Tetrahedron Vol. 38, No. 15, pp. 2279 to 2283, 1982.
Printed in Great Britain.

0040-4020/82/152279-05$03.00/0
Pergamon Press Ltd.

RETROALDOL-ALDOL ISOMERIZATION OF PERHYDROAZULENIC HYDROXYKETONES

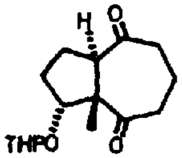
P. Kok[1a], N.D. Sinha, P. Sandra, P.J. De Clercq[1b] and M.E. Vandewalle*

State University of Ghent, Department of Organic Chemistry,
Laboratory for Organic Synthesis,
Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

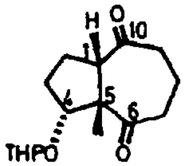
(Received in U.K. 18 March 1982)

Abstract - The retroaldol-aldol isomerization of the epimeric hydroxyketones 3 and 5 was found to yield predominantly 4 and 6, respectively, under kinetic conditions in the presence of chelating lithium cations. In hydroxylic medium 4 is the preferred kinetic product. Under equilibration conditions 4 and 5 predominate.

Our recent syntheses of pseudoguaianolides[2] have essentially centered about the versatility of the intermediate 1, in which both the trans-fusion and the configuration at C-4 are firmly established[3]. This trans-fused diketone is obtained from 2-methylcyclopentenone (5 step sequence, 61 % overall yield), via the corresponding cis-fused diastereoisomer 2[4].

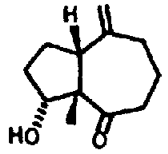


1

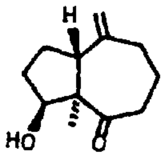


2

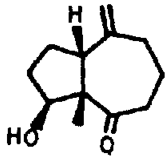
En route to the pseudoguaianolides the necessary one-carbon unit at C-10 was introduced by a chemoselective Wittig reaction (i.e., 1 to 5). Although the naturally occurring pseudoguaianolides carry a 5-β angular methyl group, for reasons of consistency in the subsequent discussion, 5 and 6 are represented here in the enantiomeric configuration. As several pseudoguaianolides possess a 4-hydroxyl group cis oriented (β in natural series) with the angular methyl substituent (i.e. 6) we decided to examine the possibility of direct inversion at C-4 via retroaldol-aldol type isomerization of hydroxyketones such as 3 and 5. From a more fundamental point of view we also wanted to have access to the four possible isomers of the system, i.e., 3-6. We now report on some interesting results of the base induced isomerization of 3 and 5, and describe syntheses of their C-4 epimers 4 and 6.



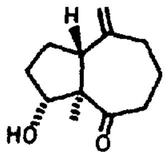
3



5



4

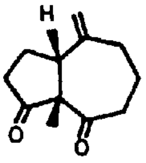


6

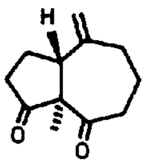
In analogy with the synthesis of 5 (m.p. 66-68°C)[5], the cis-fused isomer 3 (m.p. 39-43°C) is obtained from diketone 2 via chemoselective Wittig reaction (methylenetriphenylphosphorane, THF; 77 % yield)[6], followed by hydrolysis (pyridinium p-toluenesulfonate, EtOH, 70°C; 80 % yield). Both 3 and 5 were subjected to different basic conditions : 0.2 % methanolic NaOH (0.135 molar conc.) at reflux for 16 h; 5 % aqueous KOH-THF (1:2, 7.3 10^{-2} molar conc.) at r.t. for 30 min; sodium hydride (1 equiv; 50 % suspension in oil) in THF (5.0 10^{-2} molar conc.)

at r.t.; lithium diisopropylamide (1 equiv) in THF at various temperatures, followed by quenching with NH_4Cl. After extractive work-up the obtained mixtures were analyzed by VPC and ^1H NMR spectroscopy. In all cases more than 90 % of the products formed consisted of the four isomers 3-6 (table).

Pure cis-fused hydroazulenone 4 was isolated from the mixture obtained from 3 (KOH, aq THF; entry 3; 66 % isolated yield). The trans-fused isomer 6 was obtained from 5 (entry 7) in poor yield. Both diastereoisomers 4 and 6 were structurally identified on spectroscopic[7] and chemical grounds : oxidation of 4 (Collins, 90 % yield) led to diketone 7, identical with the oxidation product of 3 and different from diketone 8, which was similarily obtained from enone 5.



7



8

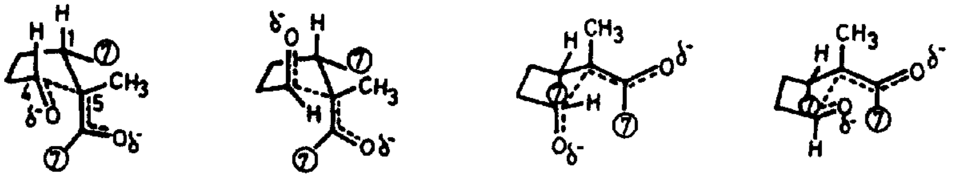
We assume that, when either 3 or 5 are treated with methanolic NaOH (entries 1 and 2), equilibrium is reached since almost identical ratios (within the experimental error of VPC analysis) of the four isomers are observed in both cases. Cis- and trans-fused compounds are formed in nearly equal amounts, 4 and, to a somewhat lesser extent, 5 being the most stable isomers. In contrast to this, our earlier observation is worth mentioning; epimerization of 2 at C-1 (NaOH, MeOH, r.t., 48 h) leads to an equilibrium in favor of the trans-fused isomer 1 (ratio 1:2 = 85:15)[3a]. This strongly suggests that in the latter experiment the endo orientation of the bulky ether group at C-4 in 2 is determining for the preferred formation of trans-fused diketone 1[8].

From the above experimental results it is clear that, for the purpose of specific inversion at C-4 without concomittant "epimerization" at C-5 (thus 3 → 4, and 5 → 6), one should have recourse to kinetic control. Examination of the possible transition states for aldol reaction (scheme) reveals that, whereas there is only one possibility for the formation of trans-fused compounds (i.e., 5a for 5; 6a for 6), two possibilities exist for the corresponding cis-fused products (i.e., 3a and 3b for 3; 4a and 4b for 4); one would expect, however, transition states 3a and 4a to be disfavored due to endo-character of the systems (i.e., C-2 is axially oriented on the 7-membered chair-like ring). Comparison of the transition states 3b and 4b further reveals the presence of a syn-diaxial interaction between O at C-4 and C-10 in the five membered ring of 3b; thus, the "threo"-transition state 4b is expected to be the favored one in the cis-fused series. In the trans-fused series, destabilization of the transition state 5a by the axial position of the developing (C-4)-oxygen bond should also favor the "threo"-transition state 6a. The somewhat unexpected formation of large amounts

Table

Entry	Start. prod.	Reaction conditions	% formed (VPC) 3	4	5	6
1	3	NaOH, MeOH, ΔT, 16 h	7	40	33	17
2	5	ibid.	7	43	35	14
3	3	KOH, H_2O-THF, r.t., 30 min	14	72	1	6
4	3	NaH, THF, r.t., 45 min	20	73	2	4
5	5	ibid., 15 min	10	31	44	15
6	3	LDA, THF, from -78°C to r.t. over 3 h	15	45	4	27
7	5	ibid.	9	25	7	57
8	3	LDA, THF, r.t., 5 min	19	65	3	13
9	5	LDA, THF, added at -20°C, 18 h at 0°C	8	25	9	58
10	3	LDA, THF, r.t., 24 h	9	41	34	15
11	5	ibid.	10	36	40	15

SCHEME

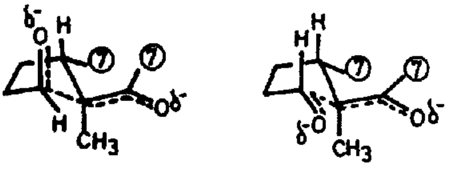


3a 4a

cis-fused endo transition states
7-membered ring in quasi C_9-form
(C-2 is axial on 7-ring)

3b 4b

cis-fused exo transition states
7-membered ring in quasi C^9-form
(C-2 is equatorial on 7-ring)



5a 6a

⑦ : 7-ring residue

trans-fused transition states
7-membered ring in quasi C^9-form
(C-2 is equatorial on 7-ring)

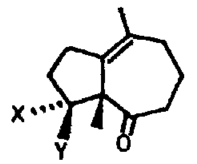
of cis-fused 4 under thermodynamic control is indicative for a preferred cis-fusion (at least when the hydroxyl at C-4 is exo-oriented) in these perhydroazulene systems; consequently, in the absence of chelating cations, the transition state 4b might well be the overall-favored one[9].

Consistent with the above rationale we found that, when 3 was treated with KOH in aqueous THF (r.t., 30 min), its C-4 epimer 4 was predominantly formed (> 70 %). The corresponding trans-fused 5, however, did not react under the same conditions and was recovered unchanged.

Selective inversion at C-4 (i.e., 3 → 4; 5 → 6) was obtained when using LDA as a base. Both 3 and 5 led to the predominant formation of 4 and 6, respectively, when treated with LDA (from -78°C to r.t. over 3 h; entries 6 and 7). This "memory-effect" may be rationalized as follows : after alkoxide formation and retroaldol reaction of 3 and 5, the transition states 4b and 6a, respectively, are formed, before any substantial change in conformation (reorientation of the aldehyde sidechain with respect to the plane of the enolate anion), as required for "epimerization" at C-5, can take place. Since a ligand association of the two oxygens with the lithium cation would retard complete equilibration to the four isomers, an even more pronounced kinetic stereoselection can be expected when using short reaction times and/or lower reaction temperatures. In practice, this also proved to be the case : when 3 was treated with LDA for 5 min (entry 8) 65 % of 4 was formed, while reaction of 5 with LDA at 0°C (entry 9)(no substantial reaction was found at -20°C) resulted in 58 % formation of 6. Interestingly, when the reaction on 3 was interrupted after 45 min almost equal ratios of 4 and 6 were found (3:4:5:6 = 12:40:12:36, respectively), suggesting similar energy contents for 4b and 6a when bounded by the lithium cation. This represents a second kinetic stage in the reaction which is clearly shown by the time dependent ratio of 6 formed upon reaction of 3 with LDA (r.t., THF) : 13 % (5 min), 37 % (45 min) and 15 % (24 hr). Upon prolonged reaction times (> 24 h at r.t.) the stereochemical result becomes consistent with thermodynamic control for the formation of alkoxide chelates, and similar ratios are obtained, both when starting from 3 and 5 (entries 10 and 11).

In the case of less tightened transition-state complexes (e.g., Na$^+$), reaction of 3 with NaH (entry 4) leads to the expected preferred formation of 4 (vide supra); product 5 under the same basic conditions (15 min) yields also predominantly product 4 (ratio 4:6 =

32:15) due to the rapid dissociation of the primary formed 6a and further reorganization to the preferred transition state 4b.



9 X=OH,Y=H
10 Y=OH,X=H

The tetrasubstituted olefin 9 (m.p. 81-82°C), obtained from 3 via treatment with prehydrogenated palladium on carbon (10 % MeOH, 30 min; 56 % isolated yield)[10] was also subjected to isomerization; an equilibrium mixture of 9 and 10[11] (ratio 1:2) was obtained when either of both products was treated with methanolic NaOH (48 h, r.t.) or THF-aqueous KOH (4 h 30, r.t.).

EXPERIMENTAL SECTION

The m.ps. are uncorrected. The NMR spectra were recorded at 360 MHz (WH-Brucker) in $CDCl_3$ with TMS as internal standard. Chemical shifts are expressed in ppm. The IR spectra were recorded in CCl_4.

The VPC analyses were performed on capillary columns (20 m x 0.5 mm I.D.) pretreated by high temperature silylation (HTS) and coated with OV-1 (df 0.3 µm)[12]. The underivatized compounds were introduced into the column via a cold on-column injector device (Carlo Erba 4160). After injection of the sample at a column temperature of 40°C, the temperature was programmed to 120° C at 20°C min^{-1})

^1H NMR spectral data : 3 : 1.27 (3H, s), 4.02 (1H, ~t, Σ^3J = 9.4 Hz), 5.00 and 4.93 (2H); 4 : 1.21 (3H, s), 4.36 (1H, dd, ^3J = 8.0 and 10.0 Hz), 4.91 and 4.76 (2H); 5 : 0.91 (3H, s), 4.24 (1H, dd, ^3J = 1.2 and 6.0 Hz), 5.03 and 4.86 (2H); 6 : 0.96 (3H, s), 4.22 (1H, broad t, ^3J = 9 Hz), 5.05 and 4.85 (2H); 7 : 1.32 (3H, s), 4.95 (2H); for 8 : 1.16 (3H, s), 5.11 and 4.86 (2H); 9 : 1.24 (3H, s), 1.74 (3H, s), 4.13 (1H, s); for 10 : 1.15 (3H, s), 1.67 (3H, s), 4.12 (1H, ddd, ^3J = 10.8, 6.8 and 3.2 Hz).
IR spectral data : 3 :. 3550, 3080, 2950, 1685, 1640, 1460, 1235, 1090, 900 cm^{-1}; 5 : 3600, 3500 (br), 3080, 2950, 1685, 1640, 1440, 1370, 1320, 1275, 1070, 900 cm^{-1}; 9 : 3620, 3500 (br), 2950, 1690, 1455, 1235, 1060 cm^{-1}; 10 : 3580, 3500 (br), 2950, 1690, 1090 cm^{-1}.
MS spectral data : 3 : m/z 195 (6), 194 (M,6), 179 (16), 161 (20), 150 (30), 137 (65), 55 (100); 5 : m/z 195 (4), 194 (M, 15), 177 (12), 161 (8), 150 (35), 137 (100), 55 (62); 10 : m/z 194 (M, 14), 176 (42), 161 (48), 123 (100).

Isomerization procedures

Procedure with NaOH-MeOH (entries 1,2).
A solution of the hydroxy-ketone (3, 5 or 9; 90 mg) in 0.2 % methanolic NaOH (3 ml) was stirred at reflux for 16 h under nitrogen. After removal of the solvent under reduced pressure, the residue was taken up in water and extracted with ether. The combined extracts were washed with saturated brine and dried over $MgSO_4$. The solvent was removed from the filtered solution on a rotary evaporator and the residual oil analyzed by VPC.

Procedure with KOH-THF (entry 3).
A solution of the hydroxy-ketone (3, 5 or 9; 80 mg) in THF (4 ml) and 5 % aqueous KOH (2 ml) was stirred for 30 min at r.t. After extraction with ether, the combined extracts were washed with saturated brine and dried over $MgSO_4$. The solvent was removed from the filtered solution on a rotary evaporator and the residual oil analyzed by VPC.

Procedure with NaH-THF (entries 4, 5).
To a suspension of NaH (50 % in oil; 24 mg) in THF (10 ml) was added at r.t. a solution of the hydroxy-ketone (3 or 5; 97 mg, 0.5 mmol) in THF (1.5 ml). The reaction mixture was worked up by pouring it into a saturated NH_4Cl solution and extraction with ethyl acetate. The extract was dried over $MgSO_4$, filtered and analyzed by VPC.

Procedure with LDA-THF (entries 10, 11).
To a solution of diisopropyl amine (0.043 ml, 0.31 mmol) in THF (6 ml) was added at 0°C a solution of n-BuLi in hexane (0.194 ml of a 1.6 N solution). After 5 min the mixture was brought to r.t. and treated with a solution of the hydroxy-ketone (3 or 5; 60 mg, 0.31 mmol) in THF (1.1 mol). Work-up was achieved as in the previous procedure.

t-8-Hydroxy-c-7-methyl-2-methylene-r-1H-bicyclo|5.3.0|decan-6-one (3).
To a suspension of methylene triphenylphosphorane (from 15.7 g, 44.0 mmol of methyltriphenylphosphonium bromide and 27.5 ml of 1.6 M n. butyllithium-hexane solution) in THF (60 ml) was added a solution of diketone 2 (4.1 g, 14.8 mmol) in THF (20 ml). After 30 min the reaction mixture was poured into a saturated NH_4Cl solution. After extraction with ether, the extracts were washed with saturated brine, dried over $MgSO_4$, and, after filtration, concentrated on a rotary evaporator. The residual oil was chromatographed on silica gel using 10 % ether-hexane as eluent, yielding t-8-(2'-tetrahydropyranyloxy)-c-7-methyl-2-methylene-r-1H-bicyclo |5.3.0|decan-6-one as an oil (3.2 g, 77 %).
A solution of this ether (3.2 g, 11.5 mol) and pyridinium p-toluenesulfonate (200 mg) in EtOH (100 ml) was heated for 3 h at 65-70°C. After concentration and addition of hexane, the precipitate was removed by filtration and the filtrate concentrated on a rotary evaporator. The residual oil was chromatographed on silica gel using ether-hexane as eluent. The alcohol 3 (1.8 g, 9.2 mmol) was obtained as a white crystalline solid (m.p. 39-43°C; 80 %).

c-8-Hydroxy-c-7-methyl-2-methylene-r-1H-bicyclo|5.3.0|decan-6-one (4).
The residual oil, obtained from the isomerization with KOH-THF, was chromatographed on silica gel with ether-hexane as eluent (gradient elution) yielding 4 as an oil (66 % isolated yield).

c-8-Hydroxy-t-7-methyl-2-methylene-r-1H-bicyclo|5.3.0|decan-6-one (5).
From the corresponding tetrahydropyranyloxy derivative (see ref. 3a) by hydrolysis with pyridinium p-toluenesulfonate; after purification on silica gel (ether-hexane) 5 is obtained as a white crystalline solid (m.p. 66-68°C).

t-8-Hydroxy-t-7-methyl-2-methylene-r-1H-bicyclo|5.3.0|decan-6-one (6).
To a solution of LDA (from 25.2 mg diisopropylamine and 0.15 ml of 1.6 M n-butyllithium-hexane solution) in THF (1 ml) was added at -78°C a solution of 5 (50 mg, 0.25 mmol) in THF (1 ml). The mixture was stirred at -78°C for 1 h, gradually warmed to r.t. over 2 h, and poured into a saturated NH_4Cl solution. After extraction

with ether, the extracts were washed with 1 % HCl solution, water and brine. After drying on $MgSO_4$, the filtered solution was concentrated in vacuo and yielded 46 mg of an oil, which was chromatographed on silica gel using methylene chloride-ether (2:1) as eluent. Due to the difficulty of the separation a poor yield of pure 6 (semi-solid) was obtained (ca 10 mg, 20 %).

2,t-7-Dimethyl-r-8-hydroxybicyclo|5.3.0|dec-1,2-en-6-one (9).
To a solution of 3 (450 mg, 2.3 mmol) in methanol (12 ml) was added 10 % Pd on C (50 mg). The mixture was stirred under hydrogen atmosphere for 30 min, filtered and concentrated in vacuo. The residual oil was chromatographed on silica gel with ether-hexane as eluent yielding 9 as a crystalline compound (m.p. 81-82.5°C; 250 mg (55 % yield).

Acknowledgment : We thank the N.F.W.O. and the "Ministerie voor Wetenschapsbeleid" for financial help to the laboratory.

References and Notes

1. (a) Bursary of the I.W.O.N.L.; (b) Research Associate of the National Fund for Scientific Research (Belgium).
2. N.H. Fischer, E.J. Olivier and H.D. Fischer, Progress in the chemistry of organic natural products (1979), 38.
3. (a) P. De Clercq and M. Vandewalle, J. Org. Chem. (1977), 42, 3447; (b) P. Kok, P. De Clercq and M. Vandewalle, Bull. Soc. Chim. Belges (1978), 87, 615; (c) P. Kok, P. De Clercq and M. Vandewalle, J. Org. Chem. (1979), 44, 4553; (d) M. Demuynck, P. De Clercq and M. Vandewalle, J. Org. Chem., (1979), 44, 4863.
4. D. Termont, P. De Clercq, D. De Keukeleire and M. Vandewalle, Synthesis (1977), 46; see also ref. 3a.
5. G.P. Rozing, P. De Clercq and M. Vandewalle, Synthesis (1978), 225.
6. The obtained product proved to be identical with a side-product originating from the Wittig reaction on 1, when DMSO was used as a solvent; previously we have assigned erroneously the structure of this product to the olefin which would result from attack at the C-6 carbonyl group (cfr. product 8 in ref. 3a). Apparently equilibration occurs under these circumstances (DMSO) and the cis-fused diketone 2 is the more reactive isomer.
7. Cis- and trans-fused compounds are easily distinguished on the basis of the markedly differing chemical shifts of their angular methyl groups, see : N.S. Bhacca and D.H. Williams, "Application of NMR spectroscopy in Organic Chemistry". Holden-Day, San Francisco, 1966.
8. For examples of preferred formation of trans-fused hydroazulenones under equilibration conditions, see : H.O. House, T. S.B. Sayer, C.-C. Yau, J. Org. Chem., (1978), 43, 2153; H.O. House, C.-C. Yau and D. Vanderveer, J. Org. Chem., (1979), 44, 3031; J.A. Marshall, W.F. Huffman, J. Am. Chem. Soc. (1970), 92, 6358; J.A. Marshall, W.F. Huffman and J.A. Ruth, J. Am. Chem. Soc. (1972), 94, 4691.
9. J.-E. Dubois, M. Dubois, Tetrahedron Lett. (1967), 4215.
10. For an alternative synthesis of the THP-derivative of 9, see ref. 3a.
11. R.A. Kretchmer and W.M. Schafer, J. Org. Chem. (1975), 38, 95.
12. M. Godefroot, M. Van Roelenbosch, M. Verstappe, P. Sandra and M. Verzele, JHRC & CC (1980), 3, 337.