Asymmetric Synthesis of 2-Substituted (4*S*)-4-Aminopyrrolidines. S_N2 Displacement at the 4-Position of the Pyrrolidine Moiety[1]

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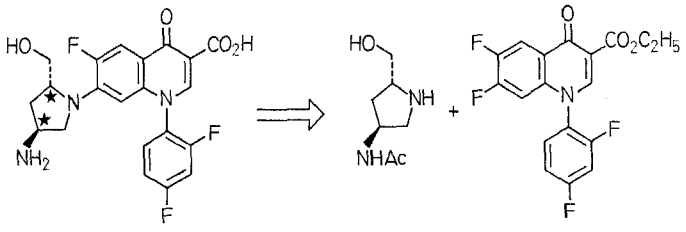
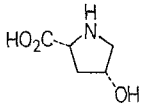
The *trans*-disubstituted-*N*-benzyl pyrrolidine **10** is prepared in enantiomerically homogeneous form from *cis*-4-hydroxy-D-proline (**4**) in an efficient sequence. The key step involves an S_N2 displacement of the methanesulfonate of alcohol **5** with azide ion and occurs without participitation of the basic ring nitrogen. The stereochemical outcome, which is contrary to that reported for the related systems **15** and **16**, suggests that a mechanism involving the proposed intermediate **19a** is improbable. The *cis*-derivative **14** is prepared by an identical sequence of reactions beginning with *trans*-4-hydroxy-L-proline. Compound **10** is the precursor to the potent DNA gyrase inhibitor **1** and several related analogs.

The quinolonecarboxylic acids constitute a class of extremely potent and orally active broad-spectrum antibacterial agents which have been shown to inhibit DNA gyrase.[2,3] As part of our effort,[4,5] to develop quinolone antibacterials with improved therapeutic efficacy and physiochemical properties as well as to aid in better understanding the mechanism of action of these agents, we required a synthesis of the (4′*S*)-7-(4′-aminopyrrolidinyl)quinolone **1** with the indicated relative and absolute stereochemistry.



1 **2** **3**



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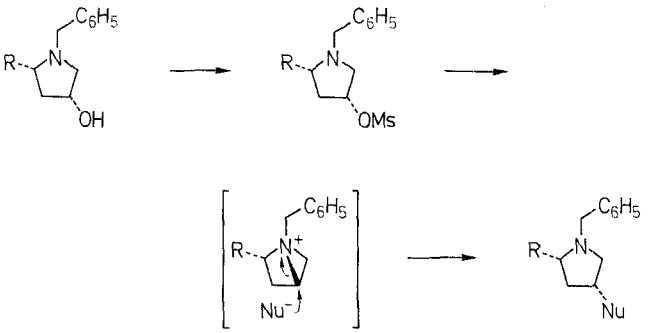
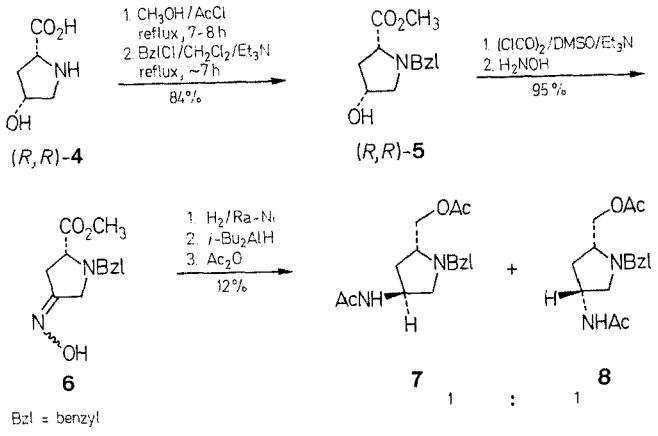
We chose *cis*-4-hydroxy-D-proline (**4**) as a chiron for **2**. Thus, the essential chemical concerns involve conversion of the hydroxy group to nitrogen with inversion of configuration and reduction of the carboxy group without epimerization. The absolute stereochemistry at the 2-position of the pyrrolidine ring has been shown to be critical for the maintenance of potent biological activity.[1,6] The strategy of inverting the stereochemistry at the 4-position of **4** by a sequence involving activation and subsequent S_N2 displacement is complicated by the possibility of participation by the nucleophilic ring nitrogen, resulting in a net retention of configuration.



Ms = CH_3SO_2

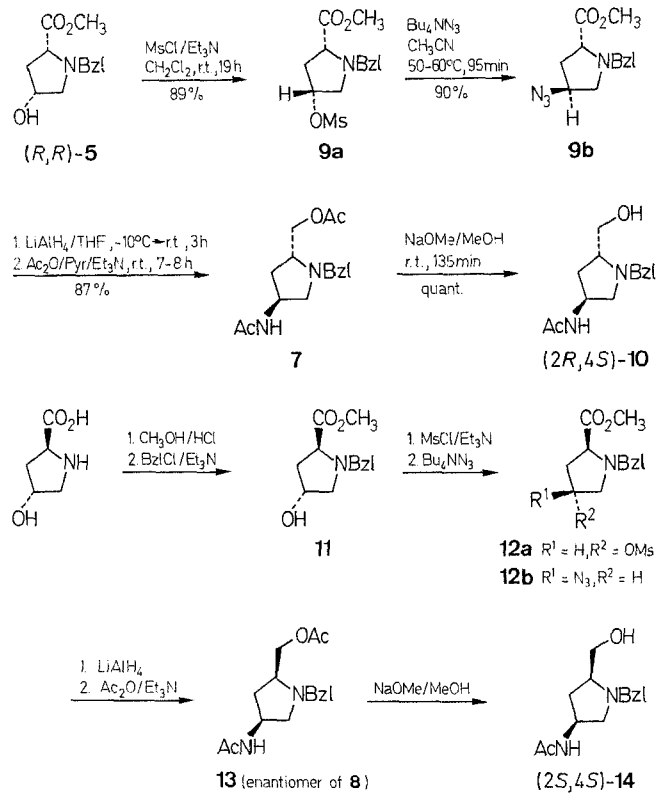
Such neighboring-group participation has been observed in 2-halomethylpyrrolidines,[7] and it has been proposed that such participation may be involved in displacements on the tosyloxypyrrolidines **15** and **16**.[8] However, we felt that our approach would not only provide a facile route to the target pyrrolidine **2** but also clarify the mechanistic question of whether such a system would undergo displacement in a manner involving a double inversion process or a direct S_N2 displacement.

Our initial approach to the synthesis of the 1-benzylpyrrolidine **7** is summarized in Scheme **A**. Conversion of *cis*-4-hydroxy-D-proline (**4**) to its methyl ester and *N*-benzylation provides **5** in 84% yield. Oxidation of the secondary hydroxy group with oxalyl chloride/dimethyl sulfoxide[9] affords the corresponding ketone which is transformed smoothly to the oxime **6** in 95% yield for the two-step sequence. Sequential reduction of the oxime and ester groups followed by acetylation of the resulting amino alcohol affords an ~ 1:1 mixture of **7** and **8** which is separable by column chromatography (12% overall yield). The isomeric oximes **6** are also separable; however, the reduction-acetylation sequence applied to either of the purified oxime isomers provides a similar 1:1 mixture of **7** and **8**. The poor yield



Scheme A

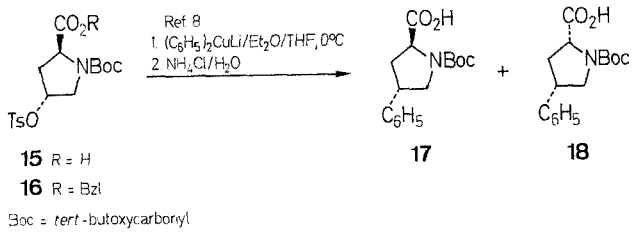
obtained in the reduction of **6** coupled with the inefficiency of performing an isomer separation led us to pursue the alternative route shown in Scheme **B**.



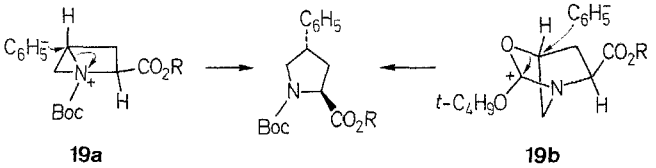
Scheme B

In this sequence, nitrogen is introduced at the 4-position with the desired absolute stereochemistry by sequential methanesulfonate formation (89% yield) and S_N2 displacement with azide ion (90% yield) to give **9b**. The ^{13}C-NMR spectrum of the product obtained indicates no contamination by the corresponding *cis*-stereoisomer. Reduction of the ester and azide groups is accomplished with lithium aluminum hydride,[21] and acetylation of the derived amino alcohol provides **7** in 87% yield. Cleavage of the primary *O*-acetyl group affords cleanly the desired displacement precursor (**10**; quantitative yield). The *cis*-isomer **14** is obtained from *trans*-4-hydroxy-L-proline by the identical sequence of reactions used to convert **5** to **10**. It should be noted that the ^{1}H-NMR spectra of **7** and **13** obtained in this manner are identical to the spectra of **7** and **8** (enantiomer of **13**) obtained by the nonselective route (Scheme **A**). The details of the stereochemical assignments of **10** and **14** are described at a later point.

Recently, workers at Squibb have described an interesting reaction in which displacement on the *trans*-hydroxyproline nucleus occurs with retention of configuration at the center of displacement.[8] Treatment of **15** with two equivalents of lithium diphenylcuprate affords the substitution products **17** and **18** in varying ratios, depending on the specific reaction conditions.



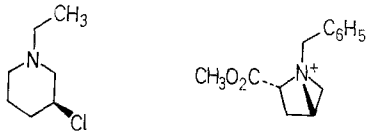
Treatment of the benzyl ester **16** under identical conditions followed by hydrogenolysis also furnishes a mixture of **17** and **18**. Similar results are obtained with a related *cis*-4-tosyloxy-L-proline derivative. Formation of all of the products involves displacement of the tosyloxy group with retention of configuration.[10] As is suggested in their account, these observations are indeed mechanistically intriguing. It is postulated that the reactions may take place by two successive inversion processes involving: (1) formation of an activated bicyclic intermediate (**19a** or **19b**, or their equivalent) with inversion, (2) ring opening by the reagent in a second inversion process.



Our results suggest that an intermediate such as **19a** is not involved, as the *N*-benzylamines employed in Scheme **B** are significantly more nucleophilic than the corresponding *N*-Boc-derivatives; however, no product derived from a double inversion process is observed. Although **19b** may provide a more likely rationale for the products observed in the cuprate reaction, one would expect such a species to be highly prone to loss of the Boc protective group, and this is not observed.[11] Furthermore, the double-bond character associated with the N-CO bond of the carbamate group would seem to provide a strong geometrical barrier to the generation of such an intermediate. Perhaps, the apparent double inversion is a result not only related to the stereoelectronic properties of the pyrrolidine reagent, but also to the complicated nature of the cuprate reagent.

That nitrogen participation is not observed in the azide displacements on the methanesulfonates of **5** and **11** is interesting, as such participation has been reported in a related piperidinyl system; it has been established that 3-chloro-1-ethylpiperidine undergoes nucleophilic displacement reactions by a two-step, neighboring-group participation mechanism.[12] Presumably, the lack of analogous participation in the pyrrolidinyl system is related to the large strain energy associated with the required aziridinium ion **20**; the strain energy of the bicyclo[2.1.0]-

pentane system has been calculated to be 56.1 kcal mol^{-1}.[13] The corresponding value for the bicyclo[3.1.0]hexane system (required for participation in the 3-chloropiperidine analog) is significantly lower, 33.5 kcal mol^{-1}.[13]



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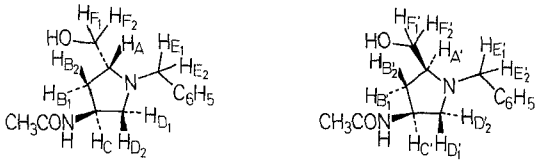
The ^{1}H-NMR resonances of **10** and **14** were assigned by a series of homonuclear decoupling and NOE experiments.[14] From an analysis of the NOE data, the stereochemistry of **10** and **14** were determined.



10 14

Compound **10**: NOEs were observed between the N-H and H_{B_2}, H_{D_2} and H_A in compound **10**. Furthermore, NOEs were detected between H_A and H_{B_2} and between H_C and H_{B_1}, H_{D_1}. These data indicate that H_A, H_{B_2}, H_{D_2} and the *N*-acetyl group are in a *cis*-relationship and that H_{B_1}, H_C and H_{D_1} are on the opposite side of the ring, as depicted in structure **10**.

Compound **14**: In compound **14**, NOEs were observed between NH/H_{D_1}', NH/H_{B_2}', NH/H_{F_1}', H_C'/H_{B_1}', H_C'/H_{D_2}' and H_A'/H_{B_1}'. As shown in structure **14**, these data indicate that the N-acetyl group in compound **14** is *cis* to H_{B_2}', H_{D_1}' and the hydroxymethyl substituent; whereas, H_C' is located on the same face of the ring as H_{B_1}', H_{D_2}' and H_A'.

Compound **10**, the key precursor used in the preparation of quinolone **1** and several related analogs, is prepared efficiently from the hydroxyproline derivative **5**; the *cis*-isomer **14** is similarly available from *trans*-4-hydroxy-L-proline. Perhaps most importantly, we have shown that displacements of the methanesulfonyloxy groups in **9a** and **12a** (derived from **5** and **11**, respectively) with azide occur with inversion of configuration by an S_N2 process, even in the presence of a basic ring nitrogen. Combined with the spectroscopic data obtained for the related *cis*- and *trans*-derivatives **10** and **14**, these results should also provide a basis for predictability and subsequent verification of stereocontrol in compounds containing a similar nucleus.

The hydroxyprolines are particularly attractive asymmetric educts because of their ready availability and their varied and differentiated functionality. Several of their derivatives have been shown to be useful as tools in asymmetric synthesis.[15] Also, they provide a convenient route to substituted aminopyrrolidines which are important in several areas of medicinal chemistry, such as in the development of antimicrobial,[2,4,5,16] schistosomicidal,[17] and antisickling[10] therapeutic agents, as well as in the synthesis of nucleotide analogs.[18] Thus, information in this area should be of wide interest and utility.

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points are uncorrected. Gravity column chromatography was done with Merck silica gel 60 (70–230 mesh ASTM) and flash chromatography[19] was done with Matrex silica Si (Particle size: 35–70 μ). TLC was performed with Analtech silica gel GF TLC plates (250 µm), and compound visualization was effected with a 2% solution of H_2SO_4 *in EtOH*, *a 5%* solution of molybdophosphoric acid in EtOH, or a 0.25% solution of ninhydrin in BuOH. Microanalyses were performed by the Microanalytical Laboratory, operated by the Analytical Department, Abbott Laboratories, North Chicago, IL.

Mass spectra were obtained with a Hewlett Packard 5985A mass spectrometer. IR spectra were determined with a Perkin Elmer 683 infrared grating spectrometer or a Nicolet 60SX FT-IR. ^{1}H-NMR spectra were determined on a General Electric GN-300 spectrometer operating at 300.1 MHz. ^{13}C-NMR spectra were measured at 75.5 MHz with a GN-300 spectrometer.

General Procedure for NOE Studies. NMR spectra were obtained on a General Electric GN-300 spectrometer operating at 300.1 MHz. Samples were prepared by dissolving 5–10 mg of compound in 0.5 mL of $CDCl_3$. NOE difference experiments were performed by subtracting the free induction decays (FIDs) obtained by irradiating signals of interest from those FIDs collected when a presaturation pulse was applied where no resonance appeared in the spectrum (control). Exponential multiplication, using a line-broadening factor of 2 Hz, followed by Fourier transformation of the difference FIDs yielded the NOE difference spectra. In the NOE experiments, a 0.4 sec presaturation time and a 5.5 sec delay between scans were employed. Since a time dependence of the NOEs as a function of presaturation time was not obtained, no effort was made to quantitate the NOE data in terms of accurate interproton distances. Rather, the observation of an NOE was used to identify qualitatively those protons in close proximity, which was sufficient for the structural studies described here.

(2*R*,4*R*)-1-Benzyl-4-hydroxy-2-methoxycarbonylpyrrolidine (5):

(2R,4R)-4-Hydroxy-2-methoxycarbonylpyrrolidine Hydrochloride: Under N_2 in a 500 mL round-bottom flask equipped with a stirbar and a reflux condenser is placed MeOH (70 mL). To the system is added AcCl (7.6 mL, 8.4 g, 107 mmol) followed by the amino acid **4** (10 g, 76 mmol). The resulting solution is heated at reflux for 7–8 h and cooled to room temperature. The solution is diluted with Et_2O (~ 500 mL), and the resulting white solid is collected by suction filtration; yield: 13.8 g (~ 100%).

(2R,4R)-1-Benzyl-4-hydroxy-2-methoxycarbonylpyrrolidine **(5)**: Under N_2 in a 250 mL round-bottom flask equipped with a magnetic stirbar and a reflux condenser are placed the hydrochloride (10.8 g, 59.6 mmol) prepared above and CH_2Cl_2 (50 mL). To this stirring solution are added Et_3N (16.6 mL, 12.0 g, 119 mmol) and benzyl chloride (13.7 mL, 15.1 g, 119 mmol). The mixture is heated at reflux for 6 h, 50 min. The resulting suspension is partitioned between $CHCl_3$ chloroform and 1 *M* aqueous NaOH, the layers are separated, and the organic phase is washed with brine, dried (Na_2SO_4) and concentrated in a rotary evaporator. The resulting orange liquid (20 g) is purified by flash column chromatography (500 g of silica gel) using EtOAc as the eluent; yield: 11.7 g (84%) of **5** as a very pale yellow oil.

$C_{13}H_{17}NO_3$	calc.	C 66.36	H 7.28	N 5.95
(235.3)	found	66.55	7.31	5.97

^{1}H-NMR ($CDCl_3$): δ = 1.95 (ddd, 1 H, J = 1.4, 4.0, 14.2 Hz); 2.39 (ddd, 1 H, J = 5.8, 10.0, 14.2 Hz); 2.64 (dd, 1 H, J = 1.4, 4.0 Hz); 3.02 (ddd, 1 H, J = 1.4, 1.4, 9.9 Hz); 3.35 (dd, 1 H, J = 4.0, 10.0 Hz); 3.64 (s, 3 H), 3.72 (d, 1 H, J = 13.0 Hz); 3.88 (d, 1 H, J = 13.0 Hz); 4.26 (dddd, 1 H, J = 1.4, 1.4, 4.0, 5.8 Hz); 7.30 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 39.1, 51.9, 58.0, 61.6, 63.2, 70.7, 127, 128. 129, 138, 175.

(2*R*,4*R*)-1-Benzyl-4-methylsulfonyloxy-2-methoxycarbonylpyrrolidine (9a):

Under N_2 in a 250 mL round-bottom flask equipped with a rubber septum and a magnetic stirbar are placed alcohol **5** (5.05 g, 21.5 mmol) and CH_2Cl_2 (6 mL). To this stirring solution, at 0 °C, is added Et_3N (13.2 mL, 9.55 g, 94.6 mmol) followed by methylsulfonyl chloride (3.73 mL, 5.41 g, 47.3 mmol). The mixture is stirred for 19 h (during which time the ice bath expires), then diluted with CH_2Cl_2 (150 mL), and washed with saturated $NaHCO_3$, water, and brine. The CH_2Cl_2 solution is dried (Na_2SO_4) and concentrated in a rotary evaporator to afford 7.7 g of orange oil. This crude material is subjected to flash

column chromatography (250 g of silica gel), gradually increasing the polarity of the eluent from 3:1 Et_2O/hexanes to 5:1 Et_2O/hexanes; yield: 6.02 g (89%) of **9a** as a pale yellow viscous oil.

$C_{14}H_{19}NO_5S$	calc.	C 53.66	H 6.11	N 4.47
(313.4)	found	53.30	6.14	4.43

MS: *m/z* = 313 (M^+), 254, 218, 158.

^{1}H-NMR ($CDCl_3$): δ = 2.34 (dddd, 1 H, *J* = 1.1, 2.6, 6.6, 15 Hz); 2.62 (ddd, 1 H, *J* = 1.5, 2.6, 5.5 Hz); 2.73 (dd, 1 H, *J* = 5.5, 11 Hz); 2.98 (s, 3 H); 3.26 (br d, 1 H, *J* = 11 Hz); 3.31 (dd, 1 H, *J* = 6.8, 8.8 Hz); 3.58 (d, 1 H, *J* = 13 Hz); 3.72 (s, 3 H); 4.03 (d, 1 H, *J* = 13 Hz); 5.16 (m, 1 H); 7.25 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 36.6, 38.7, 52.0, 57.3, 58.2, 63.2, 77.7, 127, 128, 129, 137, 173.

(2*R*,4*S*)-4-Azido-1-benzyl-2-methoxycarbonylpyrrolidine (9b):
Under N_2 in a round-bottom flask equipped with a magnetic stirbar and a rubber septum are placed the methanesulfonic ester **9a** (5.12 g, 16.4 mmol) and acetonitrile (5 mL). To this stirring solution is added tetrabutylammonium azide (11.6 g, 40.9 mmol).[20] This stirring solution is heated at 50–60°C for 95 min, diluted with EtOAc and washed with H_2O and brine. The combined aqueous washings are extracted with EtOAc, the combined organic fractions are dried (Na_2SO_4), and the solvent is removed with a rotary evaporator to afford 9.54 g of orange oil. The crude material is purified by flash column chromatography (100 g of silica gel) using 2:3 Et_2O/hexanes as the eluent to give azide **9b** as a pale yellow liquid; yield: 3.83 g (90%).

$C_{13}H_{16}N_4O_2$	calc.	C 60.01	H 6.20	N 21.53
(260.2)	found	60.13	6.30	21.21

MS: *m/z* = 260 (M^+), 201, 91.

IR ($CHCl_3$): ν = 2105, 1770 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.16 (ddd, 1 H, *J* = 4.8, 8.5, 13 Hz); 2.33 (ddd, 1 H, *J* = 6.3, 7.4, 14 Hz); 2.53 (dd, 1 H, *J* = 5.1, 10 Hz); 3.30 (dd, 1 H, *J* = 6.4, 10 Hz); 3.56 (dd, 1 H, *J* = 6.7, 8.2 Hz); 3.64 (d, 1 H, *J* = 13 Hz); 3.67 (s, 3 H); 3.90 (d, 1 H, *J* = 13 Hz); 4.10 (m, 1 H); 7.25 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 35.8, 51.8, 57.67, 57.72, 58.9, 63.5, 127, 128, 129, 138, 173

(2*R*,4*S*)-2-Acetoxymethyl-4-acetylamino-1-benzylpyrrolidine (7):
Under N_2 in a round-bottom flask equipped with a magnetic stirbar and a rubber septum are placed compound **9** (3.50 g, 13.5 mmol) and THF (14 mL). The system is immersed in an ice/acetone bath. To the stirring solution is added $LiAlH_4$ (1.99 g, 52.3 mmol). The resulting mixture is stirred for ~ 30 min, at which time a vigorous exothermic reaction occurs (*Caution*),[21] and the mixture solidifies. To the system is added THF (20–25 mL) and the mixture is stirred at room temperature for 3 h. The system is cooled in an ice/acetone bath, and a mixture of 1 M aqueous NaOH (10 mL) and THF (100 mL) is added cautiously. The cold bath is removed, the mixture is stirred at room temperature, Na_2SO_4 (~ 5 g) is added to the system, and the mixture is stirred at room temperature. The white granular precipitate is removed by suction through a pad of celite, and the filtrate is concentrated in a rotary evaporator to afford 3.05 g of very pale yellow oil. In a round-bottom flask are placed this oil and pyridine (11 mL). To the system are added Et_3N (3.76 mL, 2.72 g, 27 mmol) and Ac_2O (6.2 mL, 6.77 g, 66.4 mmol). This solution is stirred at room temperature under N_2 for 7–8 h, diluted with EtOAc (200 mL), and washed with H_2O and brine. The combined aqueous washings are extracted with CH_2Cl_2 (3 × 50 mL), the combined organic fractions are dried (Na_2SO_4) and the solvent is removed using a rotary evaporator. The crude product is purified by flash column chromatography (35 g of silica gel) using Et_2O followed by EtOAc as the eluent to give **7** as an orange oil which partially crystallizes upon standing; yield: 3.41 g (87%). This material is used in subsequent transformations without further purification. An analytical sample may be prepared by a second column chromatography; mp 72–74°C.

$C_{16}H_{22}N_2O_3$	calc.	C 66.18	H 7.64	N 9.65
(290.4)	found	66.05	7.67	9.64

MS: *m/z* = 290 (M^+), 231, 217, 91.

^{1}H-NMR ($CDCl_3$): δ = 1.75 (ddd, 1 H, *J* = 7.4, 8.8, 13 Hz); 1.91 (s, 3 H); 2.07 (s, 3 H); 2.12 (m, 2 H); 3.02 (m, 1 H); 3.24 (dd, 1 H, *J* = 6.6, 9.2 Hz); 3.48 (d, 1 H, *J* = 13 Hz); 4.09 (m, 3 H); 4.34 (m, 1 H); 5.34 (br, 1 H); 7.28 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 20.9, 23.2, 35.7, 47.4, 58.2, 59.2, 60.1, 66.0, 127, 128, 129, 138, 170, 171.

(2*R*,4*S*)-4-Acetylamino-1-benzyl-2-hydroxymethylpyrrolidine (10):
Under N_2 in a 1 L round-bottom flask equipped with a magnetic stirbar and a rubber septum are placed compound **7** (2.94 g, 10.1 mmol) and MeOH (18 mL). To this stirring solution is added MeONa (718 mg, 13.3 mmol). The resulting solution is stirred at room temperature for 135 min, diluted with $CHCl_3$ (~ 150 mL), and washed with H_2O and brine. The combined aqueous washings are extracted with $CHCl_3$, the combined organic fractions are dried (Na_2SO_4), and the solvent is removed with a rotary evaporator to give the alcohol **10** as a yellow oil; yield: 2.54 g (~ 100%). The product becomes a light tan solid upon concentration from Et_2O/hexanes; mp 111–113°C. This material is used in subsequent transformations without further purification. An analytical sample may be obtained by recrystallization from Et_2O; $[\alpha]_D^{25}$ + 36° (*c* = 0.38, $CHCl_3$).

$C_{14}H_{20}N_2O_2$	calc.	C 67.71	H 8.12	N 11.28
(248.3)	found	67.31	8.14	11.25

MS: *m/e* = 249 $(M + H)^+$, 230, 217, 158, 91.

^{1}H-NMR ($CDCl_3$): δ = 1.75 (ddd, H_{B_2}, *J* = 7.3, 9.2, 13 Hz); 1.91 (s, CH_3); 2.18 (dd, H_{D_2}, *J* = 8.8, 9.2 Hz); 2.26 (ddd, H_{B_1}, *J* = 6.3, 8.6, 13 Hz); 2.77 (br s, OH); 2.95 (dddd, H_A, *J* = 2.1, 3.5, 6.3, 9.2 Hz); 3.36 (dd, H_{D_1}, *J* = 6.4, 9.2 Hz); 3.43 (d, H_{E_2}, *J* = 13 Hz); 3.44 (dd, H_{F_2}, *J* = 2.1, 11 Hz); 3.67 (dd, H_{F_1}, *J* = 3.5, 13 Hz); 3.98 (d, H_{E_1}, *J* = 13 Hz); 4.31 (ddddd, H_C, *J* = 6.4, 6.5, 7.3, 8.6, 8.8 Hz); 5.72 (br d, NH, *J* = 6.5 Hz); 7.27 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 23.2, 34.8, 47.8, 58.0, 59.7, 61.7, 62.9, 127, 128, 129, 138, 170.

Analogous procedures were used to convert *trans*-4-hydroxy-L-proline to **14**. Physical and spectral data for intermediates are given below.

(2*S*,4*R*)-1-Benzyl-4-hydroxy-2-methoxycarbonylpyrrolidine (11):

$C_{13}H_{17}NO_3$	calc.	C 66.36	H 7.28	N 5.95
(235.3)	found	66.06	7.20	5.70

MS *m/z* = 235 (M^+), 176, 91.

^{1}H-NMR ($CDCl_3$): δ = 2.08 (ddd, 1 H, *J* = 3.0, 8.0, 13 Hz); 2.26 (ddd, 1 H, *J* = 7.3, 7.7, 13 Hz); 2.48 (dd, 1 H, *J* = 3.7, 10 Hz); 3.33 (dd, 1 H, *J* = 5.5, 10 Hz); 3.65 (dd, 1 H, *J* = 7.7, 8.0 Hz); 3.66 (s, 3 H); 3.69 (d, 1 H, *J* = 13 Hz); 3.90 (d, 1 H, *J* = 13 Hz); 4.46 (dddd, 1 H, *J* = 3.0, 3.7, 5.5, 7.3 Hz); 7.30 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 39.5, 51.7, 58.1, 61.1, 63.6, 70.1, 127, 128, 129, 138, 174.

(2*S*,4*R*)-1-Benzyl-4-methylsulfonyloxy-2-methoxycarbonylpyrrolidine (12a):

$C_{14}H_{19}NO_5S$	calc.	C 53.66	H 6.11	N 4.47
(313.4)	found	53.39	6.11	4.36

MS: *m/z* = 313 (M^+), 254, 158, 91.

^{1}H-NMR ($CDCl_3$): δ = 2.42 (m, 2 H); 2.77 (dd, 1 H, *J* = 6.4, 11 Hz); 2.98 (s, 3 H); 3.42 (dd, 1 H, *J* = 6.1, 11 Hz); 3.63 (dd, 1 H, *J* = 7.4, 7.4 Hz); 3.67 (d, 1 H, *J* = 13 Hz); 3.68 (s, 3 H); 3.91 (d, 1 H, *J* = 13 Hz); 5.22 (m, 1 H); 7.25 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 36.8, 38.3, 51.9, 57.6, 58.0, 63.3, 78.9, 127, 128, 129, 137, 173.

(2*S*,4*S*)-4-Azido-1-benzyl-2-methoxycarbonylpyrrolidine (12b):

$C_{13}H_{16}N_4O_2$	calc.	C 60.01	H 6.20	N 21.53
(260.2)	found	60.18	6.26	21.37

MS: *m/z* = 260 (M^+), 201, 91.

IR ($CHCl_3$): ν = 2110, 1735 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.14 (dddd, 1 H, *J* = 1.1, 2.9, 6.3, 14 Hz); 2.52 (ddd, 1 H, *J* = 7.7, 9.6, 14 Hz); 2.64 (dd, 1 H, *J* = 5.9, 10 Hz); 3.08 (dd, 1 H, *J* = 1.1, 10 Hz); 3.34 (dd, 1 H, *J* = 6.2, 9.2 Hz); 3.56 (d, 1 H, *J* = 13 Hz); 3.72 (s, 3 H); 3.92 (m, 1 H); 4.02 (d, 1 H, *J* = 13 Hz); 7.25 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 35.7, 52.0, 57.6, 57.9, 58.4, 63.6, 127, 128, 129, 137, 173.

(2*S*,4*S*)-2-Acetoxymethyl-4-acetylamino-1-benzylpyrrolidine (13):

$C_{16}H_{22}N_2O_3 \cdot 1/3\ H_2O$	calc.	C 64.84	H 7.71	N 9.45
(290.4)	found	64.69	7.55	9.45

MS: *m/z* = 291 $(M + H)^+$, 231, 217, 158, 91.

^{1}H-NMR ($CDCl_3$): δ = 1.59 (dddd, 1 H, J = 1.8, 1.8, 5.8, 14 Hz); 1.94 (s, 3 H); 2.10 (s, 3 H); 2.38 (ddd, 1 H, J = 7.4, 9.6, 14 Hz); 2.48 (dd, 1 H, J = 5.3, 10 Hz); 2.74 (br d, 1 H, J = 10 Hz); 2.85 (m, 1 H); 3.38 (d, 1 H, J = 13 Hz); 4.07 (d, 1 H, J = 13 Hz); 4.13 (m, 2 H); 4.38 (m, 1 H); 5.99 (br d, 1 H, J = 7.4 Hz); 7.28 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 21.4, 23.8, 36.6, 47.9, 58.8, 60.3, 61.0, 66.5, 127.6, 128.7, 129.2, 139, 169, 171.

(2*S*,4*S*)-4-Acetylamino-1-benzyl-2-hydroxymethylpyrrolidine (14):

$[\alpha]_D^{25} - 55°$ (c = 0.38, $CHCl_3$).

$C_{14}H_{21}NO_2$ Exact Mass calc. 249.1602, found 249.1579.

^{1}H-NMR ($CDCl_3$): δ = 1.67 (dddd, H_{B_2}', J = 1.4, 1.4, 5.2, 14 Hz); 1.90 (s, CH_3); 2.40 (ddd, H_{B_1}', J = 7.8, 9.9, 14 Hz); 2.60 (dd, H_{D_2}', J = 5.2, 10 Hz); 2.83 (dddd, H_A', J = 1.6, 3.0, 5.2, 9.9 Hz); 2.93 (dd, H_{D_1}', J = 1.4, 10 Hz); 3.16 (br s, OH); 3.42 (dd, H_{F_2}', J = 1.6, 11 Hz); 3.47 (d, H_{E_2}', J = 13 Hz); 3.63 (dd, H_{F_1}', J = 3.0, 11 Hz); 3.94 (d, H_{E_1}', J = 13 Hz); 4.35 (ddddd, H_C', J = 1.4, 1.5, 5.2, 7.0, 7.8 Hz; 6.48 (br d, NH, J = 7.0 Hz); 7.27 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 23.3, 35.4, 47.5, 58.1, 61.0, 61.4, 63.3, 127, 128, 129, 138, 169.

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