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Article

An Easy Access to Two Epimeric *N*-Substituted (2*S*)-2-(2´-Hydroxypropyl)pyrrolidines

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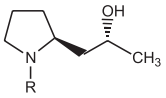
Uma fácil e eficiente síntese para obtenção de β-aminocetonas **5a**, **6** e γ-aminoálcoois **1a**, **2a**, **3**, **4** enantiomericamente puros a partir de L-prolinol **7** e L-prolina **15** é descrita. A etapa principal da reação foi o uso do reagente de Tebbe que permitiu a transformação da função éster a um enol éter que após hidrólise formou a cetona sem nenhuma racemização.

An easy and efficient route for the synthesis of enantiomerically pure β-aminoketones **5a**, **6** and γ-aminoalcohols **1a**, **2a**, **3**, **4** from L-prolinol **7** and L-proline **15** is described. One of the key steps is the use of Tebbe´s reagent allowing the transformation of the ester function to an enol ether without any racemization.

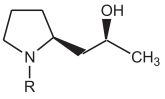
Keywords: β-aminoketones, γ-aminoalcohols, racemization, Tebbe's reagent

Introduction

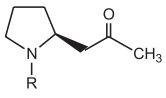
In our ongoing research on the total synthesis of glycoheterocyclic compounds, we needed compounds (*2S*,*2´R*)- and (*2S*,*2´S*)-*N*-(*p*-toluenesulfonyl)- and (*2S*,*2´R*)- and (*2S*,*2´S*)-*N*-(methoxycarbonyl)-2-(2´-hydroxypropyl)pyrrolidines **1a**, **2a 3** and **4** respectively. Before starting the present work, we surveyed the literature and found no record of *N*-tosyl alcohols **1a** and **2a**.



1a: R = Ts



2a: R = Ts



5a: R = Ts

3: R = CO_2CH_3

4: R = CO_2CH_3

6: R = CO_2CH_3

There are entries for the racemic alcohols **3** and **4**,[1,2] and also of enantiomerically pure **4**.[3] Our interest developed knowing the fact that pyrrolidine derivatives possess biological activities.[4,5]

For obtaining the aforementioned alcohols, our first approach was to prepare ketones **5a** and **6** in the enantiomerically pure forms. In fact racemic **5** was prepared earlier in four steps by a tandem S_N2-Michael addition reaction without any description about their optical purity.[6] Racemic **6** is also known.[1] This contribution therefore gives a detailed account of acquiring compounds **1a**, **2a**, **3**, **4**, **5a** and **6** starting from (*S*)-prolinol **7** or (*S*)-proline **15** (Schemes 1 and 3).

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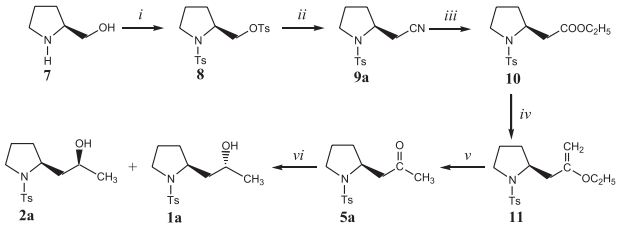
Results and Discussion

We envisaged the synthesis of ketone **5a** starting from (*S*)-prolinol **7** involving a series of steps (Scheme 1). The use of Tebbe´s reagent[7] to transform **10**→**5a** turned out to be interesting because this reagent is used in a non-basic medium. Thus, racemization does not take place on substrates with enolizable chiral centers or other base sensitive groups.

Initially, we decided to ditosylate compound **7**[8] in order to obtain **8** and its transformation to nitrile **9a**.[8] The last product was converted to ester **10**. Treatment of **10** with Tebbe's reagent and subsequent hydrolysis of enol ether led to ketone **5a** which was reduced to **1a** and **2a** with sodium borohydride (Scheme 1).

The ^{1}H NMR spectra of **1a** and **2a** are consistent with the proposed structures. Compound **5a** was found to be enantiomerically pure by ^{1}H NMR spectroscopy as verified by the chiral shift reagent, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate.



Scheme 1. *i:* TsCl, Py, rt, 12h, 89%; *ii:* NaCN, DMSO, rt, 72h, 90%; *iii:* EtOH, HCl(g), rt, 24h, 60%; *iv:* 1) Tebbe's reagent, THF, 0 °C, 30 min; 2) Et_2O, NaOH 0.1 mol L^{-1}; *v:* HCl 2 mol L^{-1}, $CHCl_3$, rt, 1.5h, 79% from **10**; *vi:* $NaBH_4$, MeOH, 0 °C, 1h, 96% (**1a**:**2a**, 2.0:1.0).

The same chiral shift reagent was used for obtaining the ^1H NMR spectrum of the racemic mixture **5a**,**5b**.

It is well known that *N*-alkyl β-amino ketones racemize rapidly in basic medium[9] and the cleavage of the pyrrolidine ring is favored when the nitrogen atom carries an electron withdrawing group.[10,11] Before the synthesis of **5a** employing Tebbe's reagent, we also visualized to prepare ketone **5a** in basic medium. For this, compound **9a** was allowed to react with MeLi which furnished **5a**,**5b** with 54% enantiomeric excess in favor of the (*S*) configuration. The *ee* was determined by measuring the optical rotation of the mixture **5a**,**5b** and comparing with the value of the pure enantiomer **5a**. Next, we attempted to obtain **5a** from **14** using acidic conditions.[12] This provided racemic **5a**,**5b**, which after reduction with sodium borohydride yielded a mixture of stereoisomers, *viz.*, **1a**, **1b** and **2a**, **2b**, respectively (Scheme 2). Each enantiomeric pair was separated by liquid chromatography over silica gel in the ratio of 2.1:1.0 (**1a,1b**:**2a,2b**); the fast moving spot **2a,2b** crystallized and its X-ray analysis showed them as a racemic mixture consisting of enantiomers (2*S*,2´*S*) **2a** and its mirror image (2*R*,2´*R*) **2b**. Since the racemic mixture gave beautiful crystals suitable for X-ray data collection, we analysed it crystallographically. The X-ray structure is depicted in Figure 1.

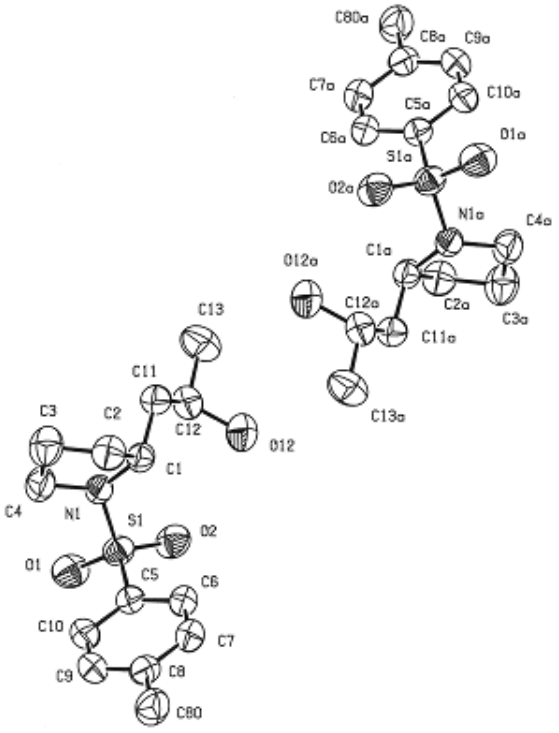
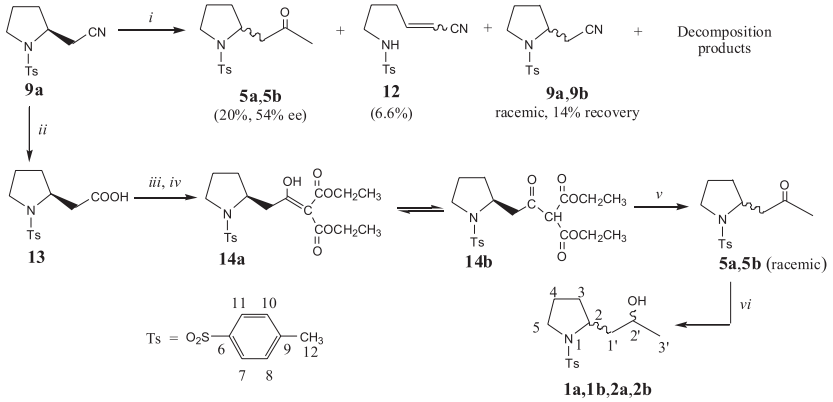


Figure 1. X-ray crystal structures presenting the enantiomeric mixture of (2*S*,2´*S*)- and (2*R*,2´*R*)-*N*-(*p*-toluenesulfonyl)-2-pyrrolidinyl-2-propanols **2a**,**2b**.

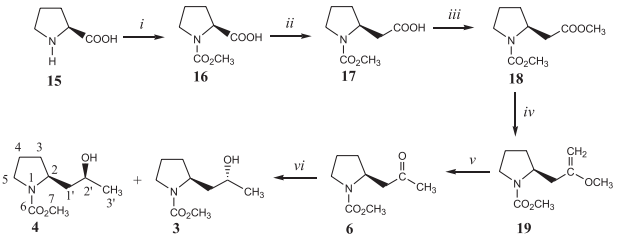
The single crystal structure analysis shows that the pyrrolidine ring is somewhat deviated and not in an envelope shape. The torsion angles C(4)-N(1)-C(1)-C(2), N(1)-C(1)-C(2)-C(3) and C(2)-C(3)-C(4)-N(1) are -19.7, 34.2 and 24.4 degrees, respectively. It further provides the bond angles C(4)-N(1)-S(1) and C(1)-N(1)-S(1) of 118.7 and 118.8 degrees which is very close to 120 degrees indicating sp^2 hybridization of the nitrogen atom. The N-S bond distance found in the current work is 1.622Å, both S=O bond distances are: 1.431 and 1.434,



Scheme 2. *i*: 1) MeLi, THF, 0 °C, 1h; 2) Aq HCl; *ii*: AcOH, 37% HCl, 100 °C, 4h, 66%; *iii*: $(COCl)_2$, DMF, CH_2Cl_2, rt, 4h; *iv*: NaH, $CH_2(CO_2CH_2CH_3)_2$, THF, Δ, 3h, 78%; *v*: H_2SO_4 4 mol L^{-1}, 100 °C, 12h, 79%. *vi:* $NaBH_4$, MeOH, 0 °C, 1h, 96% (**1a**,**1b**:**2a**,**2b**, 2.1:1.0).

respectively. These values are very close to the data reported in the literature for *N*-tosyl-8-azaspiro(4,5)-deca-1,3-diene, which have N-S = 1.631; S=O = 1.446; S=O = 1.417Å, respectively.[13] Another interesting observation was found. The dihedral angles N(1)-S(1)-C(5)-C(6) and N(1)-S(1)-C(5)-C(10) are 85.2 and -90.5 degrees showing that the *p*-tolyl ring is almost perpendicular to N(1)-S(1) bond. Other bond distances and bond angles observed are normal. Both (*R*) and (*S*) configurations of **2** can be visualized easily in the diagram (Figure 1).

Next, an alternative route for the synthesis of the known compounds **3** and **4** has been developed by us starting from *N*-methoxycarbonyl-(*S*)-proline **16**,[14] which in turn was obtained from (*S*)-proline **15**. Homologation of **16** by Arndt-Eistert method[15] gave **17** which was converted to ester **18**. The conversion of ester **18** to vinyl ether **19** utilizing Tebbe's reagent, followed by an acidic hydrolysis gave ketone **6** in an excellent yield. Sodium borohydride reduction of **6** afforded **3** and **4** in the ratio of 2.0:1.0 (Scheme 3). Alcohols **3** and **4** were separated in their pure forms by liquid chromatography over silica gel. Their structures and configurations agreed with the data reported earlier.[1-3]



Scheme 3. *i:* CH_3OCOCl, $NaHCO_3$, THF, rt, 16h, 80%; *ii:* 1) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C-rt, 4h; 2) CH_2N_2, Et_2O, 0 °C, 5h; 3) Ag_2O, H_2O, dioxane, 90 °C, 6h, 46%; *iii:* CH_2N_2, Et_2O, 0 ºC, 1h, 100%; *iv:* 1) Tebbe's reagent, THF, 0 °C, 30 min; 2) Et_2O, NaOH 0.1 mol L^{-1}; *v*: HCl 1 mol L^{-1}, $CHCl_3$, rt, 1.5h, 83% from **18**; *vi:* $NaBH_4$, MeOH, 0 °C, 1h, 90% (**3**:**4**, 2.0:1.0).

Conclusion

In conclusion, we have been able to synthesize ketones **5a** and **6** without any epimerization using Tebbe´s reagent and also the known diastereoisomers **3** and **4** by an alternative route not elaborated previously. Compounds **6** and **4** may be considered as precursors of (-)-hygrine and (-)-hygroline,[1-3] which are natural alkaloids. A new synthetic procedure has been developed for alcohols **1a**, racmic **1a,1b**, **2a** and racemic **2a,2b** starting from (*S*)-prolinol **7**.

Experimental

Melting points were determined on an Electrothermal digital melting points apparatus (model IA9100) and are uncorrected. Specific rotations were measured on a Perkin-Elmer polarimeter model 241. NMR spectra were recorded with a Bruker AM 300MHz for NMR ^1H and 75.5MHz for NMR ^{13}C using TMS as an internal standard. Chemical shifts (δ) are expressed as ppm and splitting patterns are designated as: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, t = triplet, q = quartet and m = multiplet. Silica gel 60 (230 – 400 mesh) was employed for liquid chromatography. Petroleum ether used in the experiments had boiling range of 40-65 °C.

*Ethyl (-)-(S)-N-(p-toluenesulfonyl)-2-pyrrolidinyl acetate (**10**).* (-)-(*S*)-*N*-(*p*-Toluenesulfonyl)-2-pyrrolidinyl acetonitrile **9a** (1.0 g, 3.79 mmol) in absolute ethanol (40.0 mL) saturated with gaseous HCl was stirred for 24h at room temperature. Solvent removal under reduced pressure, dissolution of the residue in ice-cold water followed by the treatment with $NaHCO_3$ furnished an alkaline solution with a pH value of ~ 9.0. Extraction with CH_2Cl_2, drying (Na_2SO_4), filtration and solvent removal left an oil. Liquid chromatography of this material over silica gel using a mixture of petroleum ether and diethyl ether (1:1) gave 0.71 g (60%) of the chromatographically pure product as solid having R_f value of 0.5 (petroleum ether:diethyl ether, 1:1). $[\alpha]_D^{25}$ -103.2 (*c* 1.04, CH_2Cl_2). IR(KBr) ν_{max}/cm^{-1}: 1735 (ν C=O), 1250 and 1050 (ν C-O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* 7.1 Hz, aliph.–CH_3), 1.51-1.90 (m, 4H, H-3, H-4), 2.44 (s, 3H, H-12), 2.53 (dd, 1H, *J* 10.1 Hz, *J* 16.0 Hz, H-1´), 3.10 (dd, 1H, *J* 3.9 Hz, *J* 16.0 Hz, H-1´), 3.11-3.17 (m, 1H, H-5), 3.41-3.48 (m, 1H, H-5), 3.93-3.99 (m, 1H, H-2), 4.14 (2q overlapping, 2H, *J* 7.1 Hz, -OCH_2-), 7.32 (d, 2H, *J* 8.2 Hz, H-8, H-10), 7.76 (d, 2H, *J* 8.2 Hz, H-7, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5 (aliph.–CH_3), 21.8 (C-12), 24.1 (C-4), 32.0 (C-3), 41.7 (C-5), 49.5 (C-1´), 56.9 (C-2), 60.8 (-OCH_2-), 127.9 (C-8, C-10), 130.1 (C-7, C-11), 134.4 (C-9), 143.9 (C-6), 171.6 (CO). The NMR spectra agreed with the literature data.[6]

*(-)-(S)-N-(p-Toluenesulfonyl)-2-pyrrolidinyl propanone (**5a**).* Tebbe's reagent (2.0 mL, 0.5 mol L^{-1} in toluene) was added to ester **10** (0.31 g, 1.0 mmol) dissolved in THF (3.0 mL) at 0 °C, and the mixture was stirred for 30 min at room temperature. Soon after, ether (15.0 mL) and seven drops of 0.1 mol L^{-1} NaOH was added to it and stirred for an additional 30 min. Solvent drying over Na_2SO_4, filtration over celite and solvent evaporation under vacuum left the crude product. This was then dissolved in $CHCl_3$ (15.0 mL) and six drops of a 2.0 mol L^{-1} HCl added to it followed by stirring for 1.5h at room temperature. Water was added (30.0 mL) to the solution followed by neutralization with

$NaHCO_3$. Extraction with CH_2Cl_2 (3 x 30.0 mL), drying (Na_2SO_4), filtration and solvent removal provided the crude solid (0.28 g). Column chromatography over silica gel using petroleum ether and ethyl acetate (6:4) gave pure **5a** which yielded colorless crystals (0.22 g, 79%) after crystallization from petroleum ether-dichloromethane, mp. 94-96 °C, $[\alpha]_D^{25}$ -116.9 (*c* 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43-1.61 (m, 2H, H-4), 1.72-1.82 (m, 2H, H-3), 2.17 (s, 3H, H-3´), 2.43 (s, 3H, H-12), 2.65 (dd, 1H, *J* 9.7 Hz, *J* 17.8 Hz, H-1´), 3.04-3.12 (m, 1H, H-5), 3.25 (dd, 1H, *J* 3.2 Hz, *J* 17.8 Hz, H-1´), 3.40-3.47 (m, 1H, H-5), 3.89-3.94 (m, 1H, H-2), 7.33 (d, 2H, *J* 7.9 Hz, H-8, H-10), 7.72 (d, 2H, *J* 8.2 Hz, H-7, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.9 (C-12), 24.1 (C-4), 30.9 (C-3´), 32.4 (C-3), 49.5 (C-5), 51.0 (C-1´), 56.2 (C-2), 128.0 (C-8, C-10), 130.1 (C-7, C-11), 134.0 (C-9), 143.9 (C-6), 207.5 (C-2´). The NMR spectra agreed with the literature data.[6]

*N-(p-Toluenesulfonyl)-2-pyrrolidinyl propanol-2 (**1a** and **2a**).* Sodium borohydride (27mg, 0.71 mmol) was added at 0 °C to compound **5a** (0.1 g, 0.36 mmol) dissolved in methanol (8.0 mL) and the contents stirred for 1h at this temperature. After this, a 2.0 mol L^{-1} HCl (0.5 mL) was added to the solution and stirred for additional 10 min. Neutralization of this solution with aqueous $NaHCO_3$, extraction with CH_2Cl_2 and work-up yielded two diastereoisomers which were separated by column chromatography over silica gel using petroleum ether and ethyl acetate (1.5:1.0) to give **1a** (66.0 mg) and **2a** (31.0 mg) (2.1:1.0). The combined yield was 96%. These compounds were recrystallized from hexane and ethyl acetate (5:1). Compound **1a**: mp. 84-85 °C, $[\alpha]_D^{25}$ -98.0 (*c* 1.04, CH_2Cl_2), R_f 0.4 (petroleum ether:EtOAc, 6:4). Anal. Calc. for $C_{14}H_{21}NO_3S$: C, 59.33; H, 7.47. Found: C, 59.26; H, 7.31. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, 3H, *J* 6.2 Hz, H-3´), 1.44-2.03 (m, 6H, H-1´, H-3, H-4), 2.42 (s, 3H, H-12), 3.14-3.22 (m, 1H, H-5), 3.37-3.45 (m, 1H, H-5), 3.85-3.93 (m, 2H, H-2, H-2´), 7.33 (d, 2H, *J* 8.1 Hz, H-8, H-10), 7.73 (d, 2H, *J* 8.2 Hz, H-7, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.9 (C-12), 24.3 (C-4), 24.7 (C-3´), 31.6 (C-3), 46.4 (C-1´), 49.2 (C-5), 58.5 (C-2), 66.6 (C-2´), 128.0 (C-8, C-10), 130.0 (C-7, C-11), 134.8 (C-9), 143.8 (C-6). Compound **2a**: mp. 92.5-94 °C, $[\alpha]_D^{25}$ -20.5 (*c* 0.83, CH_2Cl_2), R_f 0.5 (petroleum ether:EtOAc, 6:4). Anal. Calc. for $C_{14}H_{21}NO_3S$: C, 59.33; H, 7.47. Found: C, 59.69; H, 7.72. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (d, 3H, *J* 6.4 Hz, H-3´), 1.31-1.88 (m, 6H, H-1´, H-3, H-4), 2.43 (s, 3H, H-12), 3.13-3.22 (m, 1H, H-5), 3.34-3.42 (m, 1H, H-5), 3.46 (bs, 1H, OH), 4.02-4.10 (m, 1H, H-2), 4.16-4.20 (m, 1H, H-2´), 7.33 (d, 2H, *J* 8.1 Hz, H-8, H-10), 7.73 (d, 2H, *J* 8.2 Hz, H-7, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.9 (C-12), 23.2 (C-3´), 24.4 (C-4), 31.7 (C-3), 45.8 (C-1´), 48.8 (C-5), 58.1 (C-2), 64.1 (C-2´), 127.9 (C-8, C-10), 130.1 (C-7, C-11), 134.7 (C-9), 144.1 (C-6).

*N-(p-Toluenesulfonyl)-2-pyrrolidinyl propanone (**5a**,**5b**).* To a solution of (-)-(*S*)-*N*-(*p*-toluenesulfonyl)-2-pyrrolidinyl acetonitrile **9a** (1.0 g, 3.79 mmol) in dry THF (26.0 mL) at 0 °C, was added 0.75 mol L^{-1} MeLi (1 equiv., 5.0 mL) very slowly for 1h under stirring. After this an aqueous solution of 1 mol L^{-1} HCl was added at the same temperature and stirred for 3h at rt. The mixture was neutralized with $NaHCO_3$, extracted with CH_2Cl_2 and dried (Na_2SO_4). Purification by column chromatography over silica gel using CH_2Cl_2 gave **5a**,**5b** (0.213 g, 20%). $[\alpha]_D^{25}$ -63.1 (*c* 1.03, CH_2Cl_2), *ee* 54%. The NMR spectra of **5a**,**5b** agreed with the literature data.[6] Racemic **9a**,**9b** was recovered (0.14 g),$[\alpha]_D^{25}$ 0 (*c* 1, $CHCl_3$). Data for **12**: oil, 66.5 mg (6.6%), R_f 0.32 (petroleum ether:EtOAc, 7:3), IR(film) ν_{max}/cm^{-1}: 2220 (ν CN). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (m, 2H, H-2), 2.28 (m, 1H, H-3), 2.38 (m, 1H, H-3), 2.40 (s, 3H, H-13), 2.98 (m, 2H, H-1), 5.34 (m, 2H, NH, H-4), 6.64 (m, 1H, H-5), 7.33 (d, 2H, *J* 7.9Hz, H-9, H-11), 7.76 (d, 2H, *J* 7.2Hz, H-8, H-12). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.9 (C-13), 27.9 (C-2), 30.3 (C-3), 42.7 (C-1), 101.0 (C-4), 117.6 (C-6), 127.4 (C-9, C-11), 130.2 (C-8, C-12), 137.0 (C-10), 144.0 (C-7), 154.7 (C-5).

*(-)-N-(p-Toluenesulfonyl)-2-pyrrolidinyl acetyl diethylmalonate (**14**).* To (-)-(*S*)-*N*-(*p*-toluenesulfonyl)-2-pyrrolidinyl acetic acid **13** (1.0 g, 3.53 mmol) in dichloromethane (10.0 mL) was added two drops of DMF and oxalyl chloride (0.5 mL, ~1.5 equiv.) at 0 °C. The mixture was stirred for 4h at room temperature and concentrated to dryness. Diethylmalonate (2.7 mL, 17.66 mmol) and 60% NaH (0.70 g, 17.66 mmol) in dry THF (10.0 mL) were stirred for 30 min at room temperature. Addition of the generated acid chloride in dry THF (15.0 mL) to this malonate suspension followed by stirring for 4h at 70 °C completed the reaction. Addition of water, extraction with dichloromethane, drying the solution over Na_2SO_4 and solvent removal provided the crude product. Purification by column chromatography over silica gel using 4:1 petroleum ether:EtOAc gave 1.17 g (78%) of an oil caracterized as a 1:1 keto-enolic mixture of **14**: TLC (petroleum ether:EtOAc, 4:1): R_f 0.54; $[\alpha]_D^{25}$ -101.8 (*c* 1.05, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28-1.34 (4t overlapping, 6H, *J* 6.9 Hz, aliph.–CH_3), 1.45-1.83 (m, 4H, H-3, H-4), 2.43 (s, 1.5H, H-12), 2.44 (s, 1.5H, H-12), 2.66 (dd, 0.5H, *J* 10.0 Hz, *J* 13.7 Hz, H-1´), 3.01 (dd, 0.5H, *J* 9.8 Hz, *J* 18.2 Hz, H-1´), 3.03-3.10 (m, 1H, H-5), 3.18 (dd, 0.5H, *J* 4.5 Hz, *J* 13.7 Hz, H-1´), 3.39 (dd, 0.5H, *J* 3.1 Hz, *J*

18.2 Hz, H-1´), 3.41-3.49 (m, 1H, H-5), 3.94-4.01 (m, 1H, H-2), 4.29 (q, 4H, *J* 7.1 Hz, -OCH_2-), 4.50 (s, 0.5H, H-3´), 7.33 (d, 2H, *J* 7.9 Hz, H-8, H-10), 7.76 (d, 2H, *J* 8.2 Hz, H-7, H-11), 13.25 (s, 0.5H, OH). Anal. Calc. for $C_{20}H_{27}NO_5S.¼H_2O$: C, 55.86; H, 6.44. Found: C, 55.91; H, 6.41.

*N-(p-Toluenesulfonyl)-2-pyrrolidinyl propanone (**5a**,**5b**).* (-)-*N*-(*p*-toluenesulfonyl)-2-pyrrolidinyl acetyl diethylmalonate **14** (1.10 g, 2.59 mmol) in 4 mol L H_2SO_4 (55.0 mL) was stirred for 12h at 100 °C. The mixture was neutralized with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water (3 x 100 mL), dried (Na_2SO_4) and concentrated to yield the crude product. Purification by column chromatography over silica gel using petroleum ether:EtOAc (7:3) gave **5a**,**5b** which after crystallization from petroleum ether:CH_2Cl_2 yielded colorless crystals (575 mg, 79%): $[\alpha]_D^{25}$ 0 (*c* 1, CH_2Cl_2). The NMR spectra agreed with the literature data.[6]

*N-(p-Toluenesulfonyl)-2-pyrrolidinyl propanol-2 (**1a**, **1b** and **2a**,**2b**).* Starting from ketone **5a**, **5b** and following the procedure described above, we obtained **1a**,**1b** and **2a**,**2b** (2.1:1). Yield 96%. Compound **1a**,**1b**: mp. 76-78°C, $[\alpha]_D^{25}$ 0 (*c* 1.05, CH_2Cl_2). Compound **2a**,**2b**: mp. 87-89°C, $[\alpha]_D^{25}$ 0 (*c* 1, CH_2Cl_2). The ^{1}H NMR and ^{13}C NMR spectra agreed with the compounds **1a** and **2a** above.

*(-)-(S)-N-Methoxycarbonyl-L-proline (**16**).* L-proline **15** (1.0 g, 8.7 mmol) in THF (15.0 mL) was put in a round-bottom flask at 0 °C and $NaHCO_3$ (3.65 g) in water (4.0 mL) was added to it. Afterwards, methyl chloroformate (3.4 mL, 43.5 mmol) was poured into the flask and the contents stirred for 16h at room temperature. Acidification of the solution with dilute HCl, extraction with CH_2Cl_2 and usual work-up gave the crude product which could be purified by column chromatography over silica using CH_2Cl_2 and ethyl acetate (1:1) as eluent. The work-up yielded **16** (1.2 g, 80%) as light yellow oil. $[\alpha]_D^{25}$ -100.4 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (m, 2H, H-4), 2.31 (m, 2H, H-3), 3.60 (m, 2H, H-5), 3.69, 3.74 (2s, 3H, H-7), 4.42 (m, 1H, H-2), 10.29 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.7, 24.6 (C-4), 29.9, 31.2 (C-3), 46.8, 47.2 (C-5), 53.2, 53.3 (C-7), 59.0, 59.5 (C-2), 155.7, 156.6 (C-6), 176.9, 177.9 (C-1´). Certain proton and carbon atoms of this compound produced two signals because of the existence of two rotamers at room temperature.

*(S)-N-Methoxycarbonyl-2-pyrrolidinyl acetic acid (**17**).* To *N*-methoxycarbonyl-L-proline **16** (0.77 g, 4.45 mmol) in dry CH_2Cl_2 (16.0 mL) was added $(COCl)_2$ (0.6 mL) and one drop of DMF at 0 °C. The mixture was stirred for 4h at room temperature. Solvent evaporation left a yellow oil which was dissolved in dry ether and then diazomethane was added at 0 °C. The contents were stirred at 0 °C for 5h followed by solvent removal which furnished the crude product. Dissolution of this product in dioxane (10.0 mL), followed by the addition of water (10.0 mL) and Ag_2O (0.10 g) and stirring at 90 °C for 6h completed the reaction. Filtration over celite, solvent removal and purification by column chromatography over silica using CH_2Cl_2 and ethyl acetate (1.5:1) afforded 0.38 g (46%) of **17** as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94 (m, 3H, 2 H-4, 1 H-3), 2.14 (m, 1H, 1 H-3), 2.40 (dd, 1H, H-1´), 3.03 (dd, 1H, H-1´), 3.40 (m, 2H, H-5), 3.69 (s, 3H, H-7), 4.19 (m, 1H, H-2), 8.76 (bs, 1H, OH).

*Methyl (-)-(S)-N-methoxycarbonyl-2-pyrrolidinyl acetate (**18**).* To (*S*)-*N*-methoxycarbonyl-2-pyrrolidinyl acetic acid **17** (0.35 g, 1.87 mmol) in dry ether at 0 °C, was added diazomethane in excess and the mixture was stirred for 1.5h at this temperature. After, solvent removal, the crude product was purified by column chromatography over silica gel using petroleum ether and ethyl acetate (1.5:1) as eluent. The work-up yielded 0.38 g (100%) of **18** as light yellow oil. $[\alpha]_D^{25}$ -50.0 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91 (m, 3H, 2 H-4, 1 H-3), 2.11 (m, 1H, 1 H-3), 2.37 (dd, 1H, H-1´), 2.98 (dd, 1H, H-1´), 3.43 (m, 2H, H-5), 3.68, 3.69 (2s, 3H, H-3´), 3.69 (s, 3H, H-7), 4.19 (m, 1H, H-2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.1, 23.9 (C-4), 30.9, 31.7 (C-3), 38.5, 39.4 (C-1´), 46.7, 47.1 (C-5), 51.9 (C-3´), 52.5, 52.7 (C-7), 54.3, 54.9 (C-2), 155.7 (C-6), 172.2 (C-2´).

*(-)-(S)-N-Methoxycarbonyl-2-pyrrolidinyl propanone (**6**).* Tebbe's reagent (2.88 mL, 0.5 mol L^{-1} in toluene) was added to ester **18** (0.29 g, 1.44 mmol) dissolved in tetrahydrofuran (3.0 mL) at 0 °C, and the mixture was stirred for 30 min at room temperature. Soon after, ether (15.0 mL) and two drops of NaOH (~ 10% aqueous solution) was added to it and stirred for an additional 20 min. After this, 12 drops of an aqueous hydrochloric acid solution (1.0 mol L^{-1}) was added and the contents stirred for 1.5h at room temperature. Water (30.0 mL) addition to the flask, neutralization with $NaHCO_3$, extration with dichloromethane (3 x 30.0 mL), drying the solvent over Na_2SO_4, filtration and solvent evaporation under reduced pressure gave an oil. Purification by liquid chromatography over silica gel using petroleum ether and ethyl acetate (1.5:1.0) provided pure **6** (0.22 g, 83%) as light yellow oil. $[\alpha]_D^{25}$ -66.1 (*c* 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ

1.28-1.34 (4t overlapping, 6H, *J* 6.9 Hz, aliph.–CH_3), 1.45-1.83 (m, 4H, H-3, H-4), 2.43 (s, 1.5H, H-12), 2.44 (s, 1.5H, H-12), 2.66 (dd, 0.5H, *J* 10.0 Hz, *J* 13.7 Hz, H-1´), 3.01 (dd, 0.5H, *J* 9.8 Hz, *J* 18.2 Hz, H-1´), 3.03-3.10 (m, 1H, H-5), 3.18 (dd, 0.5H, *J* 4.5 Hz, *J* 13.7 Hz, H-1´), 3.39 (dd, 0.5H, *J* 3.1 Hz, *J* 18.2 Hz, H-1´), 3.41-3.49 (m, 1H, H-5), 3.94-4.01 (m, 1H, H-2), 4.29 (q, 4H, *J* 7.1 Hz, -OCH_2-), 4.50 (s, 0.5H, H-3´), 7.33 (d, 2H, *J* 7.9 Hz, H-8, H-10), 7.76 (d, 2H, *J* 8.2 Hz, H-7, H-11), 13.25 (s, 0.5H, OH). Some carbons gave two peaks because the compound exists as rotamers at room temperature.

*N-Methoxycarbonyl-2-pyrrolidinyl propanol-2 (**3** and **4**).* To (-)-(*S*)-*N*-methoxycarbonyl-2-pyrrolidinyl propanone **6** (0.21 g, 1.14 mmol) in methanol (10.0 mL) at 0 °C was added $NaBH_4$ (86 mg, 2.27 mmol) under stirring and the agitation continued for 1h more maintaining this temperature. After this, an aqueous solution of HCl (2.0 mL, 1.0 mol L^{-1}) was added to it and stirred for an additional 10 min. Neutralization of this solution with aqueous $NaHCO_3$, extraction with dichloromethane and work-up yielded two diastereoisomers which were separated by column chromatography over silica gel using petroleum ether and ethyl acetate (1:1), both as light yellow oils. The yields of **3** (125 mg) and **4** (66 mg) together turned out to be 90%. Compound **3**: R_f 0.36 (petroleum ether:EtOAc, 1:1), $[\alpha]_D^{25}$ -73.5 (*c* 1.13, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (d, 3H, *J* 6.0Hz, H-3´), 1.35-1.96 (m, 6H, 2 H-1´, 2 H-3, 2 H-4), 3.31 (m, 2H, H-5), 3.62 (s, 3H, H-7), 3.79 (m, 1H, H-2), 3.98 (m, 1H, H-2´). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.1 (C-4), 24.4 (C-3´), 31.8 (C-3), 44.9 (C-1´), 46.4 (C-5), 52.6 (C-7), 56.1 (C-2), 66.3 (C-2´), 156.4 (C-6). Compound **4**: R_f 0.44 (petroleum ether:EtOAc, 1:1), $[\alpha]_D^{25}$ -3.0 (*c* 0.72, CH_2Cl_2). Lit:[3] $[\alpha]_D^{25}$ -2.0 (*c* 0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, 3H, *J* 6.4Hz, H-3´), 1.36-1.62 (m, 3H, 1 H-3, 2 H-4), 1.90-2.04 (m, 3H, 2 H-1´, 1 H-3), 3.38 (m, 2H, H-5), 3.65-3.83 (m, 1H, H-2), 3.71 (s, 3H, H-7), 4.22 (m, 1H, H-2´), 4.77 (bs, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.9 (C-3´), 23.9 (C-4), 31.5 (C-3), 45.8 (C-1´), 46.6 (C-5), 53.0 (C-2), 55.0 (C-7), 64.0 (C-2´), 157.9 (C-6).

Supplementary Information

Crystallographic data (excluding structure factors) for racemic **2a,2b** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 244859. Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK ; fax: +44 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).

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