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AN EFFICIENT SYNTHESIS OF (R)-(+)- AND (S)-(-)-PROPRANOLOL FROM RESOLVED 5-IODOMETHYLOXAZOLIDIN-2-ONES

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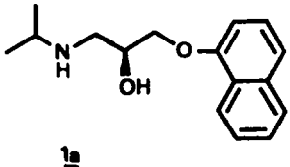
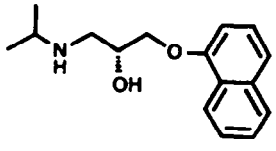
Abstract (1'S*,5S,R)-3-(1'-phenyleth-1'-yl)-5-iodomethyloxazolidin-2-ones, 4a,b, have been synthesized and easily resolved by silica gel chromatography. Each pure diastereomer has been then converted to (S)-(-)-propranolol 1a and (R)-(+)-propranolol 1b, respectively. An empirical correlation of configuration and ^{1}H NMR chemical shift for alternate diastereomers has been devised and has proved to be applicable in assigning the configuration of 5-substituted 3-(1'-phenyleth-1'-yl)oxazolidin-2-ones.

In a previous study [1] the growing importance of aminoalcohols in organic synthesis, due to the presence of this moiety in many biologically active compounds, prompted us to realize the synthesis of (5R,S)-5-(iodomethyl)oxazolidin-2-ones through the iodocyclofunctionalization of allylic amines, in order to easily obtain 3-amino-1,2-diols and aminoalcohols.
In this paper we report an efficient resolution [2] of the diastereomeric mixture of (1S*,5S,R)-3-(1'-phenyleth-1'-yl)-5-(iodomethyl)oxazolidin-2-ones 4a,b, utilizing the commercially available (S)-1-phenylethylamine as the optically active portion of the molecule.[3] These intermediates are successively converted into the pure (S)-(-)-propranolol 1a and (R)-(+)-propranolol 1b.



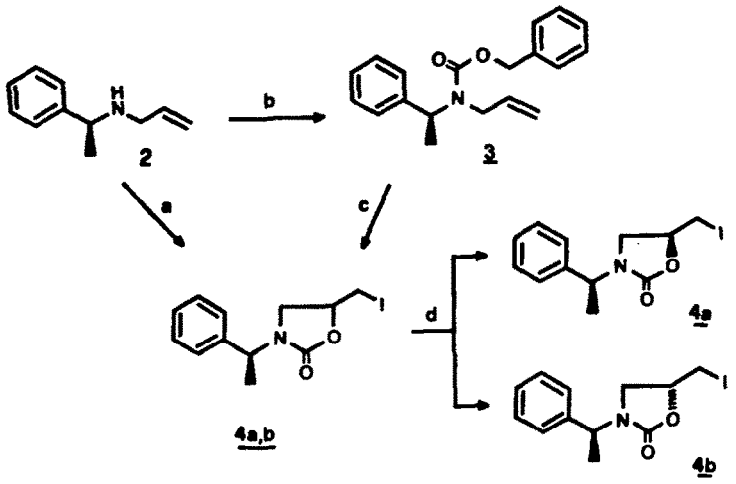
1a



1b

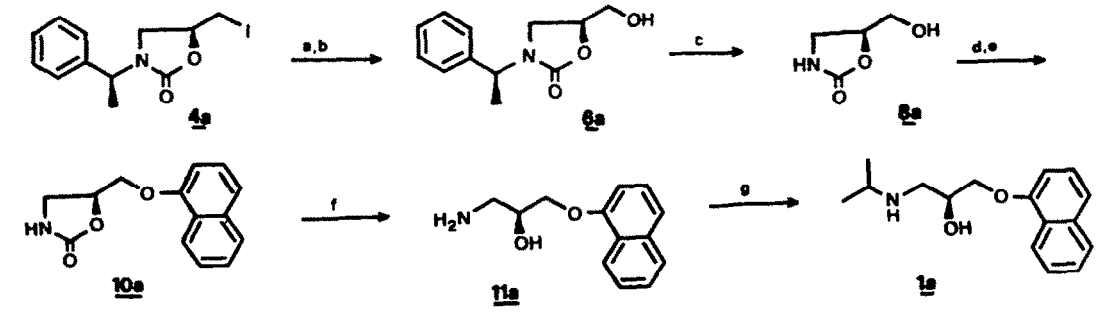
In addition we develop a conformational model that allows the attribution of the configuration of the newly introduced stereogenic center on the basis of the chemical shifts in the ^{1}H NMR spectra of the diastereomeric oxazolidin-2-ones. The (S)-N-(1-phenyleth-1-yl)-N-(2-propen-1-yl)amine hydrobromide 2, obtained in 80% yield from (S)-1-phenylethylamine and 3-bromo-1-propene, is treated in $CHCl_3$ at room temperature with two equivalents of I_2 adsorbed on Amberlyst A 26 in the CO_3^{--} form to afford in good yield a 1:1 diastereomeric mixture of (1'S*,5S,R)-3-(1'-phenyleth-1'-yl)-5-(iodomethyl)oxazolidin-2-ones 4a,b, as determined by ^{13}C NMR spectrum and g.l.c. analysis of the reaction mixture. In an alternative pathway the chiral allylic amine is converted to the

reaction mixture. In an alternative pathway the chiral allylic amine is converted to the corresponding N-benzyloxycarbonyl derivative 3, that is successively cyclized with I_2 in $CHCl_3$.[4] An easy and complete separation of the diastereomeric mixture is reached by chromatography on silica gel, and pure 4a (R_f = 0.5) and 4b (R_f = 0.37) are obtained with hexane:ethyl acetate 80:20.



a. Amberlyst A 26 in the CO_3^{--}/I_2 form, MeOH b. $C_6H_5CH_2OCOCl$ c. I_2, $CHCl_3$ d. silica gel chromatography

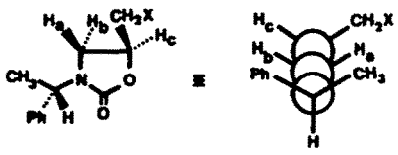
By displacement of iodine on pure 4a or 4b, performed with Amberlyst A 26 in the AcO^- form in refluxing benzene, the acetoxy derivatives 5a or 5b are isolated in good yield. Successive basic hydrolysis with dry K_2CO_3 in ethanol affords the alcohols 6a or 6b. Reductive cleavage of C-N bond [5] of each diastereomer 6a and 6b with Li/NH_3 gives 5-(hydroxymethyl)oxazolidin-2-ones 8a or 8b, that are converted to the corresponding methanesulfonate esters 9a or 9b. The methanesulfonyl group is then substituted by the naphtholate anion supported on the resin Amberlyst A 26 and the derivatives 10a or 10b are obtained in good yield. The cleavage of the heterocyclic ring is then performed with $LiOH/H_2O$/MeOH at reflux to give the aminodiols 11a or 11b. The isopropyl group is eventually introduced by treating an ethanolic solution of 11a or 11b with acetone, followed by reductive cleavage of the oxazolidine with $NaBH_4$:[6] (S)-(-)-propranolol 1a or (R)-(+)-propranolol 1b are obtained, whose absolute configuration at C-2 is assigned from comparison of the optical rotations to the values of the known compounds.[7]



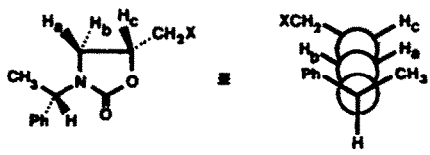
a. Amberlyst A 26 in the AcO^- form, refluxing benzene b. K_2CO_3, EtOH c. Li/NH_3 d. CH_3SO_2Cl, pyridine, CH_2Cl_2 e. Amberlyst A 26 in the α-naphtholate form, benzene f. LiOH, H_2O, refluxing MeOH g. acetone, $NaBH_4$, EtOH

From the ^1H NMR spectra of alternate diastereomeric 5-substituted oxazolidin-2-ones, the internal diastereotopic protons H_a and H_b are non-equivalent and $\Delta\delta_{H_a,H_b}$ in the (1'S*,5R)-series is always larger than in the (1'S*,5S)-series. The phenomenon of ^1H NMR non-equivalence of internal or external diastereotopic groups is widely used to establish the enantiomeric purity of alcohols and amines through the preparation of diastereomeric derivatives. Dale and Mosher,[8] and more recently Trost,[9] proposed a model for the mandelate esters, represented by a unique model for each diastereomer via an extended Newman projection where the substituent shielded by the phenyl ring is always upfield. On the basis of ^1H NMR chemical shifts, we propose a model for 5-substituted oxazolidin-2-ones that rationalizes the data given in Table 1 and satisfies the data for H_a and H_b and those for H_c and CH_2X, by considering the phenyl group and CH_2X shieldings. In fact in the (1'S*,5S)-series H_a resonates at higher field than in the (1'S*,5R)-series, because of the shielding due to the CH_2X group. Moreover in the (1'S*,5R)-series H_b shows its proton shift upfield of H_b in the (1'S*,5S)-series, since it experiences shielding from both he phenyl ring and the CH_2X group.As a result of the phenyl group shielding, in the (1'S*,5S)-series, H_c, juxtaposed with the aromatic ring, resonates upfield in respect to H_c of the (1'S*,5R)-series, whereas the opposed pattern is observed for the CH_2X protons. Hence our model provides an empirical correlation of extensive data, and allows to assign the absolute configuration at C-5 in the 3-(1'-phenyl-eth-1'-yl)oxazolidin-2-ones on the basis of the chemical shifts of H_a and H_b.

Table 1. ^1H NMR chemical shifts correlation of (S*,S*)- and (S*,R*)-oxazolidin-2-ones



(S*,S*)-



(S*,R*)-

	δ_{H_a}		δ_{H_b}		δ_{H_c}		δ_{CH_2X}	
	(S*,S*)-	(S*,R*)-	(S*,S*)-	(S*,R*)-	(S*,S*)-	(S*,R*)-	(S*,S*)-	(S*,R*)-
X = I	3.25	3.65	3.25	2.9	4.4	4.6	3.3	3.2
X = OAc	3.25	3.6	3.25	2.9	4.6	4.65	4.2	4.1
X = OH	3.4	3.5	3.15	3.0	4.4	4.55	3.7	3.6
X = ONaphtlyl	3.55	3.8	3.3	3.2	4.75	4.8	4.25	4.05

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from LAH immediately prior to use. All reactions involving organometallic reagents were conducted under argon atmosphere. Melting points (Pyrex capillary) were determined on a Buchi 510 hot stage apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer Model 682 infrared recording spectrophotometer. ^{1}H NMR spectra were determined on a Varian EM 390 (90 MHz) spectrometer. ^{13}C NMR spectra were measured at 20 MHz with a Varian FT 80-A spectrometer. Chemical shifts are reported as δ units (ppm) relative to tetramethylsilane (Me_4Si) as internal reference. Optical rotations were measured with a Perkin-Elmer 241 digital polarimeter at room temperature. Thin-layer chromatography was performed on silica gel HF_{254} and column chromatography on silica gel 60 (Merck, 0.040-0.063 mesh).

(S)-N-(1-Phenyleth-1-yl)-N-(prop-2-en-1-yl)amine hydrobromide (2).

A mixture of (S)-1-phenylethylamine (20 mmol; 2.42 g) and 3-bromo-1-propene (2.9 g; 24 mmol) was stirred for 1 h at 0 °C. The resulting oil was chromatographed on silica gel using ethyl acetate:methanol (95:5) as the eluting solvent, to yield 3.85 g of (2) (80%) as white crystals: m.p. 154 °C; ^{1}H NMR ($CDCl_3$): δ 1.9 (d, 3H; J = 6 Hz), 3.15 - 3.8 (m, 2H), 4.45 (q, 1H; J = 6 Hz), 5.2 - 5.6 (m, 2H), 5.9 - 6.5 (m, 1H), 7.3 - 7.8 (m, 5ArH), 8.7 (bs, 2H, NH, HBr); ^{13}C NMR ($CDCl_3$): δ 20.6, 47.5, 57.8, 124.1, 127.6, 128.2, 129.4, 135.5.

(S)-N-(1-Phenyleth-1-yl)-N-(prop-2-en-1-yl)-N-(benzyloxycarbonyl)amine (3)

To a solution of the hydrobromide (2) (4.82 g; 20 mmol) in 25 ml water:acetone (4:1) were added sequentially at 0 °C $NaHCO_3$ (3.36 g; 40 mmol) and benzyloxycarbonyl chloride (3.5 g; 22 mmol) in acetone (20 ml). After 1 h ether (200 ml) was added and the organic layer was washed with 10% aqueous $NaHSO_4$ (100 ml) and then with 10% aqueous Na_2CO_3 (100 ml), dried (Na_2SO_4) and concentrated in vacuo to give an oil which was purified by silica gel chromatography using cyclohexane:ethyl acetate (9:1) as the eluting solvent, to afford 5.55 g of (3) (96%) as a colorless oil; I.R. (neat) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.45 (d, 3H; J = 6Hz), 3.3 - 4.0 (m, 2H), 4.8 - 5.1 (m, 2H), 5.2 (s, 2H), 5.3 - 5.9 (m, 2H), 7.1 - 7.7 (m, 10ArH).

(1'S*,5S*,R*)-3-(1'-Phenyleth-1'-yl)-5-(iodomethyl)oxazolidin-2-one (4a,b)

Method A Amberlyst A 26 in the CO_3^{--} form (6 g;≈3.8 mequiv/g) was added to a solution of I_2 (5.1 g; 20 mmol) in $CHCl_3$ (100 ml). After the suspension was slowly stirred until the colour disappeared, a solution of the hydrobromide (2) (2.41 g; 10 mmol) in $CHCl_3$ (20 ml) was added all at once and the reaction was stirred for 12 h at room temperature. The resin was filtered off and washed with methanol (30 ml); removal of the solvent in vacuo afforded in a quantitative yield a mixture 1:1 of diastereomers (4a) and (4b) as a yiellow oil.

Method B To a solution of (3) (5.9 g; 20 mmol) in $CHCl_3$ (100 ml), I_2 (10 g; 40 mmol) was added at room temperature. After 5 h, the reaction was diluted with $CHCl_3$ (100 ml), the organic phase washed with 10% aqueous $Na_2S_2O_3$ (100 ml) and dried (Na_2SO_4). The solvent was then removed in vacuo to give a pure mixture 1:1 of diastereomers (4a) and (4b) in a quantitative yield. The separation of diastereomers was achieved by silica gel chromatography with cyclohexane:ethyl acetate (7:3) as the eluting solvent, to yield first the less polar (1'S*,5S*)-isomer (4a) (2.9

g; 44%) in pure form as an oil. Further elution gave the more polar (1'S*,5R*)-isomer (4b) in pure form (3.1 g; 46%) as white crystals.

(1'S*,5S*)-isomer (4a): R_f = 0.5 (cyclohexane:ethyl acetate 65:35); IR (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.6 (d, 3H; J = 7 Hz), 3.25 (m, 2H), 3.3 (m, 2H), 4.4 (m, 1H, H_c), 5.2 (q, 1H; J = 7 Hz), 7.3 (m, 5ArH); ^{13}C NMR ($CDCl_3$): δ 7.1, 15.9, 45.6, 51.2, 71.0, 126.5, 127.5, 128.3, 138.8, 156.1; α_D -11.8° (c = 5; $CHCl_3$).

(1'S*,5R*)-isomer (4b): R_f = 0.37 (cyclohexane:ethyl acetate 65:35); m.p. 136 °C; IR (nujol): 1745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.6 (d, 3H; J = 7 Hz), 2.9 (dd, 1H, H_b; J_{ab} = 9 Hz; J_{bc} = 6.5 Hz), 3.2 (m, 2H), 3.65 (t, 1H, H_a; J_{ab} = 9 Hz; J_{ac} = 9 Hz), 4.6 (m, 1H, H_c), 5.3 (q, 1H; J = 7 Hz), 7.3 (m, 5ArH); ^{13}C NMR ($CDCl_3$): δ 6.2, 16.1, 45.7, 51.2, 71.6, 126.7, 127.6, 128.4, 138.7, 155.9; α_D -5.54° (c = 5; $CHCl_3$). Found: C, 31.42; H, 3.07%. $C_{12}H_{14}NO_2I$ requires C, 31.47; H, 3.08%

(1'S*,5S*)-3-(1'-Phenyleth-1'-yl)-5-(acetoxymethyl)oxazolidin-2-one (5a)

To a solution of (4a) (6.62 g; 20 mmol) in benzene (50 ml), Amberlyst A 26 in the AcO^- form (10 g; ~3.8 mequiv/g) was added and the suspension was refluxed for 6 h. The resin was then filtered off and washed with methanol (50 ml). After removal of the solvent, the residue was chromatographed on silica gel using cyclohexane:ethyl acetate (7:3) as the eluting solvent, to yield 3.7 g of (5a) (70%) as white crystals: m.p. 95 °C; IR (nujol) 1750 and 1745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H; J = 7 Hz), 2.0 (s, 3H), 3.25 (m, 2H, H_a and H_b), 4.2 (m, 2H), 4.6 (m, 1H, H_c), 5.15 (q, 1H; J = 7 Hz), 7.3 (m, 5ArH); ^{13}C NMR ($CDCl_3$): δ 16.3, 20.6, 42.0, 51.5, 64.5, 70.5, 127.0, 127.9, 128.7, 139.2, 156.8, 170.4; α_D -8.76° (c = 5; $CHCl_3$). Found: C, 63.99; H, 6.52%. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51%.

(1'S*,5S*)-3-(1'-Phenyleth-1'-yl)-5-(hydroxymethyl)oxazolidin-2-one (6a)

The compound (5a) (5.26 g; 20 mmol), dissolved in ethanol (20 ml), was stirred with dry K_2CO_3 (2.76 g; 20 mmol) at room temperature for 6 h. The suspension was filtered off and the organic layer was evaporated in vacuo, to give (6a) in a quantitative yield as a white solid: m.p. 102 °C; IR (nujol) 3400 and 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.5 (d, 3H; J = 7 Hz), 3.15 (t, 1H, H_b; J_{ab} = 9 Hz; J_{bc} = 9 Hz), 3.4 (dd, 1H, H_a; J_{ab} = 9 Hz; J_{ac} = 6 Hz), 3.7 (m, 2H), 3.9 (bs, 1H, OH), 4.4 (m, 1H, H_c), 5.15 (q, 1H; J = 7 Hz), 7.3 (m, 5ArH); ^{13}C NMR ($CDCl_3$): δ 16.3, 41.5, 51.5, 62.8, 73.9, 127.0, 127.8, 128.7, 139.5, 157.8; α_D -28.4° (c = 5; $CHCl_3$). Found: C, 65.03; H, 6.80%. $C_{12}H_{15}NO_4$ requires C, 65.03; H, 6.82%.

(5S)-5-(Hydroxymethyl)oxazolidin-2-one (8a)

A solution of lithium metal (210 mg; 30 mmol) in anhydrous ammonia (120 ml) was stirred at -60 °C and (6a) (2.21 g; 10 mmol) was added all at once, dissolved in THF:t-BuOH (55 ml; 10:1). After 3' the reaction was quenched by addition of solid NH_4Cl (1.6 g; 30 mmol), the ammonia was allowed to evaporate and the volatiles were removed in vacuo. The residue was suspended in pyridine (10 ml), AcCl (1.56 g; 40 mmol) was added at 0 °C and the mixture was stirred overnight. The reaction was then diluted with water (20 ml), extracted twice with $CHCl_3$ (2 x 50 ml) and the organic phase was washed with 1 M HCl (20 ml) and dried (Na_2SO_4). After removal of the solvent in vacuo, the

residue was chromatographed on silica gel using cyclohexane:ethyl acetate (1:9) as the eluting solvent, to give 1.12 g (70%) of the acetyl derivative (7a) as a colorless oil; IR (neat) 1745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.1 (s, 3H), 3.3 - 3.9 (m, 2H), 4.4 (d, 2H), 4.8 (m, 1H), 6.7 (bs, 1H, NH). This compound (1.2 g; 7 mmol), dissolved in ethanol (10 ml), was stirred with dry K_2CO_3 (1.4 g; 10 mmol) at room temperature for 6 h. The suspension was then filtered off and the organic layer was evaporated in vacuo, affording (8a) in a quantitative yield as a colorless oil; IR (neat) 3400, 3300 and 1750 cm^{-1}; ^1H NMR (CD_3OD): δ 3.25 - 3.80 (m, 4H), 4.6 (m, 1H), 4.8 (bs, 2H, OH,NH); ^{13}C NMR (CD_3OD): δ 42.9, 63.5, 78.5; α_D +29.7°(c = 2.7; EtOH). Found: C, 41.09; H, 6.02%. $C_4H_7NO_3$ requires C, 41.03; H, 6.03%.

(5S)-5-(Methanesulfonyloxymethyl)oxazolidin-2-one (9a)

To a solution of (8a) (1.1 g; 5 mmol) in pyridine (20 ml), was added at 0 °C methanesulfonyl chloride (1.37 g; 12 mmol) dissolved in CH_2Cl_2 (10 ml). After 3 h volatiles were removed in vacuo and the residue was chromatographed on silica gel using CH_2Cl_2:methanol (95:5) as the eluting solvent, to afford 1.85 g of (9a) (95%) as white crystals: m.p. 113 °C; IR (nujol) 1750 cm^{-1}; ^1H NMR (CD_3OD): δ 3.15 (s, 3H), 3.4 - 3.8 (m, 2H), 4.2 - 4.6 (m, 2H), 4.8 (bs, 1H, NH), 5.0 (m, 1H); ^{13}C NMR (CD_3OD): δ 37.4, 42.8, 70.8, 75.2; α_D +30.9° (C = 0.7, EtOH).

(5S)-5-(1-Naphthyloxymethyl)oxazolidin-2-one (10a)

To a solution of (9a) (0.97 g; 5 mmol) in benzene:DMF (30 ml; 1:1), Amberlyst A 26 in the 1-naphtholate form (5 g; 3.8 mequiv/g) was added and the suspension was refluxed for 5 h. The resin was then filtered off and washed with methanol (20 ml), the solvent was removed in vacuo and the residue chromatographed on silica gel, using cyclohexane:ethyl acetate (1:1) as the eluting solvent, to give 1.1 g of (10a) (90%), as white crystals: m.p. 149 °C; IR (nujol) 1750 cm^{-1}; ^1H NMR (CD_3OD): δ 3.6 - 4.0 (m, 2H), 4.15 - 4.55 (m, 2H), 4.7 (bs, 1H, NH), 5.15 (m, 1H), 6.8 - 8.25 (m, 7ArH); ^{13}C NMR (CD_3OD): δ 42.5, 69.1, 75.4, 105.2, 121.4, 123.0, 126.0, 126.9, 127.3, 128.4, 135.9, 155.7; α_D +12.2° (c = 0.8; EtOH). Found: C, 68.99; H, 5.38%. $C_{14}H_{13}NO_3$ requires C, 69.12; H, 5.39%.

(2S)-1-(1-Naphthyloxy)-3-aminopropan-2-ol (11a)

To a solution of LiOH (0.48 g; 20 mmol) in H_2O:methanol (10 ml; 9:1), (10a) (1.2 g; 5 mmol) was added and the mixture was refluxed for 3 h. The solution was allowed to reach room temperature and extracted with benzene. After drying (Na_2SO_4) and removal of the solvent, 1 g (95%) of (11a) was obtained as an oil; IR (neat) 3400 cm^{-1}; ^1H NMR (CD_3OD): δ 2.7 - 3.1 (m, 2H), 3.9 - 4.25 (m, 3H), 4.8 (bs, 3H, OH, NH_2), 6.85 - 8.45 (m, 7ArH); ^{13}C NMR (CD_3OD): δ 45.4, 71.4, 71.8, 105.8, 121.3, 122.9, 126.0, 126.9, 127.3, 128.4, 135.9, 155.7; α_D -11° (C = 0.86, EtOH). Found: C, 72.01; H, 6.97%. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96%.

(2S)-1-(1-Naphthyloxy)-3-(isopropylamino)propan-2-ol (1a)

In a solution of (11a) (1.08 g; 5 mmol) in absolute ethanol (10 ml), acetone (0.44 g; 7.5 mmol) was slowly dropped and after 0.5 h $NaBH_4$ (0.37 g; 10 mmol) was directly added. The mixture was stirred for a further 0.5 h, then treated with 1 M HCl (6 ml) and successively with 1 M NaOH (3 ml). Volatiles were removed in vacuo and the residue was chromatographed on silica gel using

ethyl acetate:methanol (9:1) as the eluting solvent, affording 1.17 g of (1a) (90%) as white crystals: m.p. 72 °C; IR (nujol) 3400, 3300, 1590 and 1580 cm^{-1}; ^1H NMR (CD_3OD): δ 1.1 (d, 6H; J = 6 Hz), 2.6 - 3.1 (m, 3H), 4.0 - 4.4 (m, 3H), 4.8 (bs, 2H, OH, NH), 6.7 - 7.8 (m, 7ArH); ^{13}C NMR (CD_3OD): δ 22.5, 22.7, 50.1, 51.0, 69.8, 72.1, 105.9, 121.4, 122.9, 126.0, 126.9, 127.3, 128.4, 135.9, 155.7; α_D -10.14° (c = 0.7; EtOH)(Lit.[7] -10.2° (c = 1.02; EtOH)). Found 74.19; H, 8.17%. $C_{16}H_{21}NO_2$ requires C, 74.1; H, 8.16%.

(1'S*,5R*)-3-(1'Phenyleth-1'-yl)-5-(acetoxymethyl)oxazolidin-2-one (5b)

Prepared as (5a):m.p. 86 °C; ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H; J = 7 Hz), 1.85 (s, 3H), 2.9 (dd, 1H, H_b; J_{ab} = 9 Hz; J_{bc} = 6 Hz), 3.6 (t, 1H, H_a; J_{ab} = 9 Hz; J_{ac} = 9 Hz), 4.1 (m, 2H), 4.65 (m, 1H, H_c), 5.20 (q, 1H; J = 7 Hz), 7.3 (m, 5ArH); ^{13}C NMR ($CDCl_3$) δ 16.4, 20.4, 41.7, 51.4, 64.2, 70.5, 126.9, 127.9, 128.7, 139.5, 156.9, 170.3; α_D -118° (c = 5; $CHCl_3$).

(1'S*,5R*)-3-(1'Phenyleth-1'-yl)-5-(hydroxymethyl)oxazolidin-2-one (6b)

Prepared as (6a): m.p. 113 °C; ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H; J = 7 Hz), 3.0 (dd, 1H, H_b; J_{ab} = 9 Hz; J_{bc} = 6 Hz), 3.5 (t, 1H, H_a; J_{ab} = 9 Hz; J_{ac} = 9 Hz), 3.6 (m, 2H), 3.7 (bs, 1H, OH), 4.55 (m, 1H, H_c), 5.15 (q, 1H; J = 7 Hz), 7.3 (m, 5ArH); ^{13}C NMR ($CDCl_3$): δ 16.8, 41.8, 51.5, 62.6, 74.0, 126.8, 127.7, 128.8, 139.6, 157.8; α_D -104° (c = 1.77; $CHCl_3$).

(5R)-5-(Hydroxymethyl)oxazolidin-2-one (8b)

Prepared as (8a): α_D -29.1° (c = 1; EtOH).

(5R)-5-(Methanesulfonyloxymethyl)oxazolidin-2-one (9b)

Prepared as (9a): α_D -31.8° (c = 0.43; EtOH).

(5R)-5-(Naphthyloxymethyl)oxazolidin-2-one (10b)

Prepared as (10a): α_D -12.1° (c = 0.46; EtOH).

(2R)-1-(1-Naphthyloxy)-3-aminopropan-2-ol (11b)

Prepared as (11a): α_D +10.7° (c = 0.66; EtOH).

(2R)-1-(1-Naphthyloxy)-3-(isopropylamino)propan-2-ol (1b)

Prepared as (1a): α_D +10.2° (c = 0.76; EtOH)(Lit.[7] +10.6° (c = 1.02, EtOH)).

(1'S*,5S*)-3-(1'Phenyleth-1'-yl)-5-(naphthyloxymethyl)oxazolidin-2-one (12a)

To a solution of (4a) (3.3 g; 10 mmol) in benzene (30 ml), Amberlyst A 26 in the naphtholate form (5 g; ~3.8 mequiv/g) was added and the suspension was refluxed for 2 h. The resin was then filtered off and washed with methanol (50 ml). After removal of the solvent, the residue was chromatographed on silica gel using cyclohexane:ethyl acetate (8:2) as the eluting solvent, to yield 3.5 g of (12a) (75%) as an oil; IR (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H; J = 7 Hz), 3.3 (t, 1H, H_b; J = 9 Hz; J = 9 Hz), 3.55 (dd, 1H, H_a; J = 9 Hz; J = 6 Hz), 4.25 (d, 2H; J = 5 Hz), 4.75 (m, 1H, H_c), 5.3 (q, 1H; J = 7 Hz), 6.9 - 8.3 (m, 7ArH); ^{13}C NMR ($CDCl_3$): δ 16.3, 42.3, 51.6, 68.3, 71.0, 104.9, 125.5, 125.6, 126.6, 127.0, 127.5, 128.0, 128.8; α_D +16.6° (c = 1; $CHCl_3$).

(1'S*,5R*)-3-(1'-Phenyleth-1'-yl)-5-(naphthyloxymethyl)oxazolidin-2-one (12b)

Prepared as (12a) from (4b); ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H; J = 7 Hz), 3.2 (dd, 1H, H_b; J = 9 Hz; J = 6 Hz), 3.6 (t, 1H, H_a; J_{ab} = 9 Hz; J_{ac} = 9 Hz), 4.05 (d, 2H; J = 5 Hz), 4.8 (m, 1H, H_c),

5.25 (q, 1H; J = 7 Hz), 6.4 - 8.0 (m, 7ArH); ^{13}C NMR ($CDCl_3$): δ 16.5, 42.1, 51.6, 67.9, 71.2, 104.9, 125.4, 125.6, 126.5, 127.0, 127.3, 127.9, 128.7; α_D -120° (c = 1; $CHCl_3$).

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