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THE ROLE OF PROLINE IN THE ASYMMETRIC STEP OF THE WOODWARD SYNTHESIS OF ERYTHROMYCIN

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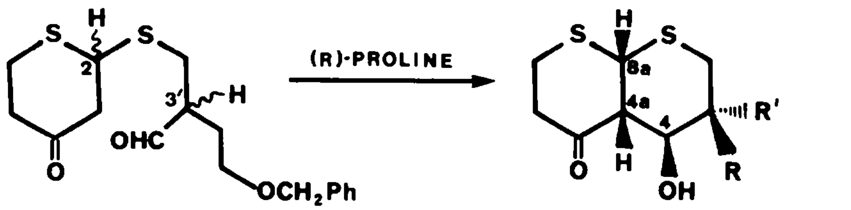
Abstract - Proline induces the enantioselectivity of the title reaction in an aldol reaction and not in a conjugate addition. This was demonstrated by the two following sets of experiments. (i) Recovered keto sulfides 4 and 5 did not show any optical activity when the racemic substrates were treated with (S)-proline; moreover (S)-proline was unable to induce chirality during the conjugate addition of thiophenol on cyclohexenone. (ii) Kinetic resolution of racemic keto aldehyde 6 occured when this compound was submitted to a (S)-proline-catalyzed aldol reaction.

The monumental achievement of the erythromycin A synthesis by Woodward et al.[2] can be looked as a conceptual yardstick in total synthesis.[3] Among the ingenious realizations described therein, one of the most striking is the key step in which asymmetric induction occurred. This enantiodifferentiating step provided chiral synthon 2 from racemic keto aldehyde 1 via a (R)-proline-catalyzed aldol reaction; on the other hand, Woodward et al. reported that a mixture of (2R,3'S)-1 and (2R,3'R)-1 gave virtually racemic products when they are treated with (S)-proline, whereas the same mixture afforded optically active ketols (80-86% ee) when proline showed the R absolute configuration.



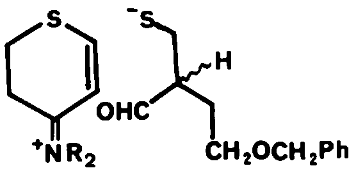
(±)-1

(+)-2 : R = $CH_2CH_2OCH_2Ph$
R' = H

(−)-3 : R = H
R' = $CH_2CH_2OCH_2Ph$

Since the starting keto aldehyde (±)-1 was a 1:1 mixture of two diasteromers, ketol (−)-3 (36% ee) was obtained along with the desired ketol (+)-2 (36% ee). Therefore (R)-proline is responsible for the stereogenicities of carbon atoms in positions 4, 4a and 8a. It is worth noting that the same relative configuration (syn-arrangement of 4a-H, 8a-H and 4-OH) was observed in the products (±)-2 and (±)-3 which resulted from silica gel-catalyzed cyclization of compound (±)-1.

In their paper, Woodward et al.[2] suggested that proline might be involved as a chiral auxiliary in species such as i and ii in addition to its known capacity for catalyzing an enantioselective aldol reaction.[4] It follows that proline would thus catalyze an enantioselective intra or/and intermolecular conjugate addition to an unsaturated ketone via an iminium intermediate.



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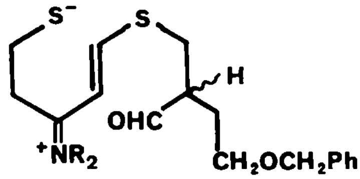
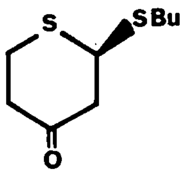


ii

Since no report of an enantioselective conjugate addition catalyzed by proline itself[5,6], to the best of our knowledge, has been published so far, we decided to investigate the role of this amino acid in the Woodward synthesis. To this end, the occurrence of an enantioselective behaviour of proline through either process was checked on related model compounds. Racemic keto sulfides 4 and 5 are substrates for the observation of possible asymmetric induction in the retro-Michael-Michael process. On the other hand, cyclization of the racemic keto aldehyde 6 may provide evidence for proline action during the aldol reaction.



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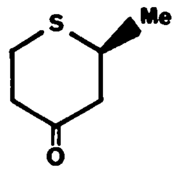

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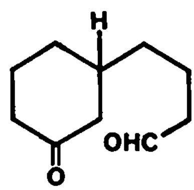

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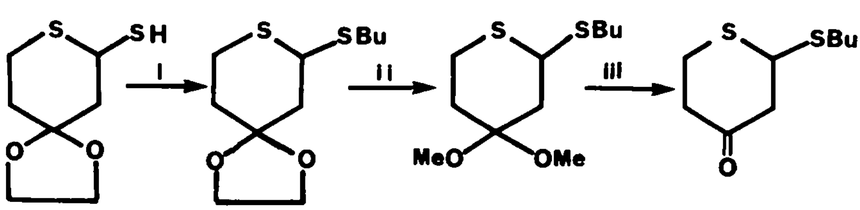
RESULTS AND DISCUSSION

Dithioketal 4 was prepared as shown in Scheme I. Exchange of protecting groups in 8 and 9, prior to regeneration of the keto group, was necessary since direct transformation of the dioxolan derivative 8 failed to give compund 4 owing to drastic hydrolysis conditions. On the other hand, the dioxolan moiety was required when synthesizing compound 7 from tetrahydrothiapyranone.[7]



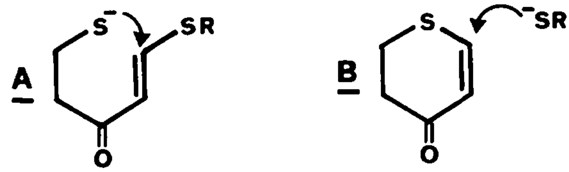
7 8 9 4

(i) NaH, BuOMs . (ii) $(MeO)_3CH$. (iii) H_2O, AcOH .

Scheme 1

Treated by (S)-proline, under the same conditions which were used[2,8] for cyclization of substrate 1, the thioketal 4 gave unidentified optically inactive material besides the recovered compound 4 which turned out to be still racemic. This result indicates that neither intramolecular nor intermolecular Michael addition (respectively paths A and B in Scheme 2) would occur with enantioselectivity. Woodward et al.[2]

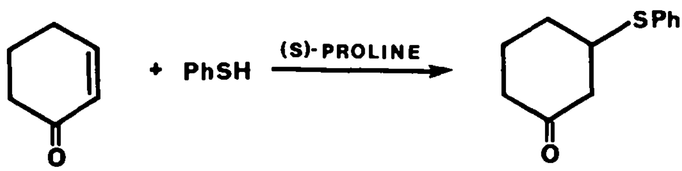
demonstrated the existence of retro-Michael-Michael additions by observing cross-additions of thioalkyl groups to a ketothioketal substrate. However, our aforementioned result can hardly be considered as decisive since the starting dithioketal was recovered only in low yield (50 %) owing to the high reactivity of compound 4 which led to formation of by-products.



Intra A and intermolecular B pathways of conjugate additions to retro-Michael products derived from β-keto dithioketals

Scheme 2

In order to know whether proline can behave as an enantioselective catalyst during an intermolecular addition of a sulfur nucleophile (see i, and path B in Scheme 2), thiophenol was added to cyclohexenone in the presence of (S)-proline, following the procedure described by Hiemstra and Wynberg[9] for the efficient catalysis of the same condensation by alkaloids. Here again, no enantioselective addition occurred: the resulting product 10, obtained in a quantitative yield, was optically inactive.

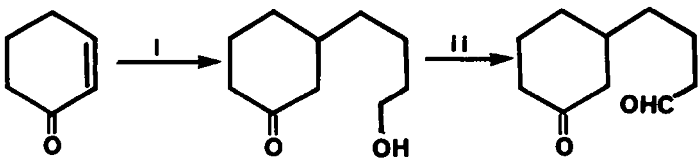


(±)- 10

Finally, the formal dissection of both reactivity patterns of the β-keto dithioketal moiety in substrate 1 was completed with the use of compound 5. This model molecule may give information about the ability of proline to catalyze enantioselectively an intramolecular conjugate addition (see ii, and path A in Scheme 2). As a result, in that case too, no optical activity was detected in the recovered material when (±)-5 was treated with (S)-proline. Though the negative outcomes of models 10 and 5 do not justify a definite conclusion about the real case (this limitation is clearly inherent in any approach that deals with "model" compounds) yet it can be concluded that an enantioselective catalysis of a conjugate addition is unlikely to operate during the proline-catalyzed cyclization of (±)-1. The other hypothesis, i.e. asymmetric catalysis of the aldol condensation, was borne out by examining the reactivity of keto aldehyde (±)-6 in the presence of (S)-proline. As a matter of fact, in this case, no retro-Michael-Michael reactions would interfere with the cyclization process.

According to the method reported by Cahiez, Alexakis and Normant,[10] Cu(I)-catalyzed condensation of alcoholate Grignard reagent to cyclohexenone afforded keto alcohol 11 which, after being oxidized by Corey-Schmidt reagent,[11] gave substrate 6 (Scheme 3).

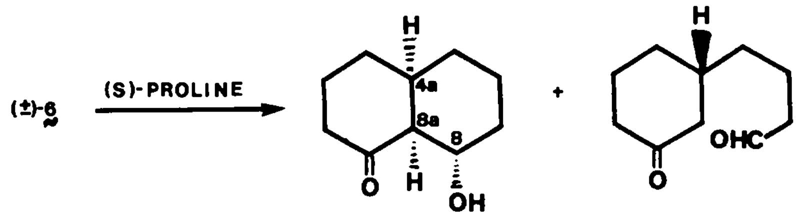
The (S)-proline-catalyzed intramolecular aldol reaction of keto aldehyde (±)-6 led to kinetic resolution of the racemic substrate. The ketol (−)-12 showed a 46 % ee, when conversion was limited to *ca* 50 %. Configuration of (4aR,8S,8aS)-(−)-12 was determined as follows.



11 6

(i) $ClMgO(CH_2)_4MgCl$, CuCN/LiCl . (ii) Pyridinium dichromate

Scheme 3



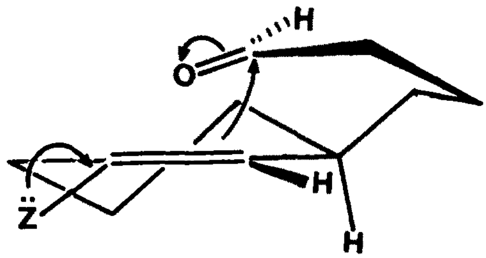
(4aR,8S,8aS)-(−)-12 (S)-(−)-6

The relative configuration of compound 12 was studied by ^{1}H NMR at 500 MHz. Complete assignement was achieved (see experimental section) through 2D COSY spectroscopy. Discrimination between *cis* or *trans* ring junction is disclosed by the value of $^3J_{H_{4a}H_{8a}}$ in the presence of the chemical shift reagent $Eu(fod)_3$. The signal of H_{8a} is a triplet of broad lines with a full width of 12.2 Hz. Since $^3J_{H_{8a}H_8}$ (measured in the H_8 multiplet) is 7.2 Hz, $^3J_{H_{4a}H_{8a}}$ cannot exceed 5 Hz. This value is incompatible with an axial/axial disposition, i.e. a *trans* ring junction; the *cis* nature of the ring junction of ketol 12 is thus established. Relative position of 8-H and 8a-H can be deduced from $^3J_{H_{8a}H_8}$ whose value (7.2 Hz) lies in between values typical of anti ($\sim$ 10 Hz) and gauche ($\sim$ 4 Hz) arrangements. Owing to the equilibrium between the two *cis* conformations, such a result implies a *trans* disposition of 8-H and 8a-H. The same value is observed for $^3J_{H_{7\alpha}H_8}$ (*trans* arrangement) whereas $^3J_{H_{7\beta}H_8}$ (*cis* arrangement) is smaller (3.6 Hz). The above result is further conforted by the report of very close values (7.9 , 7.9 and 3.8 Hz) in the corresponding 1-H resonance in isomenthol.[12]

Absolute configuration of the (8S)-carbon atom in the secondary alcohol function was disclosed by the Horeau method of kinetic resolution of phenylbutyric anhydride. This assignement, combined with the relative configuration determined as shown above, provides the knowledge of the structure of ketol(−)-12. The enantiomeric excess of (−)-12 was measured by integrating the resolved ^{1}H NMR signals (at 500 MHz) corresponding to 8-H and 8a-H in the presence of the chiral shift reagent $Eu(hfc)_3$.

The aldol condensation of (±)-6 led to recovery of the less reactive enantiomer (−)-6 ; its S configuration was deduced by comparison of the absolute configuration of (−)-12 which results necessarily from cyclization of (R)-(+)-6.

Stereoselective formation of *cis* bicyclic compounds from substituted cyclohexanones is well-documented.[13] The stereochemical course of the cyclization affording a *cis* ring junction can be ascribed to stereoelectronic control [14] which leads to an axial attack of the aldehyde moiety onto the endocyclic double bond of the enol

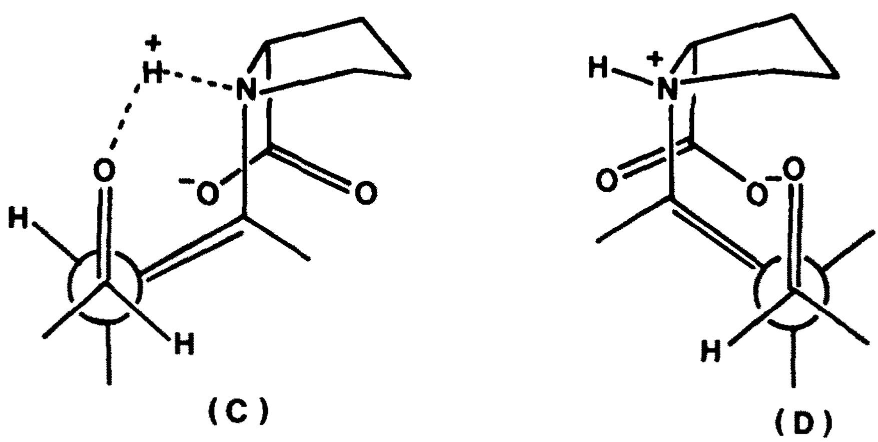


Stereochemistry of the silica gel-catalyzed cyclization (Z = hydroxy) leading to (±)-12 and of the (S)-proline-catalyzed cyclization (Z = N-prolino) leading to (−)-12.

Figure 1

(catalysis by silica gel) or the enamine derivative (catalysis by proline) of the keto group (Fig. 1).

The enantiodifferentiation observed here is fully consistent with the model we have already suggested:[15] the carboxylate group of (S)-proline being set in the position suited to stabilise electrostatically the developing iminium cation, a stabilising hydrogen bond between the nitrogen and the aldehyde oxygen can be made only when starting from (R)-6. On the other hand, the synclinal approach of the enamine double bond to the carbonyl group (Fig. 1 and 2) is worthy to note. This arrangement is in agreement with Seebach model [16] about mutual approaches of trigonal centres.



Reactive conformations of enamines derived from (R)-6 (C) and from (S)-6 (D); the second (S)-proline molecule, which transfers the proton, is omitted for the sake of clarity.

Figure 2

Given that natural (S)-proline was used here (Woodward et al.[2] treated (±)-1 with (R)-proline in order to get the required ketol enantiomer) it can be observed that both the intramolecular aldol condensation of keto aldehyde (±)-6 and the cyclization of (±)-1 follow exactly the same stereochemical course. It can therefore be stated that the aldol reaction alone can account for the asymmetric induction observed in the synthesis of erythromycin A. In the Woodward synthesis, retro-Michael-Michael processes, albeit non-enantioselective, allowed the interconversion of the starting 2S/2R substrates: kinetic resolution thus led to consumption of the 2R enantiomer of (±)-1 which was the more reactive towards the (R)-proline catalyzed enantioselective aldol reaction; therefore the less reactive 2S enantiomer of (±)-1 was continuously converted to its 2R isomer. The fact that (S)-proline was less efficient than (R)-proline when starting from optically active (2R)-1 can be explained by both the above kinetic resolution and the interconversion which presumably led to partial racemization of (2R)-1.

In conclusion, it appears that the use of a racemic starting material in which retro-Michael reactions are inoperative clearly shows that the case in hand is relevant to enantioselective aldol reaction and not to enantioselective Michael addition.

Acknowledgements

We are grateful to Professors D. Arigoni and A. Vasella for helpful discussions.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$ solution) were recorded on a Jeol FX 90 Q spectrometer except for the ^{1}H NMR spectrum of 12 (vide infra). Chemical shifts (δ) are given in ppm, downfield from tetramethylsilane as internal standard. Infrared spectra were recorded on a Beckman 4240 spectrophotometer (CCl_4 solution). Optical rotations were determined with a Perkin-Elmer 141 polarimeter. 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 $MgSO_4$, the solvent was removed under reduced pressure. Flash chromatography was performed on silica gel 60 (200-400 mesh) eluting with petroleum ether (b.p. 35-70°) (PE) / ether (E) mixtures.

2-Butylthiotetrahydrothiapyran-4-one 4

2-Mercapto-4,4-ethylenedioxythiapyran 7 (0.56 g)[7] in THF solution (5 ml) was treaced with sodium hydride (0.1 g) at 20°. The resulting precipitate was dissolved by addition of DMSO (0.5 ml) in the reaction mixture. After stirring for 1 h at 20°, butyl mesylate (0.5 g) in THF (4.5 ml) was added. Usual work-up (PE / E = 70 / 30) yielded 2-butylthio-4,4-ethylenedioxythiapyran 8 (0.64 g). ^{1}H NMR 3.95 (s, 4, $C\underline{H}_2$ of the tetrahydropyranyl ring), 0.85 (t, 3, $C\underline{H}_3$). ^{13}C NMR 107.7, 64.4, 44.9, 43.8, 35.9, 31.7, 30.9, 27.3, 21.8, 13.5. Anal. Calcd for $C_{11}H_{20}O_2S_2$: C, 53.18 ; H, 8.11. Found : C, 53.36 ; H, 8.1.

The thiapyran 8 described above (0.16 g) was treated with trimethyl orthoformate (0.6 g) in methanol solution (3 ml) in the presence of p-TsOH (0.02 g). After stirring at room temperature for 15 h, usual work-up (PE / E = 85 / 15) gave 2-butylthio-4,4-dimethoxytetrahydrothiapyran 9 (0.11g). ^{1}H NMR 3.95 (dd, J = 13.5 and 3 Hz, 2-H), 3.20 and 3.15 (s, 3, OMe), 0.90 (t, 3, $CH_2C\underline{H}_3$). ^{13}C NMR 99.5, 47.3, 43.8, 41.6, 33.3, 31.7, 30.9, 26.7, 21.9, 13.6. Anal. Calcd for $C_{11}H_{22}O_2S_2$: C, 52.75 ; H, 8.85 . Found : C, 52.72 ; H, 8.88.

A solution containing the preceding compound 9 (0.1 g) and acetic acid (0.7 ml) in water (1.9 ml) was stirred at room temperature for 2 days. Usual work-up (PE / E = 80 / 20) afforded 2-butylthiotetrahydrothiapyran-4-one 4 (0.62 g). ^{1}H NMR 4.3 (m, 1, 2-H), 0.91 (t, 3, $C\underline{H}_3$). ^{13}C NMR 205.6, 49.7, 48.0, 43.0, 31.6, 31.1, 26.2, 21.9, 13.5. Anal. Calcd for $C_9H_{16}OS_2$: C, 52.89 ; H, 7.89 . Found : C, 53.14 ; H, 7.94.

Treatment of 2-butylthiotetrahydrothiapyran-4-one with (S)-proline

An acetonitrile solution (3 ml) of compound 4 (0.061 g) was treated with (S)-proline (0.035 g). After stirring for 3 days at room temperature, usual work-up yielded the starting racemic pyranone 4 (0.030 g) and unidentified optically inactive material.

3-Phenylthiocyclohexanone 10

Thiophenol (1.1 g) was reacted with cyclohexen-2-one (0.96 g) in the presence of (S)-proline (0.23 g) in acetonitrile solution (10 ml). After stirring for 28 h at room temperature, benzene (30 ml) was added. The benzene solution was successively extracted with 2N HCl, 2N NaOH and with saturated NaCl solution. The dried ($MgSO_4$) solution was evaporated. The crude product showed no optical activity and its spectral data (IR and ^1H NMR) were in agreement with literature data[17] for 3-phenylthiocyclohexanone.

Treatment of 2-methyltetrahydrothiapyran-4-one with (S)-proline

An acetonitrile solution (2 ml) of compound (±)-5[18] (0.08 g) was stirred in the presence of (S)-proline (0.04 g) for 24 h at room temperature. After being filtered the mixture was submitted to the usual work-up which yielded compound (±)-5 (0.07 g) identical in all respects with the starting material.

3-(4-Hydroxybutyl) cyclohexanone 11

Copper (I) cyanide (0.29 g) and lithium chloride (0.18 g) were dissolved in anhydrous THF (325 ml). 2-Cyclohexen-1-one (5.8 g) was added to this mixture which was then cooled at -10°. To this solution was added dropwise at -10° a 0.4 M THF solution (170 ml) of the ω-alcoholate Grignard reagent derived from 1-chloro-4-hydroxybutane. This reagent was prepared according to a published procedure.[10,19] The reaction mixture was allowed to warm to room temperature and was hydrolyzed by introducing a saturated aqueous NH_4Cl solution into the reaction vessel. An addition of 5N HCl led to the solubilization of magnesium salts. A 8N NH_4OH solution was then added until the solution turned to a blue color. The mixture was extracted with ether and the organic layers were washed by an ammonia buffer of saturated NH_4Cl aqueous solution until the aqueous layers were uncolored. The dried ($MgSO_4$) solution was evaporated and the residue flash-chromatographed on silica (PE / E = 80 / 20) giving compound 11 (4.6 g).[20] ^1H NMR 4.0 (s, 1, OH), 3.6 (m, 2, 4'-CH_2), 1.2-2.45 (m, 15). ^{13}C NMR 211.6, 61.4, 47.4, 40.8, 38.5, 35.7, 32.1, 30.6, 24.7, 22.4. IR 3640, 1717 cm^{-1} (lit.[20] (neat) 3400, 1712).

3-(4-oxobutyl) cyclohexanone 6

Compound 11 (2.3 g) dissolved in methylene chloride (20 ml) was treated with pyridinium dichromate (5.5 g) according to the procedure of Corey and Schmidt,[10] for 19 h at room temperature. Flash chromatography of the residue (PE / E = 60 / 40) yielded aldehyde 6 (1.0 g). ^1H NMR 9.76 (t, 1, J = 1.5 Hz, CHO). ^{13}C NMR 211.4, 202.0, 47.8, 43.7, 41.3, 38.7, 35.8, 31.0, 25.0, 19.1. IR 2720, 1730, 1715 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39 ; H, 9.59. Found : C, 71.38 ; H, 9.62.

(4aR,8S,8aS)-(−)-cis-Octahydro-8-hydroxy-1 (2H)-naphtalenone 12

An acetonitrile solution (16 ml) of keto aldehyde (±)-6 (1 g) was treated with (S)-proline (0.15 g) for 20 h at room temperature. The reaction mixture was filtered and the collected proline was washed with Et_2O. The filtrate was evaporated and chromatography afforded the following products. (i) Mixture[22] of $\Delta^{9,10}$-octal-1-one and $\Delta^{8,9}$-octal-1-one (0.06 g), PE / E = 60 / 40. (ii) (3S)-Keto aldehyde 6 (0.2 g), PE / E = 60 / 40. $[\alpha]_D^{20}$ = -2.5° (c 4, $CHCl_3$). (iii) Ketol 12 (0.47 g), PE / E = 30 / 70. $[\alpha]_D^{20}$ = -27.9°, $[\alpha]_{578}^{20}$ = -29.4°, $[\alpha]_{546}^{20}$ = -34.4°, $[\alpha]_{436}^{20}$ = -73.2°, $[\alpha]_{365}^{20}$ = -169.4° (c 4, $CHCl_3$). ^{13}C NMR 213.05, 67.05, 58.9, 40.1, 37.2, 32.8, 29.0, 28.1, 24.3, 20.15. IR 3630, 1710 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39 ; H, 9.59. Found : C, 69.86 ; H, 9.56. ^1H NMR spectra of ketol 12 were recorded on a Bruker 500 spectrometer ($CDCl_3$ solution). 1D spectra were measured with: spectrum width

2500 Hz. For the COSY spectrum, the spectrum width was 2000 Hz and the resolution achieved in the frequency domain was 2 Hz. Multiplets appeared at : 2.32 (2-H), 2.44 (2-H), 2.00 (3-H), 1.77 (3-H), 1.65 (4-H), 1.77 (4-H), broad signal at 1.40-1.45 (5-H), 1.58 (6-H), 1.64 (6-H), 1.41 (7-H trans to 8-H), 1.94 (7-H cis to 8-H), 2.45 (8a-H), 2.36 (4a-H).

Determination of the absolute configuration of ketol 12 by the method of Horeau

(±)-α-Phenylbutyric anhydride (0.200 g), ketol (–)-12 (0.045 g) and pyridine (1.5 ml) were mixed and kept at 20° for 6 h. The titration and the work-up procedure of method A described by Horeau[23] were used. Laevorotatory enantiomer of 2-phenylbutyric acid was recovered (opt. yield : 15 %).

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