Proline Catalyzed Asymmetric Cyclization.

Theory of the Reaction Mechanism.

*Zoltan G. Hajos**

Formerly with Hoffmann-La Roche, Inc. Nutley, NJ 07110.

The second part of the investigation is the Proline Catalyzed Asymmetric Cyclization II.

*Present address: 802-A Pompton Road, Monroe Township NJ 08831-7261

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ABSTRACT: evidence is presented in this publication for the carbinolamine mechanism illustrated by intermediate **B** for the proline catalyzed intramolecular asymmetric cyclizations to the 6,5-bicyclic ketol and its six membered ring homologue. The contents of this paper are based on experimental as well as energy minimization evidence. The minimization studies gave conclusive evidence to the divergent behavior of the 6,5- and the 6,6-bicyclic systems. The communication also contains the synthesis and characterization of the optically active 6,6-bicyclic ketol.

KEYWORDS: proline catalyzed intramolecular asymmetric cyclizations; bicyclic 6,5- and 6,6-ketols; energy minimization; carbinolamine mechanism

Introduction

In the year 1971 a patent was published describing several (S)-(-)-proline catalyzed Robinson annulation reactions[1]. In 1974 the contents of the patent have been incorporated into a scientific publication[2]. In 1985 Professor Claude Agami and associates published an interpretation of this proline catalyzed Robinson annulation which they named the Hajos-Parrish reaction[3]. Recently Sami Bahmanyar and Kendall N. Houk published a paper on "The Origin of Stereoselectivity in Proline-Catalyzed Intramolecular Aldol Reactions"[4]. We would like to give a brief overview and discuss our own data to reach a reasonably satisfactory interpretation of the reaction mechanism.

Results and discussion

There are essentially two reaction mechanisms possible for the intramolecular asymmetric catalytic cyclizations with (S)-(-)-proline. The enamine and the carbinolamine mechanisms.We

have pictured both of these in our original publication[2]. In a recently published essay John J.M. Wiener correctly states: " The use of chiral amines as asymmetric catalysts was first reported in 1974 by Hajos and Parrish in the context of a Robinson annulation catalyzed by L-proline"[5]. The enamine mechanism can best be presented by using Scheme 1 of Wiener's essay with the author's permission.

Scheme 1

At this point we would like to emphasize the ^{18}O-labeled experiments described in our original publication[2]. The asymmetric conversion of the triketone **1** with (S)-(-)-proline in the presence of ^{18}O-labeled water showed extremely small ^{18}O incorporation (7.2%) during the ring-closure to the optically active bicyclic ketol **(S)-(+)-2**. Since ^{18}O incorporation is a prerequisite to the conversion of **A2** to **(S)-(+)-2** in the enamine mechanism, the very small ^{18}O enrichment clearly contradicts this (Scheme 1). The determination involved the mass spectrometric analysis of ^{18}O-labeled CO_2 of the respective samples. On the other hand, reasonably high ^{18}O incorporation (33.1%) occurred in the control experiment. In this reaction the reaction product of the asymmetric cyclization, the bicyclic ketol **(S)-(+)-2** was treated with ^{18}O-labeled water in the presence of (S)-(-)-proline.

Sarkar, Jois, Kasthuri and Dasgupta in their proline mediated intramolecular studies object to an enamine mechanism based on spectroscopic evidence[6]. Rajagopal, Moni, Subramanian and Swaminathan studied the ATR-FTIR spectra of the triketone **1** and (S)-(-)-proline. They found no absorption for the double bond of an enamine. Therefore, they too excluded the enamine intermediate for the intramolecular asymmetric cyclization reaction[7].

It is well known that it is more difficult to form enamines of aliphatic ketones. The field had

been pioneered and developed by Professor Gilbert Stork and his associates. His paper gives an excellent insight to the problems in this area of chemistry[8]. Professor Stork pointed out that "simple monosubstituted acetone (and acetone itself) are not usually satisfactorily converted into enamines by the existing methods. Pyrrolidine enamine was obtained in only 22% yield after 175 hours refluxing with benzene and p-toluenesulfonic acid. Using molecular sieves they could increase the yield to 51%".

On the other hand, Otto and Schick have described the facile addition of pyrrolidine to 2-methyl-cyclopentane-1,3-dione. They obtained the reaction product of the 5-ring diketone in 87% yield in the presence of some propionic acid in refluxing toluene [9]. It is mechanistically less likely therefore for the triketone **1** to proceed to the optically active bicyclic ketol **(S)-(+)-2** via an enamine mechanism. Contradicting this too is the fact that the reaction has been executed under extremely mild catalytic reaction conditions using 3 mol% of (S)-(-)-proline at ambient temperature[2].

There is, however, no problem to accept the enamine mechanism for the antibody-catalyzed enantioselective Robinson annulation reported by Zhong, Hoffmann, Lerner, Danishefsky and Barbas III[10]. It is well known that antibody catalyzed reactions may proceed contrary to the small molecule catalyzed reactions. Antibodies for instance catalyze ring closures in formal violation of Baldwin's rules[11].

However, for the small molecule catalyzed asymmetric Robinson annulation reaction we propose the more plausible mechanism involving the addition of (S)-(-)-proline to one of the cyclopentanedione keto groups of the triketone **1.** In the carbinolamine intermediate **B** formed the center of asymmetry of (S)-(-)-proline would be only 3 bonds away from the angular methyl

group of the prochiral center, as opposed to the 5 bond distance in the transition state **A1** of the enamine mechanism (Scheme 1). This has been described in our original paper[2], and ApSimon and Seguin have corroborated it[12]. The stereochemistry of the carbinol-amine group of **B** is presented according to Professor Michael E. Jung's suggestion[13].

Our energy minimization studies are in good agreement with Professor Agami's results[3] involving a second (S)-(-) proline molecule. However, in agreement with the carbinolamine mechanism we position the second proline molecule near the side-chain keto group to promote the enolization of the butanone keto group in intermediate **B** (Figure 1).

Figure 1

This then represents what may be called the Unified Theory of the Proline Catalyzed Asymmetric Cyclization. It does not even contradict the template suggestion of Rajagopal, Moni, Subramanian and Swaminathan[7]. An example of the (S)-(-)-proline catalyzed asymmetric Robinson annulation reaction is shown below. It involves the conversion of the triketone **1** to **(S)-(+)-2**, (3aS,7aS)-(+)-Hexahydro-3a-hydroxy-7a-methyl-1,5-indanedione[2, 16] (Scheme 2).

Scheme 2

Using CambridgeSoft Corporation's Chem3D MM2 energy minimization menu[14] based on Allinger's Molecular Mechanics force field version 2[15] we determined the nearest local energy minima of several transition states of type **B**. We assume that the (S)-(-)-proline catalyzed

cyclization proceeds through intermediate **B** to give the optically active ketol of type **2**. The results are shown in Tables 1 and 2.

Table 1

The results of Table 1 show the total minimized energies of the transition states of type **B** in the (S)-(-)-proline catalyzed intramolecular aldol addition reactions leading to the optically active 6,5-bicyclic *cis*-methyl and *cis*-ethyl ketols (n=1; R=Me and R=Et). The 6,5-methyl as well as the 6,5-ethyl ketols show a preference for an (S)-oriented transition state **B** of a lower local total energy minimum (14.69 kcal with the methyl and 16.71 kcal with the ethyl ketol). Indeed, the chemical as well as the optical yields were quite high in these asymmetric catalytic conversions (100% chemical and 93.4% optical yield for the 7aS-methyl and 98.6% chemical and 94.7% optical yield for the 7aS-ethyl 6,5-bicyclic *cis* ketols) [2].

For comparison we have included in Table 1 our calculations based on the enamine intermediate postulated by Professor Agami [3] with the exogenous second (S)-(-)-proline molecule. Our calculations show a large preference for our carbinolamine intermediate (53.95 kcal lesser energy minimum). On the other hand we found an energy difference of 34.51 kcal between the enamine intermediates with and without the second proline molecule in favor of the original Agami postulate.

Table 1 also shows that in the case of the 6,6-bicyclic cis-methyl ketol of type **4** (n=2; R=Me) the energy difference between the (S)-oriented and (R)-oriented transition states **B** has been less (3.72 kcal) than with the 6,5-bicyclic ketols (14.69 kcal energy difference with the enantiomeric methyl and 16.71 kcal with the ethyl ketols). In agreement with these calculations

we found a lesser 73% ee in the (S)-(-)-proline catalyzed cyclization leading to the 6,6-bicyclic system [17]. Unaleroglu, Aviyente, and Arseniyadis investigated the energy profiles of the 6,5- and 6,6-bicyclic systems in the lead tetraacetate mediated one-pot multistage transformations[18]. They too found a surprising difference between the energetic behavior of the two series.

It should be pointed out that it was rather difficult to isolate (S)-(-)-**4**. The conversion of the homologous triketone **3** to the optically active 6,6-bicyclic methyl ketol (S)-(-)-**4** is shown in Scheme 3.

Scheme 3

To avoid dehydration to the enedione, the Wieland-Miescher ketone, the reaction had to be stopped at a reasonably early stage. Therefore, a sizable amount of the prochiral triketone **3** has been recovered. It was thus possible to isolate (S)-(-)-**4** in 52% chemical and approximately 73% optical yield[17]. The crude compound (S)-(-)-**4** has been dehydrated to the Wieland-Miescher ketone of 75% optical purity by refluxing with a catalytic amount of p-toluenesulfonic acid in benzene. This is a less impressive result than the 93.4% ee obtained with the 6,5-bicyclic system[2]. The energy minimization studies shown in Table 1 render a theoretically important interpretation for this difference.

As already mentioned, the Wieland-Miescher ketone has been obtained in high chemical and optical yield by the antibody catalyzed enantioselective conversion of the prochiral triketone **3** by Zhong, Lerner, Danishefsky, and Barbas, III [10]. Therefore, a significant difference has to exist between the antibody catalyzed and the (S)-(-)-proline catalyzed reaction mechanisms. An enamine mechanism has been postulated for the antibody catalyzed reaction, and the aldol addition intermediate (S)-(-)-**4** has not been observed.

In our own synthetic studies[2] contrary to the synthesis of the 6,6-bicyclic ketol (S)-(-)-**4** it has been much easier to isolate and characterize the 6,5-bicyclic Pro-Me-ax-S-*cis*-ketol (S)-(+)-**2** (Scheme 2 and Table 2), and its ethyl homologue the Pro-Et-ax-S-*cis*-ketol (Table 2). The configuration of the former corresponds to the "non steroidal" that of the latter to the "steroidal" configuration as shown by circular dichroism and by X-ray diffraction studies[2]. These results are in good agreement with the total minimized energies of these ketols obtained by using CambridgeSoft Corporation's Chem3D MM2 energy minimization menu[14] based on Allinger's Molecular Mechanics force field version 2[15]. The results of the total minimized energies of these ketols are summarized in Table 2.

Table 2

Conclusion

We have postulated two possible reaction mechanisms for the proline catalyzed enantio-selective intramolecular aldol cyclizations: the enamine and the carbinolamine routes. We favor the carbinolamine route based on theoretical considerations, ^{18}O incorporation studies, and last but not least on our energy minimization results presented in this paper. We determined the nearest local energy minima of several transition states of type **B** using CambridgeSoft Corporation's Chem3D MM2 energy minimization menu[14]. We assume that the (S)-(-)-proline catalyzed cyclization proceeds through the carbinolamine intermediate **B** to the optically active 6,5-bicyclic ketol of type **2.** Conversion to the 6,6-bicyclic ketol of type **4** proceeds similarly through the homologous intermediate **B**. Our minimization studies gave conclusive evidence to the divergent behavior of the 6,5- and the 6,6-bicyclic systems. They support the high 93.4% ee observed with the 6,5-bicyclic ketols and explain the lower 73% ee found with the 6,6-system[17].

The synthesis of the optically active 6,6-bicyclic ketol (S)-(-)-**4** is described in the Experimental section.

Experimental[19]

(-)-3,4,4a, 5,8,8a-hexahydro-4aß-hydroxy-8aß-methyl-1,6-(2H,7H)-naphthalenedione ((**S)-(-)-4**).

A total of 19.6 g. of 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione was dissolved in 100 ml of anhydrous N,N-dimethylformamide. The resulting solution was cooled to 0°C. and 115 mg. of S(-)proline was added in small portions over a period of 30 minutes. The reaction mixture was permitted to come to RT and a nitrogen atmosphere was maintained over the suspension, which was also protected from light. After 24 hours, 115 mg. additional S(-)proline was added to the mixture and a similar addition of S(-)proline was repeated after 48 hours. The reaction was terminated after a total of 72 hours of stirring. The solvent was evaporated by high vacuum distillation. The dark residue that was dissolved in 400 ml. diethyl ether, stirred with 5.0 g. of activated charcoal and filtered through 5.0 g. of silica gel to give an orange colored filtrate that upon storage for 16 hours at 0°C. deposited 3.4 g. (17.3%) of crude crystalline **(S)-(-)-4**; optical rotation $[\alpha]_D^{25}$ -19.83° (c 1.22, in chloroform); mp 131.5 - 141.5°C. Evaporation of the solvent in vacuo from the mother liquor gave an oil that subsequently produced two additional crystalline crops: one of 2.4 g. (12.2%); $[\alpha]_D^{25}$ -18.2° (c 1.015 in chloroform); mp 129 - 133°C and another of 1.26 g. (6.4%); $[\alpha]_D^{25}$ –15.39° (c 1.04, in chloroform); mp 131 - 135°C.

Chromatography on silica gel of the remaining oil gave a total of 3.28 g. (16.2%) of the aforesaid crude product, $[\alpha]_D^{25}$ -11.57° (c 1.0, in chloroform) and 6.95 g. (35.5%) of starting trione. The overall yield of crude reaction product was calculated as 10.24 g. (52.1%).

An optically pure sample was obtained by recrystallization from ether mp 134.5 - 135.5°C; $[\alpha]_D^{25}$ -21.97°, (c 1.1013 in chloroform; ir (chloroform) 3625, 3450 (OH), and 1725 cm^{-1} (6-ring ketones);1H-NMR ($CDCl_3$) δ 1.31 singlet (8a-CH3), 2.52 singlet (4a-OH). Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.39; H, 8.19.

Acknowledgment.

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(19) All melting points were determined in a Thomas-Hoover mp apparatus and are corrected; uv spectra were taken in ethyl alcohol with a Cary Model 14M spectrophotometer; ir spectra were taken in absolute chloroform with a Beckman IR-9 recording spectrophotometer; nmr spectra were taken in $CDCl_3$ on an HA-100 spectrometer with TMS as an internal standard; optical rotations were taken with a Perkin-Elmer Model 141 polarimeter.

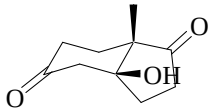
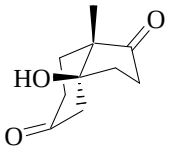
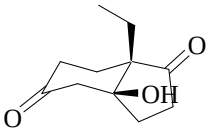
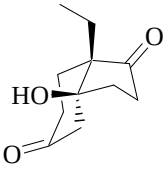
TABLE 1

Intermediate B	Configuration	Total Minimized Energy
n=1; R=Me	2S, 3S	-136.4687
n=1; R=Me	2R, 3R	-121-7778
n=1; R=Et	2S, 3S	-132.2760
n=1; R=Et	2R, 3R	-115.5651
n=2; R=Me	2S, 3S	-129.8767
n=2; R=Me	2R, 3R	-126.1602
Enamine Intermediate [a]		
n=1; R=Me	2S, 3S	-82.5194
Enamine Intermediate [b]		
n=1; R=Me	2S, 3S	-48.0097

[a] Enamine intermediate with second (S)-(-)-proline molecule as pictured in Reference 3.

[b] Enamine intermediate without the second (S)-(-)-proline molecule.

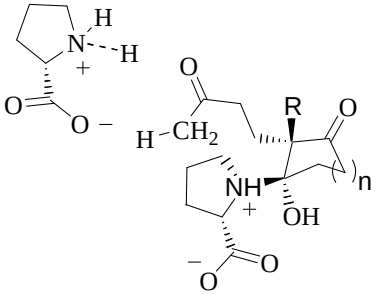
TABLE 2

NAME [a]	STRUCTURE	TOTAL MINIMIZED ENERGY
Pro-Me-*ax*-S-cis-ketol [b]		25.0685
Pro-Me-*eq*-S-cis-ketol		25.3454
Pro-Et-*ax*-S-cis-ketol		29.1832
Pro-Et-*eq*-S-cis-ketol [b]		27.9912

[a] Pro indicates (S)-(-)-proline catalyst; S refers to the configuration at 7a of the 6,5-bicyclic ketol; *ax* or *eq* refers to the stereochemistry of the alkyl group at 7a in the six membered ring of the bicyclic ketol ; *cis* refers to the stereochemistry of the bicyclic ketol.

[b] Configuration of compound as shown by circular dichroism and X-ray studies[2].

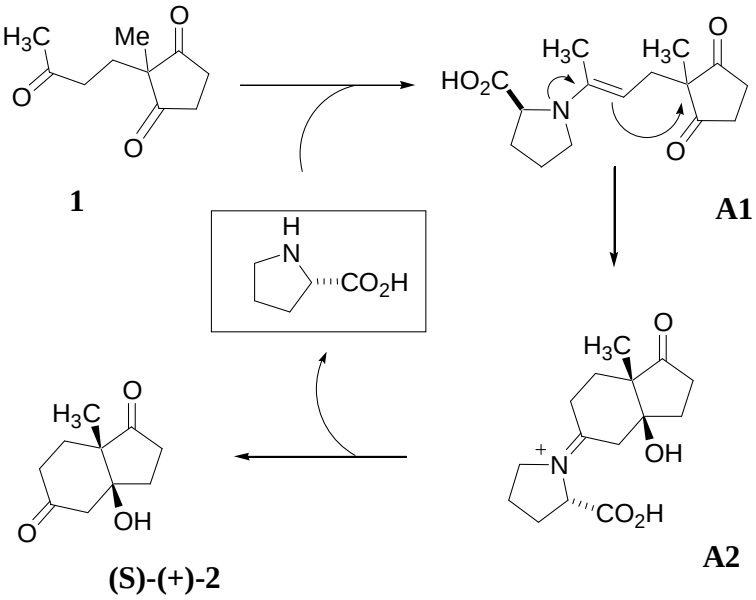
Figure 1



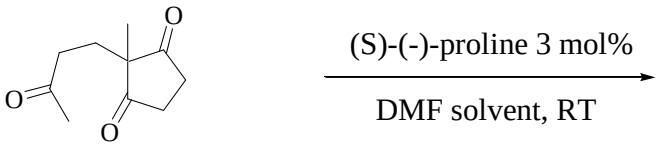
Intermediate **B** n=1; R= Me or Et

n=2; R=Me

Scheme 1

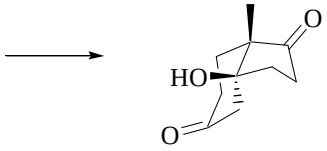

H3C
Me
O
O
O
1
HO2C
H3C
H3C
O
N
O
A1
H
N
CO2H
H3C
O
+
N
OH
CO2H
A2
H3C
O
O
OH
(S)-(+)-2

Scheme 2



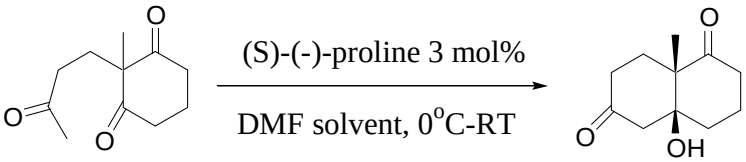
1

Intermediate **B**



(S)-(+)-**2**

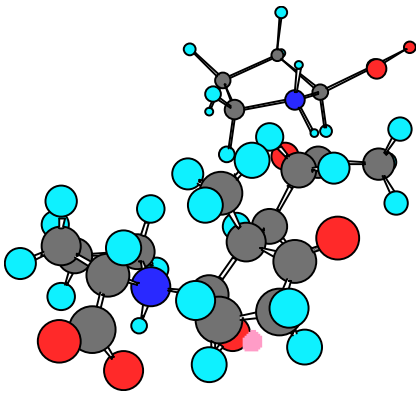
Scheme 3



3

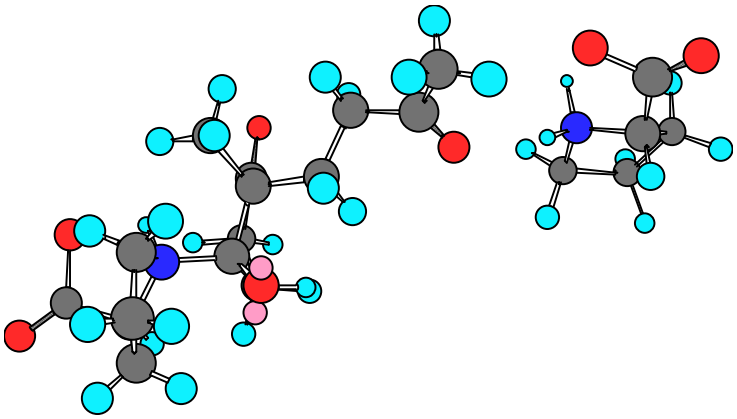
(S)-(-)-**4**

Table 1, Intermediate B; n=1;R=Me Configuration: 2S,3S



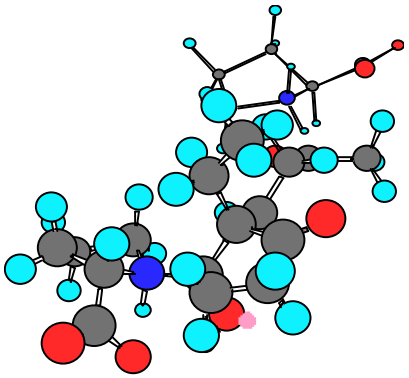
Warning: Arbitrary dihedral chosen for C(14)-C(3)-C(4)-C(1) C(14)-C(3)-C(4)-C(1)
Warning: Arbitrary dihedral chosen for C(9)-C(10)-C(11)-C(13) C(9)-C(10)-C(11)-C(13)
Warning: Arbitrary dihedral chosen for C(25)-C(26)-N(27)-C(28) C(25)-C(26)-N(27)-C(28)
Adding lone pairs to O(7) O(7)
Pi System: 31 30 32
Pi System: 23 22 24
Warning: Some parameters are guessed (Quality = 1).
Iteration 348: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 2.3436
Bend: 26.4459
Stretch-Bend: 0.5140
Torsion: 28.0850
Non-1,4 VDW: -1.0040
1,4 VDW: 20.1050
Charge/Charge: -198.0486
Charge/Dipole: -15.0886
Dipole/Dipole: 0.1789
Total: -136.4687

Table 1, Intermediate B; n=1; R=Me Configuration: 2R,3R



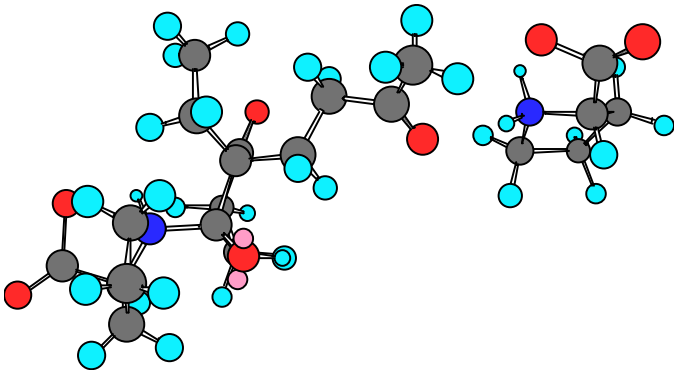
Warning: Arbitrary dihedral chosen for C(13)-C(3)-C(4)-C(1) C(13)-C(3)-C(4)-C(1)
Warning: Arbitrary dihedral chosen for C(8)-C(9)-C(10)-C(12) C(8)-C(9)-C(10)-C(12)
Warning: Arbitrary dihedral chosen for C(25)-C(26)-N(27)-C(28) C(25)-C(26)-N(27)-C(28)
Adding lone pairs to O(6) O(6)
Pi System: 31 30 32
Pi System: 22 21 23
Warning: Some parameters are guessed (Quality = 1).
Iteration 354: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 3.1551
Bend: 23.0905
Stretch-Bend: 0.5147
Torsion: 30.9728
Non-1,4 VDW: -0.4388
1,4 VDW: 19.6319
Charge/Charge: -197.1083
Charge/Dipole: -2.2556
Dipole/Dipole: 0.6599
Total: -121.7778

Table 1, Intermediate B; n=1;R=Et Configuration: 2S,3S



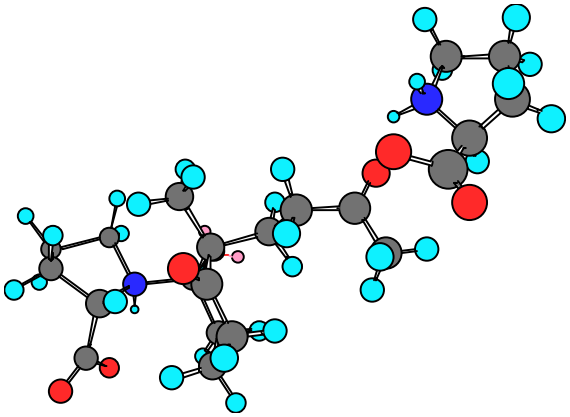
Warning: Arbitrary dihedral chosen for C(14)-C(3)-C(4)-C(1) C(14)-C(3)-C(4)-C(1)
Warning: Arbitrary dihedral chosen for C(9)-C(10)-C(11)-C(13) C(9)-C(10)-C(11)-C(13)
Warning: Arbitrary dihedral chosen for C(26)-C(27)-N(28)-C(29) C(26)-C(27)-N(28)-C(29)
Adding lone pairs to O(7) O(7)
Pi System: 32 31 33
Pi System: 23 22 24
Warning: Some parameters are guessed (Quality = 1).
Iteration 385: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 2.8496
Bend: 28.2781
Stretch-Bend: 0.7006
Torsion: 30.3329
Non-1,4 VDW: -0.1394
1,4 VDW: 21.1128
Charge/Charge: -198.0784
Charge/Dipole: -17.5715
Dipole/Dipole: 0.2385
Total: -132.2760

Table 1, Intermediate B; n=1;R=Et Configuration: 2R,3R



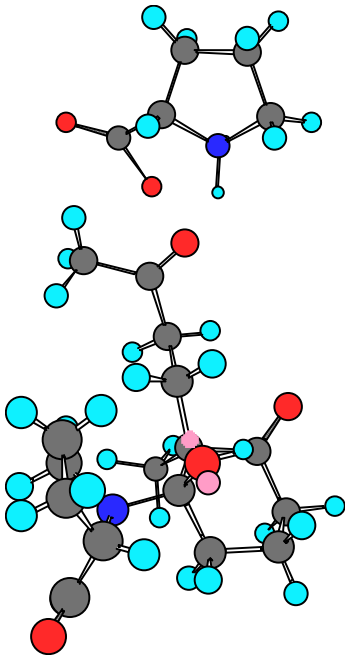
Warning: Arbitrary dihedral chosen for C(13)-C(3)-C(4)-C(1) C(13)-C(3)-C(4)-C(1)
Warning: Arbitrary dihedral chosen for C(8)-C(9)-C(10)-C(12) C(8)-C(9)-C(10)-C(12)
Warning: Arbitrary dihedral chosen for C(26)-C(27)-N(28)-C(29) C(26)-C(27)-N(28)-C(29)
Adding lone pairs to O(6) O(6)
Pi System: 32 31 33
Pi System: 22 21 23
Warning: Some parameters are guessed (Quality = 1).
Iteration 375: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 4.0041
Bend: 25.3300
Stretch-Bend: 0.7007
Torsion: 32.3052
Non-1,4 VDW: 0.8053
1,4 VDW: 20.7144
Charge/Charge: -197.0761
Charge/Dipole: -2.9718
Dipole/Dipole: 0.6230
Total: -115.5651

Table 1, Intermediate B; n=2;R=Me Configuration: 2S,3S



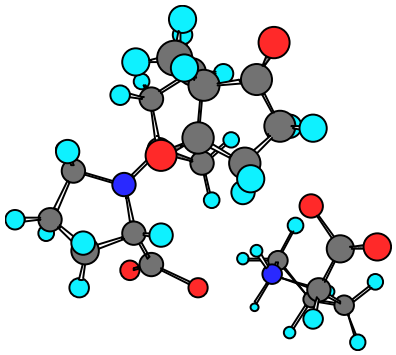
Warning: Arbitrary dihedral chosen for C(18)-C(17)-C(26)-C(27) C(18)-C(17)-C(26)-C(27)
Warning: Arbitrary dihedral chosen for C(25)-C(31)-C(32)-C(34) C(25)-C(31)-C(32)-C(34)
Warning: Arbitrary dihedral chosen for C(1)-C(2)-N(3)-C(4) C(1)-C(2)-N(3)-C(4)
Adding lone pairs to O(20) O(20)
Pi System: 23 22 24
Pi System: 7 6 8
Warning: Some parameters are guessed (Quality = 1).
Iteration 337: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 3.4405
Bend: 22.8281
Stretch-Bend: 0.9453
Torsion: 28.9047
Non-1,4 VDW: -2.3160
1,4 VDW: 21.4834
Charge/Charge: -195.3485
Charge/Dipole: -10.9130
Dipole/Dipole: 1.0986
Total: -129.8767

Table 1, Intermediate B; n=2; R=Me Configuration: 2R,3R



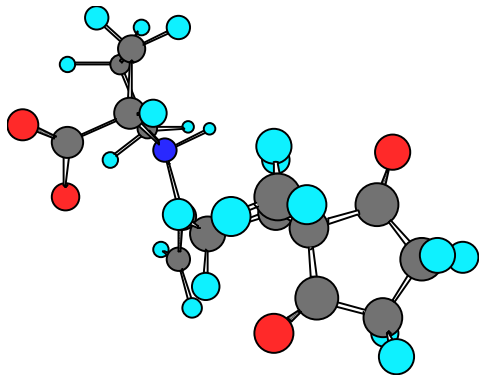
Warning: Arbitrary dihedral chosen for C(18)-C(17)-C(25)-C(26) C(18)-C(17)-C(25)-C(26)
Warning: Arbitrary dihedral chosen for C(24)-C(30)-C(31)-C(33) C(24)-C(30)-C(31)-C(33)
Warning: Arbitrary dihedral chosen for C(1)-C(2)-N(3)-C(4) C(1)-C(2)-N(3)-C(4)
Adding lone pairs to O(19) O(19)
Pi System: 22 21 23
Pi System: 7 6 8
Warning: Some parameters are guessed (Quality = 1).
Iteration 363: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 3.9342
Bend: 22.1939
Stretch-Bend: 0.9118
Torsion: 28.8000
Non-1,4 VDW: -2.2869
1,4 VDW: 22.7496
Charge/Charge: -196.4936
Charge/Dipole: -7.0248
Dipole/Dipole: 1.0557
Total: -126.1602

Table 1, Enamine Intermediate [a]; n=1; R=Me Configuration: 2S,3S



Warning: Arbitrary dihedral chosen for C(5)-C(1)-C(2)-C(3) C(5)-C(1)-C(2)-C(3)
Warning: Arbitrary dihedral chosen for C(15)-N(16)-C(17)-C(13) C(15)-N(16)-C(17)-C(13)
Warning: Arbitrary dihedral chosen for C(21)-C(22)-C(23)-C(24) C(21)-C(22)-C(23)-C(24)
Pi System: 29 28 30
Pi System: 19 18 20
Pi System: 12 11 16
Warning: Some parameters are guessed (Quality = 1).
Iteration 326: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 1.7077
Bend: 19.6728
Stretch-Bend: 0.1821
Torsion: 20.2928
Non-1,4 VDW: 1.6597
1,4 VDW: 11.9025
Charge/Charge: -139.0510
Charge/Dipole: -5.8203
Dipole/Dipole: 6.9344
Total: -82.5194

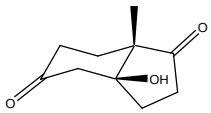
Table 1, Enamine Intermediate [b]; n=1; R=Me Configuration: 2S,3S

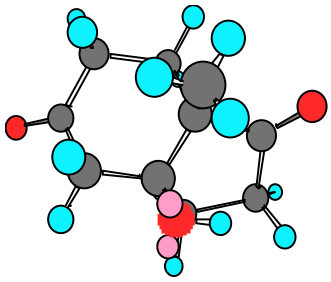


Warning: Arbitrary dihedral chosen for C(5)-C(1)-C(2)-C(3) C(5)-C(1)-C(2)-C(3)
Pi System: 19 18 20
Warning: Some parameters are guessed (Quality = 1).
Iteration 208: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 1.2752
Bend: 12.9581
Stretch-Bend: 0.1345
Torsion: 15.9097
Non-1,4 VDW: -1.0652
1,4 VDW: 10.2869
Charge/Charge: -93.1655
Charge/Dipole: 1.8925
Dipole/Dipole: 3.7640
Total: -48.0097

Table 2, **Pro-Me-ax-S-cis-ketol** [a]

Compound Energy minimized structure

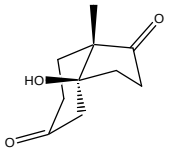
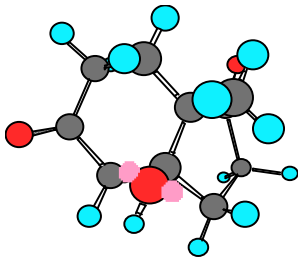




Adding lone pairs to O(13) O(13)
Note: Some parameters are not finalized (Quality = 3).
Iteration 95: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 0.8888
Bend: 3.5886
Stretch-Bend: 0.1161
Torsion: 14.4174
Non-1,4 VDW: -3.4784
1,4 VDW: 6.9812
Dipole/Dipole: 2.5547
Total: 25.0685

[a]Pro indicates (S)-(-)-proline catalyst; S refers to the configuration at 7a of the 6,5-bicyclic ketol; *ax* or *eq* refers to the stereochemistry of the alkyl group at 7a in the six membered ring of the bicyclic ketol ; *cis* refers to the stereochemistry of the bicyclic ketol.

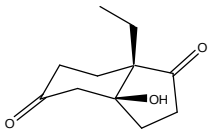
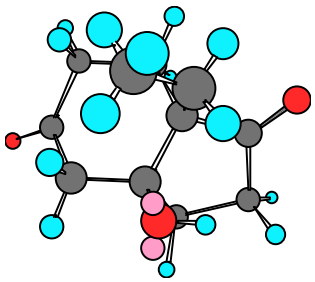
Table 2, **Pro-Me-eq-S-cis-ketol** [a]

Compound	**Energy minimized structure**
	

Adding lone pairs to O(12) O(12)
Note: Some parameters are not finalized (Quality = 3).
Iteration 86: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 0.9328
Bend: 4.2733
Stretch-Bend: 0.1275
Torsion: 14.5096
Non-1,4 VDW: -3.0591
1,4 VDW: 6.8971
Dipole/Dipole: 1.6642
Total: 25.3454

[a]Pro indicates (S)-(-)-proline catalyst; S refers to the configuration at 7a of the 6,5-bicyclic ketol; *ax* or *eq* refers to the stereochemistry of the alkyl group at 7a in the six membered ring of the bicyclic ketol ; *cis* refers to the stereochemistry of the bicyclic ketol.

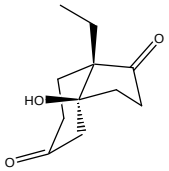
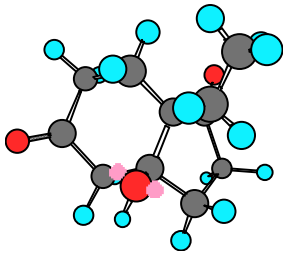
Table 2, **Pro-Et-ax-S-cis-ketol** [a]

Compound	Energy minimized structure
	

Adding lone pairs to O(14) O(14)
Note: Some parameters are not finalized (Quality = 3).
Iteration 111: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 1.2823
Bend: 5.1057
Stretch-Bend: 0.2256
Torsion: 15.4381
Non-1,4 VDW: -3.6582
1,4 VDW: 8.2665
Dipole/Dipole: 2.5232
Total: 29.1832

[a]Pro indicates (S)-(-)-proline catalyst; S refers to the configuration at 7a of the 6,5-bicyclic ketol; *ax* or *eq* refers to the stereochemistry of the alkyl group at 7a in the six membered ring of the bicyclic ketol ; *cis* refers to the stereochemistry of the bicyclic ketol.

Table 2, **Pro-Et-eq-S-cis-ketol** [a]

Compound	Energy minimized structure
	

Adding lone pairs to O(13) O(13)
Note: Some parameters are not finalized (Quality = 3).
Iteration 99: Minimization terminated normally because the gradient norm is less than the minimum gradient norm
Stretch: 1.2296
Bend: 4.7720
Stretch-Bend: 0.2119
Torsion: 15.4296
Non-1,4 VDW: -2.8491
1,4 VDW: 7.5859
Dipole/Dipole: 1.6113
Total: 27.9912

[a]Pro indicates (S)-(-)-proline catalyst; S refers to the configuration at 7a of the 6,5-bicyclic ketol; *ax* or *eq* refers to the stereochemistry of the alkyl group at 7a in the six membered ring of the bicyclic ketol ; *cis* refers to the stereochemistry of the bicyclic ketol.