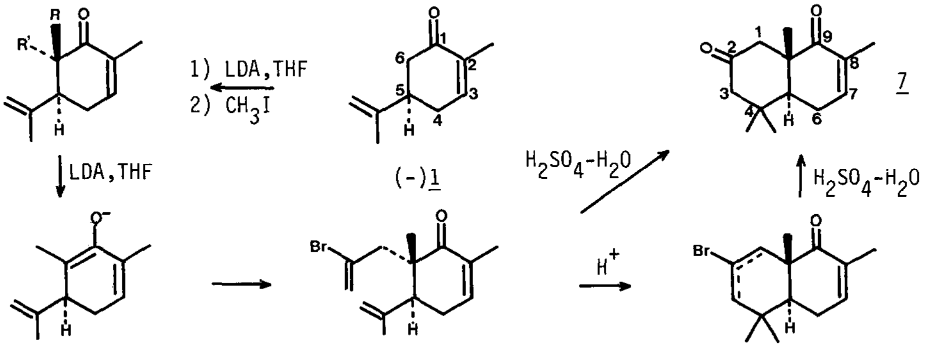
This novel annulation of carvone will ultimately lead to cis or trans fused diketones B and also to their enantiomers starting from (+) 1. Compounds of type A may be prepared by two consecutive regiospecific alkylations at C_6 of the kinetic enolate of the enone function and it is anticipated that both isomers at C_6 may be available depending on the order of addition of the two alkyl groups. The final cyclisation step may then be carried out with various acids under anhydrous or aqueous conditions.

SYNTHESIS OF TRANS DIKETONE 7

In 1984 Cory has shown that carvone is easily methylated at C_6 using LDA/CH_3I in THF at 0°C. The mixture of epimers 3a,b, thus obtained was then converted to the kinetic enolate 4 and subsequently submitted to a stereospecific vinylsulfone bicycloannulation[5].

3a R=Me
R'=H

3b R=H
R'=Me



(-)1

7

4

5

6a (Δ-1,2), 6b(Δ-

In our hands kinetic deprotonation of carvone 1 (LDA, THF, -10°C) followed by methyl iodi addition (10 eq., -10°C) affords an 83% yield of a mixture of 3a and 3b[6].

As described above kinetic deprotonation of 3a,b followed by trapping the resulting di nolate 4 with 2,3-dibromopropene-1 (1.2 eq.) leads to a single compound 5 in 84% yield[7]. Stereochem try of 5 may be anticipated, on the basis of similar alkylation of β' substituted cyclohexane dieno tes[8], to result from axial attack on the less hindered face (i.e. opposite to the isopropenyl group C_5).

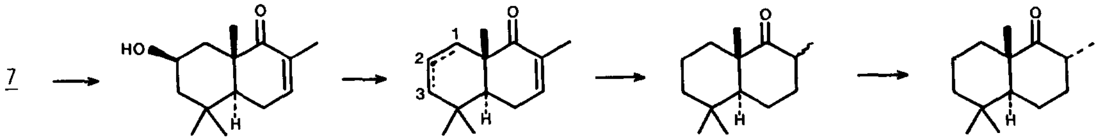
Cyclisation of 5 was first carried out in 80% H_2SO_4 at room temperature and after 24 hrs single more polar compound is detected by TLC.

Chromatography over silica gel affords 7 in 52% yield, m.p. 61-62°C, α_D = -49.3° (c = 1.1 $CHCl_3$) easily characterized by ^1H and ^{13}C NMR (J Resolved spectrum)[7].

Cyclisation of 5 proceeds also in trifluoroacetic acid (20°C, 24 hrs) to give an unsepar mixture of isomeric vinylic bromides 6a and 6b (77%) while HF (-40°C to + 20°C, 4 hrs) affords only (87%)[7]. Subsequent hydrolysis of the mixture 6a,b in H_2SO_4-H_2O gives 7 in 60% overall yield from 5.

CONVERSION OF 7 TO 10a

In order to unambiguously prove the stereochemistry and optical purity of 7 reductio of 7 to 10a, a known degradation product of natural terpenes[9], was carried out.



8

9a (Δ2,3)
b (Δ1,2)

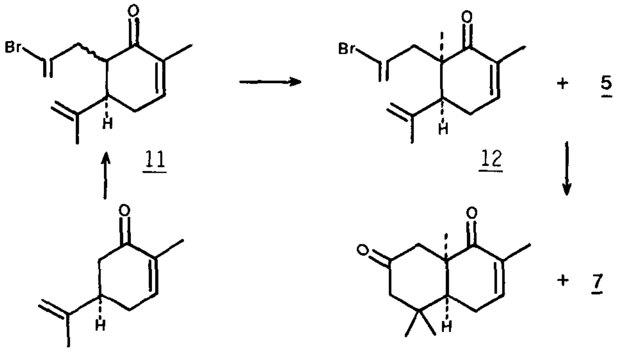
10a,b

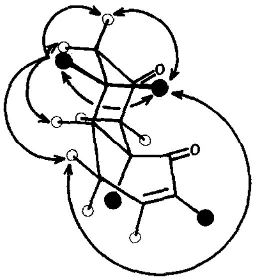
10a

Selective reduction of the carbonyl group at C_2 ($NaBH_4$, 0.35 molar eq., 0°C) gives a sin alcohol 8 (74% , m.p. = 105-107°C, α_D = -41.6° (c = 1, $CHCl_3$) whose axial configuration is confirmed by ^1H NMR[7]. This result is in agreement with the reported stereochemistry of reduction of 2-keto 4,4-dimethyl cholestane derivatives[10]. Dehydration of 8 using $POCl_3$-Pyridine affords a mixture of isomeric alkenes 9a,b (ratio 9a/9b ∿ 1,5/1 as judged by ^1H NMR)[7] which is then hydrogenated (H_2, 1 atm., Pd/C, 12 hrs) to a mixture of C_8 epimeric ketones 10a,b whose base catalysed equilibration (MeONa, MeOH) gives, in 65% overall yield from 8, the known ketone 10a, m.p. = 46-49°C (m.p. Litt.[9] = 49-50°C), α_D = -38.5°, c = 1, $CHCl_3$ (α_D Litt.[10] = -36.9°, c = 1, $CHCl_3$)[7].

SYNTHESIS OF CIS KETONE 13

The above result demonstrates that a trans fused decalone is readily and stereospecifically available in three steps from carvone and therefore it is of interest to see if the corresponding cis fused decalone 13 may be obtained by inverting the two alkylation steps.





NOE's of the gem dimethyl group

Kinetic deprotonation of 1 followed by trapping the corresponding dienolate with 2,3 dibromopropene leads to 11 (54%)[7]. Treatment of this mixture with LDA followed by addition of methyl iodide (1.2 eq.) in presence of HMPA (1 eq.) at - 10°C affords a mixture of the dialkylated derivative 12 and of the already described 5 in a 45/55 ratio as judged by ^1H NMR[7]. This lack of stereoselectivity has previously been observed in the alkylation of similar endocyclic enolates and recently rationalized by Tomioka.[11] Sulfuric acid catalysed cyclisation of this mixture affords after chromatography over silica gel the trans fused ketone 7 (36.7%) and 13, m.p. 112-113°C, α_D = + 54.4° (c = 1, $CHCl_3$), (29.7%). Detailed examination of the ^1H and ^{13}C NMR spectra and observation NOE's (NOEDIFF experiments) unambiguously prove the cis fused structure and conformation of this material[7].

CONCLUSION

The synthesis of diketones 7 and 13 illustrates a novel type of annulation of carvone which represents a rapid (and perhaps more general) route toward both series of optically active terpenes. Extension of this methodology as well as the preparation of natural terpenes are underway.

ACKNOWLEDGEMENTS : We thank C. BERRIER for NOEDIFF experiments and Professor J.D. CONNOLLY (University of Glasgow for helpful discussions. One of us (B.R.) thanks CNRS for a research grant.

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6 - NMR analysis of this oily mixture shows the presence of two secondary methyl groups (d., J = 6.5 Hz) at 1.07 ppm and 0.92 ppm in a ratio of about 1.3. Base catalyzed isomerization (MeONa, MeOH 20°C, 16h) results in an increase of the signal at 1.07 ppm (ratio 2.8). (The signals appear respectively at 1.05 ppm and 0.89 ppm in C_5D_5N).

Therefore the major epimer should be 3b. This compound may be partly obtained by crystallization from the mixture.

3b : m.p. 38°C, NMR : 1.06 (d., J = 6.5 Hz, 3H), 1.70 (s, 3H), 1.76 (s, 3H), 4.80 (s, 2H), 6.69 (s, W_H = 12 Hz, 1H).

7 - All new compounds have been characterized by elemental analysis and spectral data (IR, MS and HR ^{1}H and ^{13}C NMR). NMR spectra were done on a BRUKER WP 200 SY in $CDCl_3$ using TMS as internal standard. Significant chemical shifts (in ppm) are given below :

5 : 1.11 (s, 3H); 1.61 (s, 3H); 1.81 (d, J = 2 Hz, 3H); 4.75 (s, 2H); 5.53 (dd, J = 20 Hz, J = 1 Hz, 2H); 6.6 (s, W_H = 9 Hz, 1H).

6a, 6b : 1.05 (s, 3H); 1.07 (s, 3H); 1.13 (s, 3H); 1.77 (s, 3H); 5.80 and 6.54 (s, 1H); 6.80 (s, W_H = 9 Hz, 1H).

6a :1.05 (s, 3H); 1.07 (s, 3H); 1.13 (s, 3H); 1.77 (s, 3H); 5.80 (s, 1H); 6.78 (s, W_H = 10 Hz, 1

7 : ^{1}H RMN : 1.01 (s, 3H); 1.04 (s, 3H); 1.09 (s, 3H); 1.75 (s, 3H); 6.74 (s, W_H = 9 Hz, 1H).

^{13}C : 16.22 (CH_3); 18.17 (CH_3); 22.99 (CH_3); 24.74 (CH_2); 31.72 (CH_3); 39.47 (C); 48.94 (CH, CH_2, C); 56,0 (CH_2); 133.16 (C); 143.1 (CH); 202.66 (C); 210.58 (C).

8 : 0.93 (s, 3H); 1.25 (s, 3H); 1.33 (s, 3H); 1.75 (s, 3H); 4.32 (t, J = 2.5 Hz, 1H); 6.70 (W_H = 11 Hz, 1H).

9a,b : 0.95 (s, 3H); 1.00 (s, 3H); 1.06 (s, 3H); 1.77 (s, 3H); 5.40 (dd, J = 11 Hz, J = 1.5 Hz); 5.51 (m, 1H); 6.06 (dd, J = 10 Hz, J = 1.5 Hz); 6.69 et 6.78 (2s, 1H).

10a : 0.89 (s, 3H); 0.93 (s, 3H); 0.98 (d, J = 6 Hz, 3H); 1.14 (s, 3H).

11 : 1.76 (s, 6H); 4.82 (s, 2H); 5.47 (s, 1H); 5.71 (s, 1H); 6.66 (s, W_H = 11 Hz, 1H)

12 + 5 : 1.11, 1.25, 1.61, 1.76 and 1.80 (5s); 4.75 (m, 2H) 5.52 (d, J = 7 Hz); 5.58 (d, J = = 1.5 Hz); 6.6 (s, W_H = 20 Hz, 1H).

13 : 0.66 (s, 3H); 1.08 (s, 3H); 1.34 (s, 3H); 1.75 (p., 3H); 1.98 (d, J = 14 Hz, $H_{1\alpha}$): 2.05 (dd, J = 14 Hz, J = 2.4 Hz, $H_{3\beta}$); 2.20 (d, J = 6.5 Hz, H_5); 2.31 (d, J = 14 Hz, $H_{3\alpha}$); 2.54 (dd, J = 20 Hz, J = 5.5 Hz, $H_{6\beta}$); 2.72 (ddq, J = 20 Hz, J = 3 Hz, J = 6.5 Hz, H 3.33-3.25 (dd, J = 2.4 Hz, J = 14 Hz, $H_{1\beta}$); 6.52 (s, W_H = 11 Hz, 1H).

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