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NEW INSIGHTS INTO THE MECHANISM OF THE PROLINE-CATALYZED ASYMMETRIC ROBINSON CYCLIZATION; STRUCTURE OF TWO INTERMEDIATES. ASYMMETRIC DEHYDRATION

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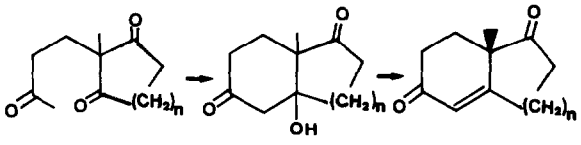
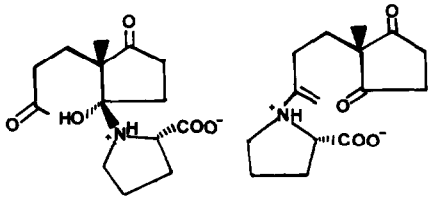
Abstract—Two sets of results give information about the mechanism of carbonyl activation by (S)-proline during asymmetric syntheses: (i) X-ray structures of two ketols produced by the proline-induced cyclization of triketones; (ii) (S)-Proline-catalyzed asymmetric dehydration of (±)-β ketols leading to optically active enones.

The proline-catalyzed ketol condensation is one of the most useful asymmetric syntheses as it leads to versatile A/B (n = 2) and C/D (n = 1) steroid ring synthons



This asymmetric Robinson annulation was independently discovered by two research groups. Eder *et al.*[2] had tried several amino-acids for this purpose and, as they added a mineral acid into the medium, they did not isolate the intermediate ketol. In their classical and elegant experiments, Hajos and Parrish[3] used (S)-proline as a catalyst in aprotic solvents to get the ketol with both excellent optical and chemical yields; the ketol was subsequently dehydrated with toluene-p sulfonic acid. Besides some other works[4] mentioning the results of various modifications of the catalyst carboxyl function, special attention should be drawn to Danishefsky's report[5] that phenylalanine is the best suited catalyst when the side chain carbonyl is linked with a group other than methyl.

However, in spite of numerous synthetic investigations,[6] the mechanism of the enantiodifferentiation is still an open matter. Actually, Hajos and Parrish in their pioneering paper,[3] tentatively proposed two processes: (i) proline activates one of the enantiotopic ring carbonyls to give an intermediate carbinolamine which then leads to the cyclization product (Jung[7] recently has corrected the stereoelectronic requirements for the cyclization to occur); (ii) proline reacts with the side chain carbonyl and the resulting enammonium group reacts with one of the diastereotopic carbonyl groups.



Seebach[8] pointed out that, in such a case, choosing between the two words "diastereodifferentiation" and "enantiodifferentiation" requires that the mechanism be elucidated.

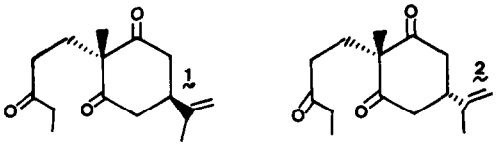
Besides this semantic problem, the knowledge of the mechanism of this reaction (properly considered as "incredible"[9] and "exciting"[10]) really is challenging, as here not only is the stereoselectivity puzzling but even the actual chemical path which would allow a ketone to react with a carbinolamine or with an enammonium group is still unknown.

We wish to report here some results which seem to support the "enamine mechanism"; they can be divided into two sets: (i) an enantioselectivity difference shown by two diastereoisomeric substrates submitted to the asymmetric cyclization; (ii) the still unreported ability of (S)-proline to act as an enantioselective dehydrating agent.

†Previous part of this series, Ref. 1.

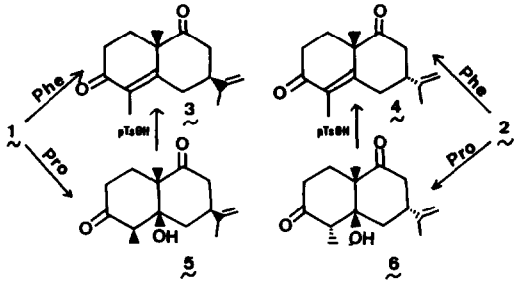
Asymmetric cyclization

The two diastereoisomeric achiral triketones **1** and **2** were selected because (i) their cyclization could make asymmetric four carbon atoms; (ii) substrate **1** is well suited as starting material for the synthesis of optically active eudesmane sesquiterpenoids; (iii) the isopropenyl substituent could give information about the ring conformation during the condensation.



Both triketones **1** and **2** were obtained together through condensation between oxycarvone and 1-penten-3-one. ^{13}C NMR spectrum of the inseparable mixture showed that the two isomers were obtained in an approximatively 60/40 ratio. Since in the cyclization experiments (*vide infra*) the *E* isomer **1** appeared as the most reactive one, analysis of the remaining mixture (where *Z* isomer **2** then prevailed) made it clear that the 60% component of the initial mixture actually was the *E* isomer **1**.

Cyclizations of triketones **1** and **2** with two chiral catalysts ((S)-phenylalanine and perchloric acid in acetonitrile, or (S)-proline in dimethylsulfoxide) are summarized in Scheme 1.



Scheme 1.

With the first chiral catalytical system, enone (+)-**3** and (+)-**4** were obtained respectively from triketones **1** and **2** (as concerns their relative configurations, *vide infra*). A ^1H NMR study with $Eu(hfc)_3$ chiral shift reagent revealed that the enantiomeric excesses of the two ketones were higher than 95%.

The absolute configuration of enone (+)-**3** was determined by using two procedures. Firstly, the enone was selectively reduced[11] to the alcohol derivative **7** by $NaBH_4$; partial resolution of this secondary alcohol **7** by the Horeau method[12] showed that this compound exhibited the absolute configuration drawn below.† Secondly, treatment of enone **3** with ethyleneglycol afforded the dioxolane derivative **8** whose circular dichroism spectrum was analogous to the well documented Cotton effects exhibited by natural steroids belonging to the testosterone series and by α-cyperone **10**[13] (Fig. 1).

†This analysis has been made by Mrs A. Nouaille and by Prof A. Horeau. We are indebted to them for their kind cooperation.

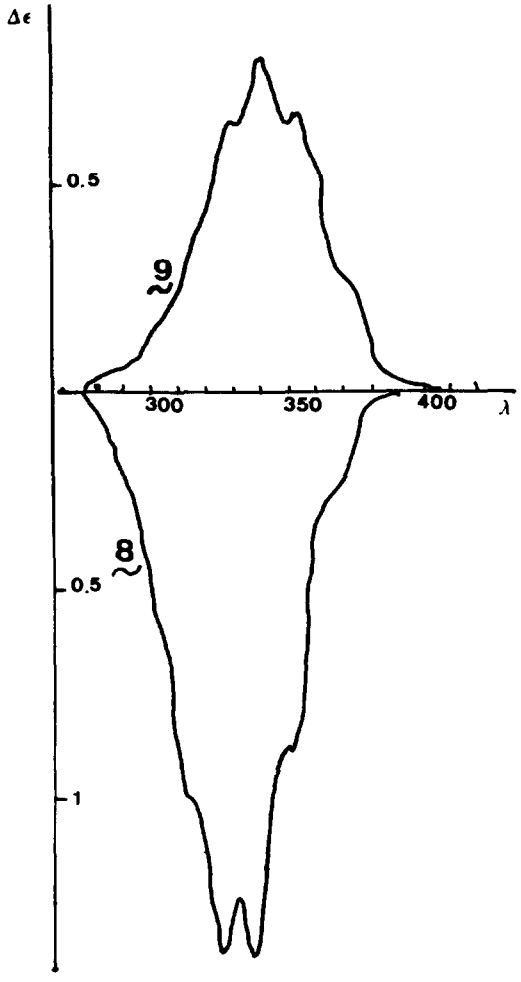
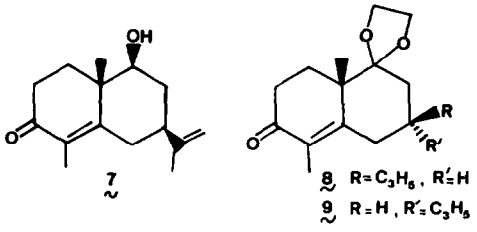
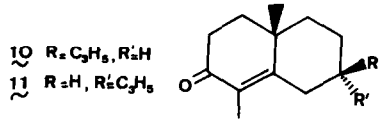


Fig. 1. CD curves of dioxolanes (+)-**8** and (+)-**9**.



As regards enone (+)-**4**, the Horeau method could not be applied as sodium borohydride reacted with neither regio- nor stereoselectivity. However dioxolane **9** was obtained. The CD spectrum of compound **9** was markedly different from that shown by its epimer **8** (Fig. 1); this difference was already reported for epi-α-cyperone **11** compared with α-cyperone **10** and was ascribed to the different orientation of the isopropenyl group.[13]



Thus the optically active enones (+)-**3** and (+)-**4** both show the "natural steroid" (8aS) configuration

(see scheme 1) in accordance with the other reported examples[6,14] of (S)-amino-acid catalyzed asymmetric synthesis (an inverse enantioselectivity has been described[15] for (S)-homoproline catalysis).

The (S)-proline-induced cyclization of ketones **1** and **2** yielded respectively ketols (−)-**5** and (±)-**6** along with a small amount of enone (+)-**3**. The structural analysis of ketols **5** and **6** were carried out by X-ray diffraction (Figs. 2 and 3); the corresponding crystal data are reported in the experimental section. With ketol (−)-**5**, the crystallization of the partially resolved mixture gave a racemate less soluble than the two enantiomers.[16] Apart from those cases where single cristals were needed, no crys-

Table 1. Selected distances (Å) and angles (deg) in ketols **5** and **6**

atoms[a]		distance/angles[b]	atoms[a]		distance/angles[b]
		Distances			
C(1)-O(11)	5	1.221(3)	C(5)-C(10)	5	1.560(3)
	6	1.219(5)		6	1.543(5)
C(6)-O(16)	5	1.222(3)	C(5)-C(6)	5	1.512(3)
	6	1.218(5)		6	1.515(6)
C(10)-O(18)	5	1.427(3)	C(3)-C(12)	5	1.521(3)
	6	1.444(4)		6	1.516(7)
C(9)-C(10)	5	1.562(3)	C(12)-C(13)	5	1.321(4)
	6	1.548(5)		6	1.325(9)
		Angles			
C(5)-C(6)-C(7)	5	114.9(2)	C(9)-C(10)-O(18)	5	105.6(2)
	6	117.0(4)		6	104.2(3)
C(5)-C(10)-C(9)	5	109.7(2)	C(9)-C(1)-O(11)	5	121.8(2)
	6	111.5(3)		6	122.0(4)
C(6)-C(5)-C(15)	5	112.8(2)	C(2) -C(3)-C(12)	5	113.2(2)
	6	112.6(4)		6	113.7(4)

[a]See Fig. 2 for the X-ray numbering of atoms. [b]Estimated standard deviations in parenthesis.

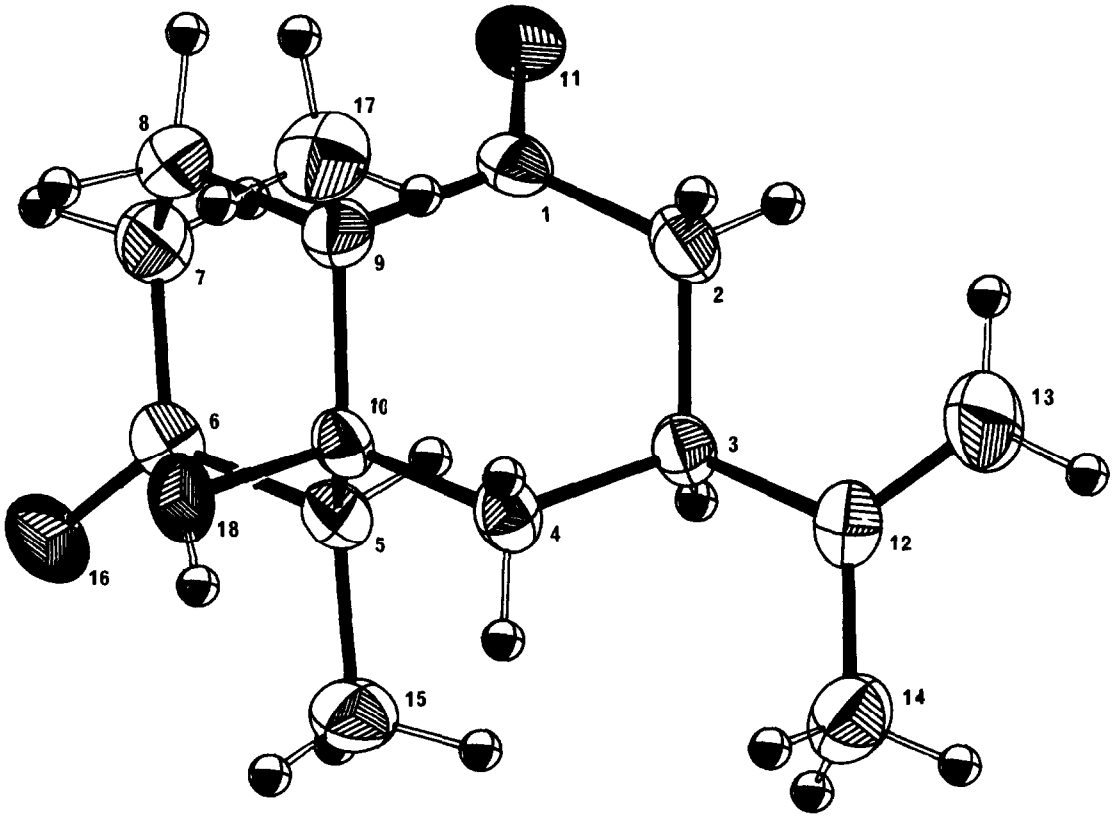


Fig. 2. ORTEP diagram (50% ellipsoids) of ketol **5**.

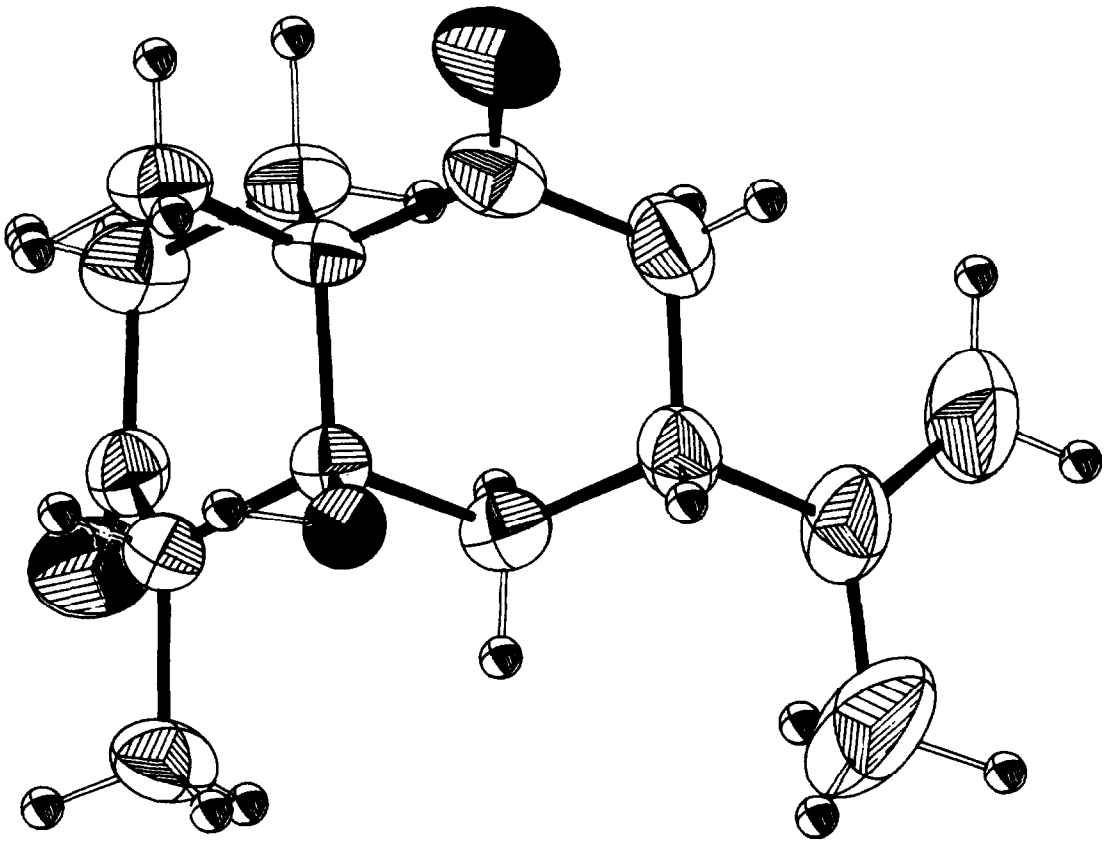


Fig. 3. ORTEP diagram (50% ellipsoids) of ketol **6**.

tallisation occurred at any stage of the experimental procedures.

The most notable point is the following: whereas ketol (−)-**5** and enone (+)-**3** were obtained with respective enantiomeric excesses of 32 and 35%, ketol **6** is not optically active. It was checked that none of these compounds were formed in the absence of proline.

Treated by toluene-p-sulfonic acid in refluxing benzene, ketol (−)-**5** and ketol (±)-**6** led respectively to enones (+)-**3** and (±)-**4**. Relatives configurations of enones **3** and **4** were thus established.

Actually, as Danishefsky and Cain[5] already pointed out, (S)-phenylalanine was the best suited catalyst to get substituted enones with the highest enantioselectivity (*vide supra*); however the primary products of the cyclization, i.e. the ketols, could only be isolated when (S)-proline was used as catalyst.

Questioning some previous stereochemical studies[17] Huffman and Hillenbrand[18] recently described achiral Robinson annulation of an undetermined mixture of triketones **1** and **2** in order to synthesize 14-nor-9-keto-α-agarofuran. Racemic enones **3** and **4** were then obtained in a 1:2 ratio by using toluene-p-sulphonic acid in benzene as catalyst; the relative configurations of these enones were attributed on the basis of conversion to eudesmane derivatives. Our own results agree with their assignments.

The fact that condensation leading to ketol **6** has occured without enantioselectivity (when proline was used as catalyst) agrees with the "enamine mechanism" proposed by Hajos and Parrish[3] which may be an oversimplification.

In this process, a hydrogen bond between the protonated nitrogen of the proline moiety and a carbonyl group is a prerequisite for the asymmetric induction. The H-bond length is one of the criteria which allow selection between the diastereotopic carbonyls. Another prerequisite is the location of the carboxyl group below the ethylenic carbon bearing the proline moiety. When occurring with an *exo* position of the vinylic methyl group (leading to ketol **5**), the cyclization can involve a chairlike transition state (Fig. 4) and, as in the other cases already described, Dreiding molecular models show that the H-bond is shorter when it involves the pro-R carbonyl group. However these requirements cannot be

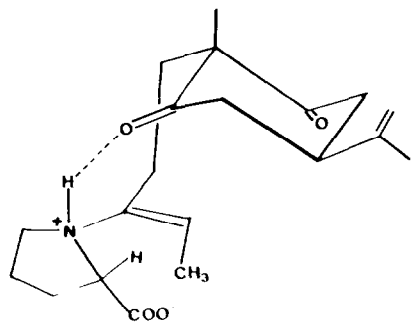


Fig. 4 Reactive conformation of enammonium intermediate leading to **5**.

obeyed in the same way during the cyclization of the substrate **2**. In the latter case when the vinylic methyl is *endo*, the same conformation shows a severe steric hindrance between this methyl group and the axial isopropenyl side chain. Thus the cyclization no longer can proceed through a chairlike transition state (Fig. 5) but rather involves a boatlike one (Fig. 6) in which that steric hindrance is relieved. In that case, molecular models show that the NH and the C=O groups are too far apart to allow the formation of a hydrogen bond with either of the two diastereotopic carbonyls.

As mentioned before, Hajos and Parrish[3] had considered two possible mechanisms and they had discarded the "enamine" one on the basis of the following result: no ^{18}O incorporation occurred into the ketol when the asymmetric cyclization was carried out in presence of ^{18}O-labelled water. Indeed this result could preclude the intermediacy of an enamine (or the formation of an oxazolidone ring in the cyclized product); however, as the same authors had also shown, in a control experiment, that the resulting ketols did incorporate ^{18}O, it should appear that the former experiment was unconclusive. It is likely that the actual site of hydrolysis is the oxazolidone carbonyl, ^{18}O should then be incorporated into the recovered proline. Apart from the stereoelectronic inaccuracy pointed out by Jung,[7] the second suggested mechanism (i.e. the carbinolamine cyclization) suffers from two major disadvantages (i) the origin of the enantioselectivity is not as clear as in the first mechanism; (ii) the cyclization implies a nucleophilic substitution on a neopentylic carbon (this steric hindrance notwithstanding, a condensation between a ketone and a carbinolamine is unprecedented, to our best knowledge).

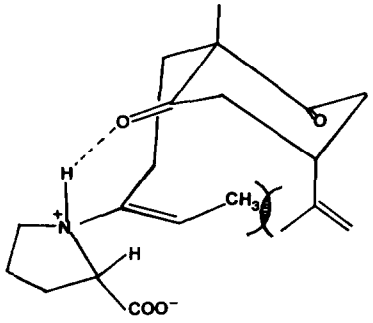


Fig. 5. Destabilized conformation of the enammonium intermediate resulting from **2**.

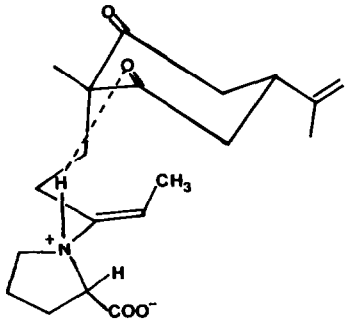


Fig. 6. Reactive conformation of the enammonium intermediate leading to **6**.

Actually the "enamine mechanism" owns several hidden parameters, of which only one is displayed by the above data. It should be noted that this mechanism has received strong support from the reported isolation[19] of an enamine intermediate during a pyrolidine catalyzed Robinson condensation.

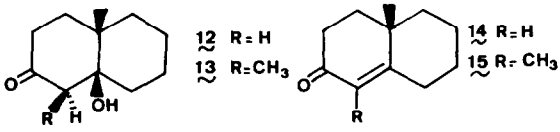
Asymmetric dehydration

Treated with an equimolar amount of (s)-proline, ketol (−)-**5** gave enone (+)-**3** whose enantiomeric excess was higher than the one exhibited by the starting ketol. Thus, in a subsequent experiment with a greater amount of (S)-proline, ketol (−)-**5** (ee 35%), obtained via the (S)-proline catalyzed cyclization, lost water yielding enone (+)-**3**; the enantiomeric excess of compound **3** thus obtained rose to 78%. More conclusively, ketol **5** was obtained by another route in the racemic form; ketol (±)-**5** was transformed to (8aS, 7S) (+)-enone **3** (ee 25%) and to (8aR, 7R) (+)-ketol **5** (ee 10%) with a 30% conversion. As (+)-enone **3** arose from (−)-ketol **5** (*vide supra*) and as the optical purity of the recovered (+)-ketol **5** corresponds to the optical purity of the formed (+)-enone **3** (the conversion value being taken into account) it appears that this asymmetric dehydration is a case of kinetic resolution.

In agreement with the principle of kinetic resolution,[20] the enantioselectivity was more apparent in the initial stages of the reaction: (+)-enone **3** was obtained with a 56% ee when conversion was limited to 20%.

On the other hand, when treated by (S)-proline, ketol (±)-**6** did not dehydrate to any appreciable extent.

Two analogous racemic ketols (±)-**12** and (±)-**13** were likewise submitted to (S)-proline catalyzed dehydration.



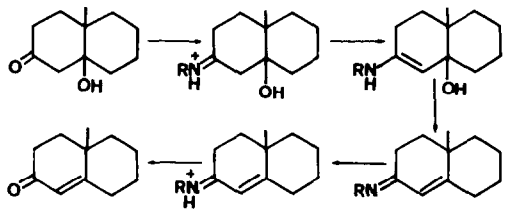
Whereas (±)-**12** lost water without any enantioselectivity, enone (±)-**14** being optically inactive, dehydration of ketol (±)-**13** occured with a high degree of enantioselectivity: enone (+)-**15** was obtained from (+)-**13** with a 76% ee at 44% conversion (for a more limited 37% conversion, the ee shown by (+)-**15** amounted to 87%).

The absolute configuration of (4aS) (+)-**15** was deduced from its circular dichroism spectrum whose Cotton effects features were similar to those exhibited by the well known (4aS) (+)-**14**.[21]

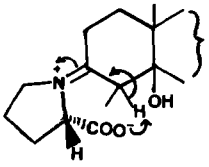
The mechanism of amine-catalyzed β-ketol dehydration was intensively studied by Spencer *et al.*[22] who demonstrated that it implies the formation of an immonium ion which is deprotonated in a rate-limiting step (see Scheme 2).

Such a nucleophilic catalysis perfectly fits with the enantioselective dehydration reported herein. The stereochemical results indeed agree with an intramolecular deprotonation by the carboxyl group of the proline moiety.

As reported above, stereoselectivity was observed only with ketols bearing a methyl group *gem* to the



Scheme 2.



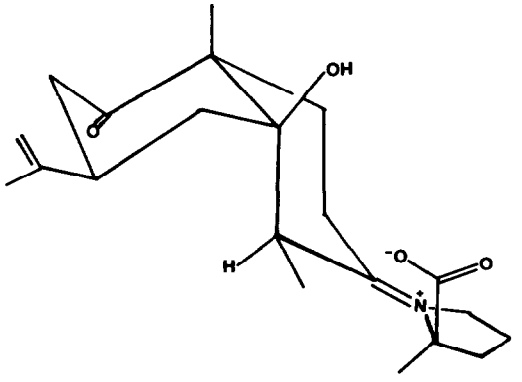


Fig. 8. Unreactive immonium intermediate resulting from (+)-**5** and (−)-**13**.

hydrogen being abstracted (ketols **5** and **13**); actually the H and COO groups are in a *syn* relationship in the immonium cations derived from ketols (−)-**5** and (+)-**13** (the carbon being deprotonated shows R configuration in both ketols) (Fig. 7) whereas the H/COO relationship is *anti* in the diastereoisomeric immonium cations derived from the enantiomeric ketols (+)-**5** and (−)-**13** (Fig. 8).

Obviously ketols (+)-**12** and (−)-**12** always bear an H atom in a *syn* relationship with the proline carboxyl group: no enantiodifferentiation appeared when racemic (±)-**12** was dehydrated.

Thus, here again, it appears that an enamine intermediate (see Scheme 2) could be implied in the course of (S)-proline catalyzed asymmetric synthesis and this fact gives further support to the "enamine mechanism" suggested by Hajos and Parrish[3] in order to explain the asymmetric ketolization.

A second important mechanistic point emerges from the asymmetric dehydration results. The fact that this reaction is a kinetic resolution (i.e. the recovered starting material has suffered no racemization) implies that the asymmetric cyclization, which occurs in the same medium with the same catalyst, is irreversible under the usual experimental conditions.

As aforesaid, the two assumptions made by Hajos and Parrish[3] in order to explain the asymmetric annulation may be considered oversimplifications. Nevertheless it must at least be said to their credit that these hypotheses set the main problem: which carbonyl reacts with proline? In that connection and within this narrow framework, our results all are in favour of a side chain carbonyl activation. Most likely the genuine and complete mechanism should be much more complicated (involving perhaps two proline molecules) and the present data only provide some of the first steps towards an overall answer.

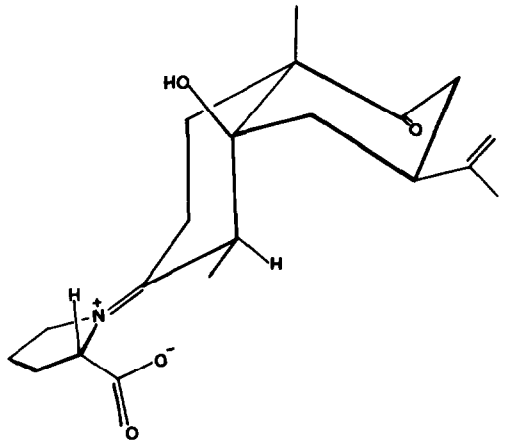


Fig. 7. Reactive conformation of the immonium intermediate resulting from (−)-**5** and (+)-**13**.

EXPERIMENTAL

General

IR spectra were recorded for CCl_4 solutions on a Beckman 4240 spectrophotometer; bands yielding structural information are reported (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were respectively carried out on a Jeol C 60 HL and on a Jeol FX 90 Q at 35° in $CDCl_3$; peak positions are reported in ppm (δ). Optical rotations were determined with a Perkin–Elmer 141 polarimeter (solvent: dioxan). Circular dichroism spectra were recorded on a Jouan Dichrograph II apparatus. X-ray data were collected with a four-circle graphite monochromated diffractometer (λCuKα = 1.5418 A). Microanalysis were performed by the Laboratory of Microanalysis of the Université P. et M. Curie. Mention of a "usual work up" means that the reaction mixture was poured into water and then extracted with ether; after being washed with water and dried over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography was executed on Merck Silica Gel 60 (70–230 mesh) eluting with petroleum ether (b.p. 35–70°) (PE)/ether (E) mixtures. Satisfactory analytical data (±0.4% for C, H) were obtained for all new compounds indicated by a molecular formula. Supplementary X-ray data have been deposited with the Cambridge Crystallographs Data Centre.

2-Methyl-5-(1-methylethenyl)-2-(3-oxo-1-pentyl)-1,3-cyclohexanedione (E + Z) **1** *and* **2**

A solution of oxycarvone[23] (4.15 g) in a methanol (25 mL)-water (75 mL) mixture was treated with 1-penten-3-one (3.15 g) and stirred at 50°C for 4 days. The remaining pentenone was then removed under reduced pressure and the usual work up, followed by column chromatography (PE/E = 75/25), provided the triketones **1** and **2** as an oil (4.7 g); IR 1720, 1700, 1650; ^1H NMR 1.00 (t, 3H, J = 8 Hz), 1.23 (s, 3H), 1.80 (s, 3H), 4.75 (m, 2H); ^{13}C NMR 202.2, 201.7, 137.1 (**2**), 136.8 (**1**), 104.0, 56.7 (**1**), 56.4 (**2**).

3,4,8,8a-*tetrahydro*-5,8aβ-*dimethyl*-3β-(1-*methylethenyl*)-1,6 (2*H*,7*H*)-*naphtalenedione* (+)-**3** *and* 3,4,8,8a-*tetrahydro*-5,8aβ-*dimethyl*-3α-(1-*methylethenyl*)-1,6 (2*H*,7*H*)-*naphtalenedione* (+)-**4**

A mixture of triketones **1** and **2** (**1**:**2** = 60:40) (1.8 g), (S)-phenylalanine (1.4 g) and 1N $HClO_4$ (3.5 mL) in acetonitrile (20 mL) was refluxed for 6 days (under argon). After cooling to room temperature, the reaction mixture was filtered and the collected phenylalanine was washed with $CHCl_3$. The filtrates were washed with 5% $NaHCO_3$ solution, then with water and dried over $NaSO_4$. The yellow oil obtained on rotatory evaporation was subjected to column chromatography (PE/E = 80/20) to give the following products. Enone (+)-**3** (0.68 g); IR 1715, 1675, 1650, 1615; ^{1}H NMR 1.42 (s, 3H), 1.83 (broad s, 6H), 4.82 (m, 2H); ^{13}C NMR 211.2 (s), 197.6 (s), 157.0 (s), 146.3 (s), 131.0 (s), 111.0 (t), 50.5 (s); $[\alpha]_D^{20} = +27°$ (*c* 1.2, dioxane). Unreacted triketones (0.62 g). Enone (+)-**4** (0.31 g); IR 1715, 1675, 1650, 1615; ^{1}H NMR 1.43 (s, 3H), 1.80 (broad s, 6H), 4.63 (broad s, 1H), 4.80 (broad s, 1H); ^{13}C NMR 212.3 (s), 197.5 (s), 157.0 (s), 146.1 (s), 132.0 (s), 111.5 (t), 49.5 (s); $[\alpha]_D^{20} = +39°$ (c 1.2, dioxane).

Hexahydro-4aβ-*hydroxy*-5β, 8aβ-*dimethyl*-3β-(1-*methylethenyl*)-1,6 (2*H*,5*H*)-*naphthalenedione* (−)-**5** *and hexahydro*-4aβ-*hydroxy*-5α, 8aβ-*dimethyl*-3α-(1-*methylethenyl*)-1,6 (2*H*,5*H*)-*naphthalenedione* (±)-**6**

A DMSO solution (20 mL) of triketones **1** and **2** (3.5 g) (**1**:**2** = 60:40) and (S)-proline (0.15 g) was heated (65°), under an argon atmosphere, for 5 days. Usual work up yielded the following products. Enone (+)-**3** (0.4 g); PE/E = 80/20; $[\alpha]_D^{20} = +5°$ (c = 1.6, dioxane). Ketol (−)-**5** (1.0 g); PE/E = 60/40; IR 3620, 1720, 1710, 1650; ^{1}H NMR 1.03 (d, 3H, J = 7 Hz), 1.25 (s, 3H), 1.78 (s, 3H), 4.80 (m, 2H); ^{13}C NMR 212.4, 211.3, 145.9, 110.6, 81.0, 54.2; $[\alpha]_D^{20} = -7°$ (c 1.0, dioxan); $C_{15}H_{22}O_3$. Ketol (±)-**6** (0.32 g); PE/E = 50/50; IR 3620, 1720, 1650; ^{1}H NMR 1.12 (d, 3H, J = 7 Hz), 1.45 (s, 3H), 1.73 (s, 3H), 4.75 (m, 2H); ^{13}C NMR 213.2, 209.3, 146.6, 110.4, 81.2, 53.8; $[\alpha]_D^{20} = 0°$; $C_{15}H_{22}O_3$.

Recrystallisation of ketols **5** and **6** in cyclohexane furnished racemate single cristals (mp 127° and 125° respectively).

Crystal data

Crystals of **5** and **6** are monoclinic, with a = 24.055 (8), b = 8.075 (3), C = 15.081 (6) and β = 112.92° (6) for **5**, and a = 19.532 (7), b = 11.747 (5), c = 12.130 (5) and β = 97.61° (6) for **6**. Space groups are C2/c, Z = 8 for **5**, and $P2_1/n$, Z = 8 for **6**. The structures were solved by direct methods and refined to R-factors of 0.044 for **5** with 1649 observed data, 0.052 for **6** with 2135 observed data. All hydrogen atoms were located and refined with the exception of the five hydrogens belonging to the isopropenyl group of one molecule of **5**, which is 180° disordered. One molecule of each crystal is shown on Figs. 2 and 3 with the 50% probability thermal ellipsoids.

4,4a,5,6,7,8-*Hexahydro*-5β-*hydroxy*-1,8aβ-*dimethyl*-7β-(1-*methylethenyl*)-2(3*H*)-*naphthalenone* (+)-**7**

Sodium borohydride (0.04 g), freshly recrystallised from diglyme, in ethanol (8 mL) was added dropwise for 1 h at 0°C to a solution of enone (+)-**3** (0.65 g) in ethanol (4 mL). The resulting mixture was stirred for 1 h at 0°C and the usual work up provided the secondary alcohol **7** (0.63 g); PE/E = 55/45; F = 35°C; IR 3620, 1675; ^{1}H NMR 1.18 (s, 3H) 1.82 (s, 3H), 3.43 (m, 1H, Γ = 18 Hz), 4.83 (m, 2H); $[\alpha]_D^{20} = +69°$ (c 1.0, dioxan).

5,5-*Ethylenedioxy*-4 4a,5,6,7,8-*hexahydro*-1,8aβ-*dimethyl*-7β-(1-*methylethenyl*)-2(3*H*)-*naphthalenone* (+)-**8**

Enone (+)-**3** (0.2 g) and ethylene glycol (0.4 g) in benzene solution (1.5 mL) were refluxed in presence of pTsOH (0.01 g) for 25 min. Water was removed by a Dean–Stark separator. Usual work up gave dioxolane **8** (0.18 g); PE/E = 80/20; F = 60°; IR 1675, 1615:^{1}H NMR 1.35 (s, 3H), 1.84 (broad s, 6H), 4.02 (s, 4H), 4.84 (m, 2H); $[\alpha]_D^{20} = +45°$ (c 0.9, dioxane); DC (c 0.22, dioxane) $\Delta\epsilon$ (λ): −0.295 (360), −0.850 (350), −1.324 (335) max, −1.201 (328), −1.324 (322) max, −0.887 (310), −0.203 (290). $C_{17}H_{24}O_3$.

5,5-*Ethylene dioxy*-4,4a,5,6,7,8-*hexahydro*-1,8aβ-*dimethyl*-7α-(1-*methylethenyl*)-2(3*H*)-*naphthalenone* (+)-**9**

Enone (+)-**4** (0.24 g) and ethylene glycol (0.47 g) in benzene solution (11 mL) were refluxed in presence of pTsOH (0.01 g) for 40 min in a Dean-Stark separator. Usual work up gave dioxolane **9** (0.12 g); PE/E = 84/16; IR 1675, 1615; ^{1}H NMR 1.35 (s, 3H), 1.80 (broads s, 6H), 4.0 (m, 4H), 4.79 (m, 2H); $[\alpha]_D^{20} = +11°$ (c 1.3, dioxane); DC (c 0.25, dioxane) $\Delta\epsilon$ (λ): +0.048 (380), +0.231 (368), +0.559 (353), +0.543 (350), +0.667 (340), +0.527 (327), +0.097 (300), +0.016 (280). $C_{17}H_{24}O_3$.

Dehydration of ketols **5** *and* **6** *with toluene-p-sulfonic acid*

Ketol (−)-**5** (0.12 g) in benzene solution (3.5 mL) was refluxed in presence of pTsOH (0.01 g) for 75 min in a Dean–Stark separator. Usual work up gave enone (+)-**3** (0.095 g); $[\alpha]_D^{20} = +8.5°$ (c 1.0, dioxane).

Ketol (±)-**6** was treated in the same way to give the racemic enone (±)-**4**.

Racemic ketol (±)-**5**

Triketones **1** and **2** (**1**:**2** = 60:40) (3.8 g) in benzene solution (17 mL) were refluxed in presence of pyrolidine (1.5 mL) during 12 h. Water was removed by a Dean–Stark separator. Usual work up gave enone (±)-**3** (1.1 g) and ketol (±)-**5** (0.3 g).

Asymmetric dehydration of ketol (±)-**5** (30% *conversion*)

A solution of ketol (±)-**5** (0.28 g) and (S)-proline (0.13 g) in DMSO (6.5 mL) was heated at 65° for 15 days (under argon). Usual work up gave enone (+)-**3** (0.08 g), $[\alpha]_D^{20} = +6°$ (c 1.2, dioxane) and ketol (+)-**5** (0.15 g), $[\alpha]_D^{20} = +2°$ (c 1.0, dioxan).

4a-*Methyl*-4,4a,5,6,7,8-*hexahydro*-2(3*H*)*naphthalenone* (±)-**14**

Ketol (±)-**12**[24] (0.5 g) in DMSO solution (10 mL) was stirred in presence of (S)-proline (0.3 g) under argon at 65° during 5 min. Usual work up furnished the enone (±)-**14** (0.2 g); $[\alpha]_D^{20} = 0°$. This compound was identical with an authentic sample.[25]

1,4a-*Dimethyl*-4,4a,5,6,7,8-*hexahydro*-2(3H)*naphthalenone* (+)-**15** (37% *conversion*)

Ketol (±)-**13**[26] (0.6 g) in DMSO solution (25 mL) was stirred in presence of (S)-proline (0.35 g) under argon at 65° during 5 days. Usual work up furnished enone (+)-**15** (0.2 g); $[\alpha]_D^{20} = +149°$ (c 0.9, dioxan); NMR features identical with those reported for (±)-**15**,[13b] CD (c 0.23, dioxan) $\Delta\epsilon(\lambda)$: +0.080 (360), −0.023 (347), −0.249 (335), 0.222 (330), −0.390 (320), −0.321 (315), −0.358 (310) max, −0.237 (300), −0.080 (280) and the recovered ketol (−)-**13** (0.3 g); $[\alpha]_D^{20} = -30°$ (c 1.1, dioxan).

Enantiomeric excess measurements

^{1}H NMR shift studies were performed by adding increasing amounts of Eu(hfc)$_3$ to the $CDCl_3$ solutions. The resonance signals for the enantiotopic hydrogens which became non-equivalent for the partially resolved compounds were : 1.83 (5-methyl in **3**), 1.80 (5-methyl in **4**), 1.25 (8a-methyl in **5**), 1.78 (isopropenyl methyl in **5**), 1.12 (5-methyl in **6**); 1.76 (1-methyl in **15**).

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