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Enantiopure *erythro*- and *threo*-1-aryl-1-[2-pyrrolidyl]-methanols: synthesis from L-proline

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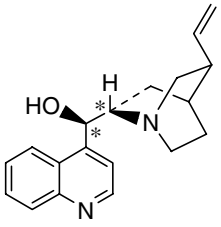
Abstract—Enantiopure (1*R*,2*S*)-*erythro*- and (1*S*,2*S*)-*threo*-isomers of four new aryl-pyrrolidyl alcohols **5aH**, **5aMe**, **5bH** and **5bMe** have been obtained in five steps from (−)-(*S*)-proline and fully characterized. The oxidation of alcohol **8** into aldehyde **9** was the most difficult step and racemization occurs during Swern oxidation but this difficulty can be overcome by using SO_3/pyridine as oxidant. Diastereomer **I** of the protected amino alcohol **10a** crystallized and was shown to be the (1*R*,2*S*)-*erythro*-isomer (*e*-**10a-I**) using X-ray crystallography. Therefore the (1*R*,2*S*)-*erythro* structure was assigned to all compounds obtained from *e*-**10a-I**, and, as a consequence, the (1*S*,2*S*)-*threo* structure was assigned to diastereomers **II**.

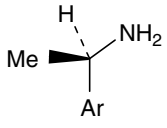
1. Introduction

Cinchonidine **1**,[1] various chiral aryl amines **2**[2,3] and amino alcohols **3**[4] and **4**[5] have been used as chiral modifiers of supported platinum catalysts for the asymmetric heterogeneous hydrogenation of α-ketoesters. Among these chiral modifiers, *erythro*-**4a** proved to be almost as efficient as natural cinchonidine **1**, which is, until now, the most efficient chiral modifier. Therefore, the synthesis of type **5** *erythro*-aminoalcohols, having two vicinal stereogenic carbons, similar to those found in the most efficient modifiers, cinchonidine **1** and **4a**, was envisaged.

We present here the synthesis, isolation and identification of enantiopure *erythro*-(1*R*,2*S*)- and *threo*-(1*S*,2*S*)-isomers of four new modifiers **5aH**, **5aMe**, **5bH** and **5bMe**.

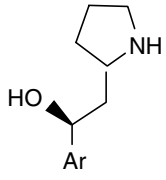


1 cinchonidine
(-)-(8*S*,9*R*)-***erythro***



2

Ar = 1-naphthyl; 9-anthryl
9-phenanthryl



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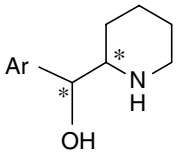
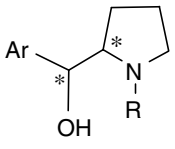
Ar = 1-naphthyl;
9-anthryl



4 *erythro* and *threo*

a: Ar = 1-naphthyl;
b: Ar = 9-anthryl



5 *erythro* and *threo*
R = H ; Me
a: Ar = 1-naphthyl
b: Ar = 9-phenanthryl

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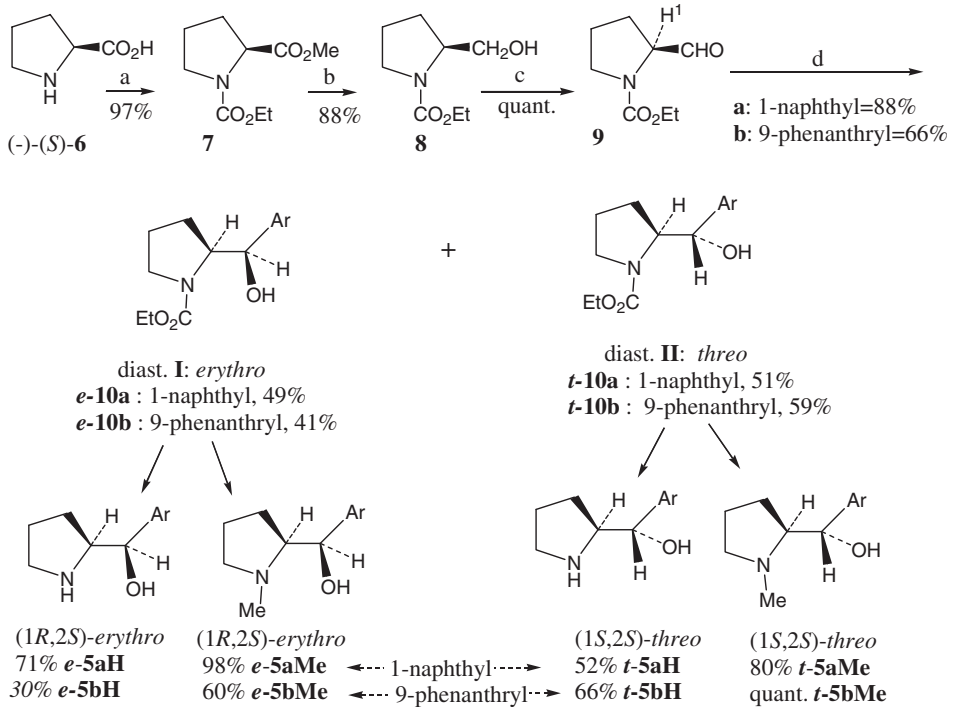
2. Synthesis

The known aldehyde **9** was obtained in three steps from enantiopure L-proline **6** ($[\alpha]_D^{25} = -84$ (*c* 4, H_2O)), Scheme 1. Protection of L-proline **6** provided ester **7** in almost quantitative yield and further reduction of ester **7** (using DIBAL-H in THF) provided alcohol **8** in 88% isolated yield. However, oxidation of alcohol **8** into aldehyde **9** was the most difficult step.

Ester **7**, alcohol **8** and aldehyde **9** have been isolated, purified and their specific rotation checked, Table 1. The specific rotations of ester **7**[6–8] and of alcohol **8**[9] were identical from one experiment to the other and consistent with literature values for enantiopure compounds (Table 1, entries 1, 2 and 3). But large variations were observed for aldehyde **9**. In fact, because of the acidity of the H^1 proton, Scheme 1, in **9** (due to the electronegativity of both CO_2Et and COH substituents), racemization occurs during Swern oxidation even when the reagents ($COCl_2$, NEt_3, DMSO) were carefully distilled and dried before use. However, oxidation with SO_3/pyridine[9] provides **9** with the highest specific rotation known ($[\alpha]_D^{25} = -91$ (*c* 0.78, EtOH)) in consistency with literature values for supposed enantiopure **9** ($[\alpha]_D^{25} = -90.8$ (*c* 0.25, EtOH)[9]), Table 1 (compare entries 4 and 5 with 6 and 7).

Therefore sample S3 was considered to be enantiopure and the specific rotation in MeOH[10] ($[\alpha]_D^{25} = -84$) was used as reference for the determination of the ee% of samples S1 and S2. Aldehyde **9** was purified either by



Scheme 1. Reagents: (a) EtOCOCl, K_2CO_3, MeOH (Refs. 7,8); (b) DIBAL-H, THF; (c) SO_3/pyridine, Et_3N, CH_2Cl_2/DMSO 1/1 (Ref. 9); (d) ArMgBr, THF.

Table 1. Specific rotation of compounds **7**–**9**

Entry			This work	Ee%	Literature
1	Ester **7**		$[\alpha]_D^{25} = -70$ (*c* 1.0, EtOH)		−71.1 (*c* 1.0, EtOH)[7]
2			$[\alpha]_D^{25} = -68$ (*c* 2.10, $CHCl_3$)[a]		−60.3 (*c* 1.26, $CHCl_3$)[8]
3	Alcohol **8**		$[\alpha]_D^{25} = -61$ (*c* 1, EtOH)		−61.9 (*c* 1.17, EtOH)[9]
4	Aldehyde **9**	S1[b]	$[\alpha]_D^{25} = -35$ (*c* 1.0, MeOH)[c]	42	
5		S2[b]	$[\alpha]_D^{25} = -76$ (*c* 0.89, MeOH)[d]	90	
6		S3[b]	$[\alpha]_D^{25} = -84$ (*c* 1.14, MeOH)[e]	100	
7		S3[b]	$[\alpha]_D^{25} = -91$ (*c* 0.78, EtOH)	100	−90.8 (*c* 0.25, EtOH)[9]

[a] The difference observed with the literature may be due to differences in quality of the solvent but also to some racemization, which might have occurred in the literature (the reaction being conducted in the presence of a base).
[b] S1, S2 and S3 = different preparations of **9**.
[c] S1: Swern with reagents not purified.
[d] S2: Swern with all reagents distilled/purified.[10]
[e] S3: SO_3/pyridine.

vacuum distillation or by chromatography over silica gel with no change in rotation.

Upon addition of the desired aryl Grignard the protected amino alcohols **10a** and **10b** were obtained as mixtures of (1*R*,2*S*)-*erythro* and (1*S*,2*S*)-*threo* (respectively, 49/51 and 41/59). In both cases the *erythro* diastereomers *e*-**10a**,**b** have been separated by flash-chromatography from the *threo* diastereomers *t*-**10a**,**b**.

erythro and/or *threo* *N*-methyl amino alcohols **5aMe** and **5bMe** were then obtained by $LiAlH_4$ reduction while the unmethylated ones **5aH** and **5bH** were obtained through NaOH saponification of the corresponding compounds **10a**,**b**, Scheme 1. It is worth noting that $LiAlH_4$ reduction provided the desired *N*-methyl amino alcohols in satisfying to high yields (60–98%) while saponifications were more difficult with lower yields, Scheme 1.

2.1. Determination of *erythro*/*threo* configuration of 5a and 5b; X-ray and NMR

Diastereomer **I** of the protected amino alcohol **10a** crystallized[11] into mono crystals suitable for X-ray analysis and was determined (in the centrosymmetrical space group *P*-1), as being the *erythro*-isomer (*e*-**10a**), Figure 1 show the (1*R*,2*S*)-*erythro*-isomer.

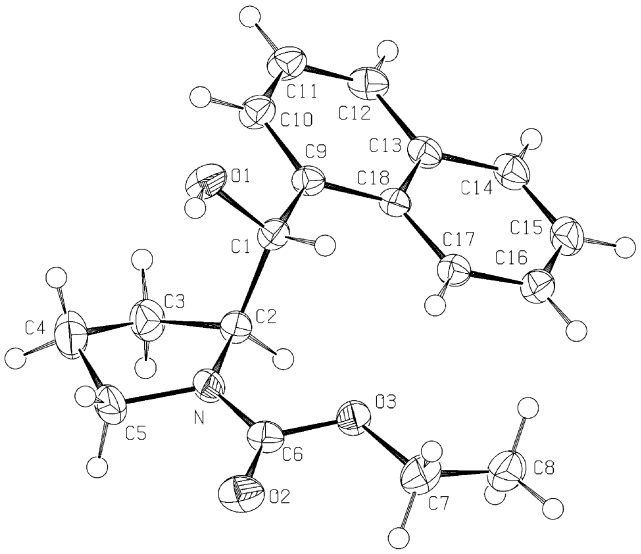


Figure 1. ORTEP view of (1*R*,2*S*)-*erythro*-isomer **10a**. Thermal ellipsoid enclose 50% of the electron density.

Therefore the *erythro* structure was also assigned to isomers **5aH-I** and **5aMe-I**, which have been obtained from the same *erythro*-isomer **10a-I**, Scheme 1. *erythro*-Isomers **5aH-I** and **5aMe-I** exhibit the smallest coupling constant ($^3J_{12}$ = 2.5–3.5 Hz) and the more deshielded chemical shift for H_1 doublets (δH_1 = 5.50–5.68 ppm), Table 2 (entries 1–4) both in $CDCl_3$ and CD_3OD. It is worth noting that the *erythro*-isomer of piperidyl alcohol **4a** was also found to have the smallest $^3J_{12}$ value and the most deshielded H_1 doublet in both solvents, Table 2 (entries 9 and 10). We, therefore, also assigned the *erythro* configuration to the diastereomers of **5bH** and **5bMe** having the smallest $^3J_{12}$ value and the most deshielded H_1 doublet, Table 2 (entries 5–8).

Table 2. ^1H NMR (400 MHz) of compounds **5a**,**b** and of **4a**[a]

	Solvent	**I** *erythro*		**II** *threo*		Δ^3J (Hz) = $^3J_{12}$ (*threo*) − $^3J_{12}$ (*erythro*) (Hz)
		δH_1[b]	$^3J_{12}$ (Hz)	δH_1[b]	$^3J_{12}$ (Hz)	
5aH	CD_3OD	5.50[c]	3.5[c]	5.26	7	3.5
	$CDCl_3$	5.64[c]	3[c]	5.17	6	3
5aMe	CD_3OD	5.58[c]	2.5[c]	5.21	7	4.5
	$CDCl_3$	5.68[c]	3[c]	5.21	4	1
5bH	CD_3OD	5.47	4	5.20	6.5	2.5
	$CDCl_3$	5.55	3	5.21	3.5	0.5
5bMe	CD_3OD	5.59	2.5	5.14	6	3.5
	$CDCl_3$	5.68	2	5.22	2	0
4a	CD_3OD	5.38	4.5	5.18	8.5	4
	$CDCl_3$	5.44	3.5	5.24	5.5	2

[a] See Ref. 5b.
[b] In ppm referred to TMS.
[c] This isomer was determined to be *erythro* from X-ray analysis of the starting *e*-**10a** (cf. above).

3. Conclusion

Both (1*R*,2*S*)-*erythro*- and (1*S*,2*S*)-*threo*-isomers of four new modifiers **5aH**, **5aMe**, **5bH** and **5bMe** have thus been obtained [in five steps from (−)-(*S*)-proline] and fully characterized.

They will be tested as chiral modifiers for heterogeneous hydrogenation of keto esters over Al_2O_3 supported platinum.

4. Experimental

^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Bruker AC 300 spectrometer with $CDCl_3$ or CD_3OD as solvents. Chemical shifts (δ) are given in ppm downfield from TMS as an internal standard. Optical rotation were determined on a Perkin–Elmer 241 MC polarimeter. TLC was performed on Merck's glass plates with silica gel 60 F_{254}. Silica gel Si 60 (40–60 μm) from Merck was used for the chromatographic purifications. (−)-L-Proline (>99% ee, *S*-configuration) was purchased from Aldrich.

4.1. Crystal structure determination

Single crystal of **10a** was mounted on a Nonius Kappa-CCD area detector diffractometer (Mo Kα λ = 0.71073 Å). The complete conditions of data collection (Denzo software[12]) and structure refinements are given below. The cell parameters were determined from reflections taken from one set of 10 frames (1.0° steps in phi angle), each at 20 s exposure. The structures were solved using direct methods (SHELXS[13]) and refined against F^2 using the SHELXS97 software.[13] The absorption was non-corrected. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated according to stereochemistry and refined using a riding

model in SHELXS97, except for H3 (OH group) detected by Fourier differences.

$C_{18}H_{21}NO_3$: $M = 299.36$ g mol^{-1}; triclinic; space group P-1; $a = 7.531(1)$ Å, $b = 10.924(1)$ Å, $c = 11.343(1)$ Å, $\alpha = 117.88(5)°$, $\beta = 109.00(5)°$, $\gamma = 90.67(5)°$, $V = 764.77(14)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.3$ g cm^{-3}, $\mu = 0.088$ mm^{-1}, $F(000) = 320$. Colourless crystal, dimensions $0.10 \times 0.12 \times 0.14$ mm^3. A total of 6540 reflections were collected with $2.17° < \theta < 29.97°$; 4418 independent reflections with 3102 having $I < 2\sigma < (I)$; 199 parameters; $R1 = 0.0546$; $wR2 = 0.1635$; Goof = 1.044; maximum residual electronic density = 0.547 e$^-$ Å^3.

Full data collection parameters, and structural data are available as Supporting information. Crystallographic data for the crystal structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC 252817. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail, deposit@ccdc.cam.ac.uk; web, http://www.ccdc.cam.ac.uk).

4.2. DIBAL-H reduction (modified literature procedure[11])

To a solution of ester **7** (30 mmol) in anhydrous THF (100 mL) was added dropwise (at −40 °C) a 1 M hexane solution of DIBAL-H (75 mL, 75 mmol), after addition the temperature was left to reach ambient and the mixture was stirred overnight. After cooling at 0 °C, MeOH (200 mL) and a saturated solution of sodium tartrate (400 mL) were successively added. Stirring was maintained until the solution became transparent, then extraction with CH_2Cl_2 was done (10 times 50 mL). The organic phases were joined, dried over Na_2SO_4 and the solvent evaporated providing the crude protected amino alcohol **8** (purified as shown by ^{1}H NMR) in 88% yield.

4.3. Oxidation step

Following the literature method.[9]

4.4. Grignard addition

To a suspension of Mg turnings (0.71 g, 29.24 mmol) in anhydrous THF (20 mL) was added dropwise and successively two drops of dibromoethane and a solution of the desired bromo-aryl derivative (29.24 mmol) in anhydrous THF (20 mL). The mixture was stirred under reflux until no Mg remained. After cooling to ambient under stirring, a solution of the aldehyde **9** (15 mmol) in anhydrous THF (20 mL) was added dropwise. The advancement of the reaction was monitored by CCM and stirring was maintained until no aldehyde was detected by CCM. After the usual work-up (addition of a saturated solution of NH_4Cl) the THF was evaporated and the remaining aqueous phase extracted with Et_2O (7 times 20 mL). The organic phases were joined, dried over Na_2SO_4 and the solvent evaporated to provide **10** as a mixture of *erythro*- and *threo*-isomers.

4.5. $LiAlH_4$ reduction

To a solution of the desired protected amino alcohol, **10a** and **10b** *erythro* or *threo* (1 mmol) in anhydrous THF (10 mL) were added by fractions, under argon, at 0 °C and under stirring 2.5 equiv of $LiAlH_4$ (powder, 0.1 g). The mixture was then stirred and heated at THF reflux for 4 h. After usual work-up (H_2O: 0.1 mL; NaOH 15%: 0.1 mL; H_2O: 0.3 mL) the mixture was stirred until the precipitate became white and powdered. After filtration the precipitate was rinsed with THF, the organic phases were joined, the solvent evaporated and the product **5aMe** and **5bMe** (*erythro* and *threo*) purified by column chromatography.

4.6. Saponification

A solution of the desired protected amino alcohol, **10a** and **10b** *erythro* or *threo* (1 mmol) and NaOH (7 mmol) in EtOH (15–20 mL) was heated under reflux for the necessary amount of time (5 h to overnight). The desired deprotected amino alcohol was then extracted from the mixture with $CHCl_3$ (6 times 15 mL), the organic phases were joined, dried over Na_2SO_4 and the solvent evaporated. The product **5aH** and **5bH** (*erythro* or *threo*) was then purified through column chromatography.

4.7. Compounds 7 and 9

Spectral characteristics identical to the literature.[8,9]

4.8. Protected alcohol 8

^{1}H NMR ($CDCl_3$): 1.25 (t, 3H); 1.58 (m, 1H); 1.85 (m, 2H); 2.05 (m, 1H); 3.31 (m, 1H); 3.5 (m, 1H); 3.6 (br m, 2H); 3.98 (br m, 1H); 4.15 (q, 2H). ^{13}C NMR (75.4 MHz): 14.7; 21.0; 28.6; 47.2; 60.3; 60.6; 67.3; 157.6.

4.9. *erythro*-10a

^{1}H NMR ($CDCl_3$): presence of two exchanging conformers **I** and **II**; 1.42 (br, 4H, Me + 1H); 2.0 (2br s, 2H); 2.55 (2br s, 1H); 3.53 (3br s, 2H); 4.28 (1br s, 2H + 1H); 6.1 (br s, 1H, 40%, conformer **I**); 6.29 (br s, 1H, 60% conformer **II**); 7.52 (m, 3H); 7.80 (m, 3H, 60%, **II**); 7.90 (m, 3H, 40%, **I**); 8.28 (br s, 1H, 40%, **I**), 8.50 (br s, 1H, 60%, **II**). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07. Found: C, 72.09; H, 7.13. $[\alpha]_D^{20} = +92$ (*c* 1.05, MeOH).

4.10. *threo*-10a

^{1}H NMR ($CDCl_3$): 1.34 (t, 3H); 1.53 (br, 1H); 1.72 (m, 2H); 3.43 (br, 1H); 3.52 (m, 2H); 4.25 (br m, 2H); 4.54 (td, 1H, $J = 8$, 8, 4 Hz); 5.32 (br d, 1H, $J = 8$ Hz); 5.88 (br s, OH); 7.49 (m, 3H); 7.61 (d, 1H); 7.8 (d, 1H); 7.87 (d, 1H); 8.36 (d, 1H). $[\alpha]_D^{20} = -38$ (*c* 0.95, MeOH).

4.11. *erythro*-10b

^{1}H NMR ($CDCl_3$): presence of two exchanging conformers **I** and **II**; 1.4 (br m, 3H); 1.6 (m, 1H); 2.0 (br, 2H); 2.6 (br, 1H); 3.51 (br m, 2H); 4.30 (br m, 3H);

6.05 (br s, 1H, 33%, **I**); 6.26 (br s, 1H, 67%, **II**); 7.61 (br m, 4H); 7.91 (br d, 1H); 8.0 (br s, 1H); 8.3 (br d, 1H, 33%, **I**); 8.65 (br m, 2H + 67%, 1H, **II**). $[\alpha]_D^{20} = +52$ (*c* 0.61, MeOH).

4.12. *threo*-10b

^{1}H NMR ($CDCl_3$): 1.33 (t, 3H); 1.52 (br, 2H); 1.76 (m, 2H); 3.5 (m, 2H); 4.25 (br m, 2H); 4.63 (br q, 1H); 5.32 (br d, 1H); 7.62 (m, 4H); 7.86 (m, 2H); 8.47 (br s, 1H); 8.72 (m, 2H). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63. Found: C, 75.53; H, 6.71. $[\alpha]_D^{20} = -57$ (*c* 0.61, MeOH).

4.13. *erythro*-5aH

^{1}H NMR ($CDCl_3$): 1.22 (m, 1H); 1.60 (m, 1H); 1.75 (m, 2H); 2.96 (m, 1H); 3.00 (m, 1H); 3.71 (m, 1H); 5.64 (d, 1H, ^3J = 3 Hz); 7.46 (m, 3H); 7.79 (m, 3H); 8.00 (∼d, 1H, ^3J = 8 Hz). ^{13}C NMR ($CDCl_3$): 24.7 (CH_2); 25.6 (CH_2); 46.9 (CH_2); 62.4 (CH); 70.2 (CH); 122.9 (CH); 123.2 (CH); 125.3 (CH); 125.7 (CH); 126.1 (CH); 127.5 (CH); 128.9 (CH); 130.3 (q); 133.6 (q); 137.6 (q). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.10; H, 7.66. $[\alpha]_D^{20} = -72$ (*c* 1.0, MeOH).

4.14. *erythro*-5aMe

^{1}H NMR ($CDCl_3$): 1.1 (m, 1H); 1.6 (m, 1H); 1.7 (m, 3H); 2.4 (m, 1H); 2.65 (s, 3H, NMe); 2.85 (m, 1H); 3.2 (m, 1H); 5.70 (d, 1H, ^3J = 3 Hz); 7.5 (m, 3H); 7.8 (∼d, 1H, ^3J = 8 Hz); 7.95 (m, 3H). ^{13}C NMR ($CDCl_3$): 23.0 (CH_2); 24.1 (CH_2); 40.0 (Me); 57.6 (CH_2); 66.7 (CH); 69.0 (CH); 122.8 (CH); 123.2 (CH); 125.2 (CH); 125.6 (2CH); 127.5 (CH); 129.0 (CH); 130.1 (q); 133.6 (q); 136.8 (q). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.51; H, 8.08. $[\alpha]_D^{20} = -52$ (*c* 1.0, MeOH).

4.15. *erythro*-5bH

^{1}H NMR ($CDCl_3$): 1.24 (m, 1H); 1.62 (m, 1H); 1.81 (m, 2H); 2.98 (m, 1H + OH + NH); 3.12 (m, 1H); 3.84 (td, 1H, ^3J = 7.5, 7.5, 3.5 Hz); 5.59 (d, 1H, ^3J = 3 Hz); 7.63 (m, 5H); 8.06 (d, 1H, ^3J = 8 Hz); 8.09 (s, 1H); 8.67 (d, 1H, ^3J = 8.5 Hz); 8.76 (d, 1H, ^3J = 8 Hz). ^{13}C NMR ($CDCl_3$): 21.1 (CH_2); 24.5 (CH_2); 47.1 (CH_2); 61.7 (CH); 70.2 (CH); 122.3 (CH); 123.3 (CH); 123.4 (CH); 123.8 (CH); 126.0 (CH); 126.3 (CH); 126.4 (CH); 126.6 (CH); 128.9 (CH); 129.6 (q); 129.8 (q); 130.5 (q); 131.6 (q); 135.4 (q). Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90. Found: C, 82.11; H, 7.01. $[\alpha]_D^{20} = -85$ (*c* 0.63, MeOH).

4.16. *erythro*-5bMe

^{1}H NMR ($CDCl_3$): 1.05 (m, 1H); 1.7 (m, 3H); 2.40 (m, 1H); 2.65 (s, 3H, NMe); 2.90 (td, 1H, ^3J = 7, 7, 2 Hz); 3.20 (br t, 1H, ^3J = 7 Hz); 5.65 (d, 1H, ^3J = 2 Hz); 7.6 (m, 4H); 7.9 (m, 2H); 8.12 (s, 1H); 8.65 (∼d, 1H); 8.75 (∼d, 1H). ^{13}C NMR ($CDCl_3$): 23.0 (CH_2); 24.1 (CH_2); 40.1 (Me); 57.7 (CH_2); 66.8 (CH); 68.8 (CH); 122.3 (CH); 123.0 (CH); 123.4 (CH); 124.0 (CH); 126.0 (CH); 126.3 (CH); 126.4 (CH); 126.7 (CH); 128.9 (CH); 129.6 (q); 129.8 (q); 130.6 (q); 131.7 (q); 134.8 (q). Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.31; H, 7.38. $[\alpha]_D^{20} = -67$ (*c* 0.63, $CHCl_3$).

4.17. *threo*-5aH

^{1}H NMR (CD_3OD): 1.5 (m, 2H); 1.94 (m, 2H); 2.85 (m, 1H); 3.10 (m, 1H); 5.24 (d, 1H, ^3J = 7 Hz); 7.50 (m, 3H); 7.61 (d, 1H); 7.80 (d, 1H); 7.90 (d, 1H); 8.30 (d, 1H). ^{13}C NMR ($CDCl_3$): 25.4 (CH_2); 28.6 (CH_2); 45.9 (CH_2); 64.0 (CH); 71.6 (CH); 123.5 (CH); 123.7 (CH); 125.5 (CH); 126.0 (CH); 128.0 (CH); 128.2 (CH); 128.8 (CH); 130.9 (q); 133.9 (q); 138.4 (q). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.12; H, 7.63. $[\alpha]_D^{20} = +48$ (*c* 1.64, MeOH).

4.18. *threo*-5aMe

^{1}H NMR ($CDCl_3$): 1.8 (m, 1H); 1.91 (m, 2H); 2.12 (4H, s, 3H, NMe overlapped with m, 1H); 1.40 (m, 1H); 3.00 (m, 1H); 3.20 (m, 1H); 5.20 (d, 1H, ^3J = 4 Hz); 7.50 (m, 3H); 7.75 (m, 2H); 7.92 (∼d, 1H); 8.05 (∼d, 1H). ^{13}C NMR ($CDCl_3$): 24.7 (CH_2); 31.2 (CH_2); 43.8 (Me); 58.1 (CH_2); 69.8 (CH); 72.7 (CH); 123.2 (CH); 123.4 (CH); 125.3 (CH); 125.4 (CH); 125.7 (CH); 127.3 (CH); 129.0 (CH); 130.4 (q); 133.9 (q); 139.8 (q). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.49; H, 8.10. $[\alpha]_D^{20} = +42$ (*c* 1.0, $CHCl_3$), $[\alpha]_D^{20} = +27$ (*c* 0.83, MeOH).

4.19. *threo*-5bH

^{1}H NMR (CD_3OD): 1.55 (m, 3H); 1.75 (m, 1H); 2.70 (m, 1H); 2.95 (m, 1H); 3.56 (m, 1H); 5.21 (d, 1H, ^3J = 6 Hz); 7.52 (m, 4H); 7.75 (s, 1H); 8.25 (d, 1H); 8.64 (d, 1H); 8.74 (d, 1H). $[\alpha]_D^{20} = +29$ (*c* 0.3, EtOH). ^{13}C NMR ($CDCl_3$): 26.0 (CH_2); 29.1 (CH_2); 46.4 (CH_2); 58.4 (CH); 71.1 (CH); 122.4 (CH); 123.3 (CH); 123.8 (CH); 124.0 (CH); 126.1 (CH); 126.4 (CH); 126.5 (CH); 126.7 (CH); 128.7 (CH); 128.8 (q); 129.9 (q); 130.0 (q); 131.4 (q); 137.3 (q). Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90. Found: C, 82.14; H, 7.00. $[\alpha]_D^{20} = +29$ (*c* 0.30, EtOH).

4.20. *threo*-5bMe

^{1}H NMR ($CDCl_3$): 1.81–2.05 (m, 3H); 2.07 (s, 3H); 2.23 (m, 1H); 2.40 (m, 1H); 3.11 (m, 1H); 3.20 (m, 1H); 5.22 (d, 1H, ^3J = 2 Hz); 7.65 (m, 4H); 7.93 (m, 1H); 8.01 (s, 1H); 8.03 (m, 1H); 8.67 (m, 1H); 8.77 (m, 1H). ^{13}C NMR ($CDCl_3$): 22.7 (CH_2); 31.9 (CH_2); 43.8 (CH_3); 58.3 (CH_2); 68.9 (CH); 72.5 (CH); 122.4 (CH); 123.4 (CH); 123.8 (CH); 123.9 (CH); 126.1 (CH); 126.3 (CH); 126.4 (CH); 126.6 (CH); 128.8 (CH); 129.7 (q); 129.9 (q); 130.8 (q); 131.5 (q); 137.9 (q). Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.33; H, 7.34. $[\alpha]_D^{20} = +17$ (*c* 1.0, $CHCl_3$).

Supporting information available: X-ray data are available free of charge via the Internet at http://pubs.acs.org.

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