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Univocal syntheses of 2- and 3-hydroxymethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine enantiomers

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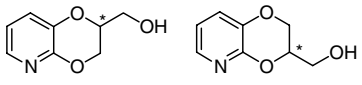
Abstract—The enantiomers of 2- and 3-hydroxymethyl substituted 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine **1** and **2**, important chiral building blocks for the preparation of several biologically active compounds, were synthesized. (*S*)- and (*R*)-**1** were obtained from either one or both the enantiomers of benzylglycerol, while (*S*)- and (*R*)-**2** were obtained from (*R*)- and (*S*)-isopropylideneglycerol, respectively. The novel efficient synthetic strategies, which do not follow routes already reported for the corresponding racemates, ensure very high regioselectivity and maintenance of the enantiomeric purity of the starting materials. The enantiomeric composition of the title compounds was determined by chiral HPLC or NMR. The key intermediate in the synthesis of non-racemic **1**, namely 1-benzyl-2-mesyl-3-tritylglycerol, is a new high melting chiral C_3 synthon, worth considering for its stability, versatility, easy isolation by simple crystallization and, potential of configuration inversion through a simple one-pot reaction sequence.

1. Introduction

The 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine system, often conceived as a 1,4-benzodioxane bioisoster, constitutes the scaffold or pharmacophoric element of many structures of therapeutic agents. Over the course of our research on peptidomimetic farnesyltransferase inhibitors[1] and on α-adrenoceptor ligands[2] bearing such a system in place of a cysteine residue and of a 1,4-benzodioxane nucleus, respectively, we needed to obtain both the enantiomers of 2-hydroxymethyl-2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine **1** and of its regioisomer with the same substituent at the 3-position **2**.



1 **2**

To the best of our knowledge, **1** has never been prepared in optically active form and only two syntheses have been reported for the corresponding racemate.[3,4] According to the literature, the former, which uses 2-chloro-3-pyridinol and 1-acetoxy-3-benzyloxy-2-propanol as the starting material, is relatively long. The latter, where 2-chloro- or 2-nitro-3-pyridinol is condensed with epichlorohydrin to give the respective 3-oxiranylmethoxypyridine and oxirane is successively opened by benzyl alcohol, is not recommended for the synthesis of enantiopure derivatives, due to the risk of racemization deriving from the duplex mechanism of the nucleophile attack on epichlorohydrin. Furthermore, the final cyclization of the resultant 1-benzyloxy-3-(pyridin-3-yloxy)propan-2-ols, 2-nitro or 2-chloro substituted at the pyridine ring, yields the benzyl ether of **1**, via a Smiles rearrangement, always together with the benzyl ether of **2**.[4] Otherwise, this positional isomer can only be the product of the above synthetic route if the ultimate intramolecular cyclization is accomplished under suitable experimental conditions.[4] Syntheses of **2** in optically active form have never been reported, but the two enantiomers have been isolated by preparative HPLC resolution of the racemate on a chiral stationary phase[5] and their absolute configurations established by vibrational circular dichroism.[6] On the contrary, the syntheses of the (*S*)- and (*R*)-forms of the azidomethyl analogue of **2** are known. They were obtained from (*S*)- and (*R*)-2-chloro-3-oxiranylmethoxypyridine, in turn prepared by condensation, under Mitsunobu conditions, of 2-chloro-3-pyridinol with optically active

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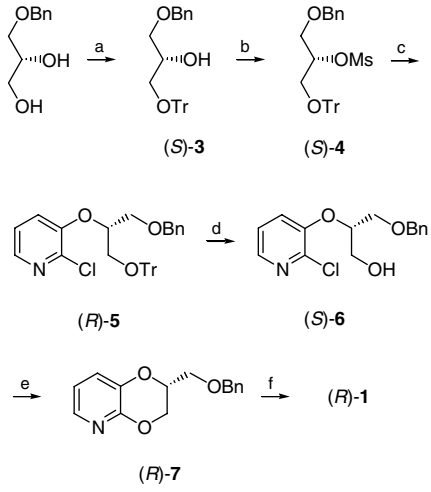
glycidol in place of epichlorohydrin.[7] Though applicable to the preparation of the enantiomers of **1** and **2**, we decided not to exploit either this synthetic route or that from 1-acetoxy-3-benzyloxy-2-propanol[3] and to base our approach on the alternative use of the enantiomeric acetonides, 1-ethers and 1,3-diethers of glycerol thus avoiding both the epoxidic and acetyl intermediates. In particular, the enantiomers of a new chiral C_3 synthon, that is 1-benzyl-2-mesyl-3-tritylglycerol, were advantageously employed as key intermediates in the syntheses of (*S*)- and (*R*)-**1**, herein described together with those of (*S*)- and (*R*)-**2**.

2. Results and discussion

As outlined in Scheme 1, the synthesis of (*R*)-**1** starts from (*R*)-1-benzylglycerol, readily and quantitatively accessible from (*S*)-isopropylideneglycerol by standard methods. The primary hydroxyl group of the diol was tritylated and the resultant diether (*S*)-**3** mesylated to give, in near quantitative yield, (*S*)-1-benzyl-2-mesyl-3-tritylglycerol (*S*)-**4**, a solid intermediate easily isolated by extraction and crystallization from diisopropyl ether. Nucleophilic displacement of mesylate by the sodium salt of 2-chloro-3-pyridinol afforded, with inversion of configuration, (*R*)-1-benzyl-2-(2-chloro-3-pyridinyl)-3-tritylglycerol (*R*)-**5**, which was isolated by simple extraction and directly detritylated by treatment with hydrochloric acid. The successive intramolecular cyclization of the primary alcohol (*S*)-**6** was carried out in dimethoxyethane and in the presence of sodium hydride yielding the (*R*)-isomer of the 2-benzyloxymethyl substituted 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine (*R*)-**7**. Finally, the benzyl group was quantitatively removed by catalytic transfer hydrogenation under microwave irradiation with cyclohexene as the hydrogen donor obtaining (*R*)-**1** as a viscous oil, which solidified upon standing.

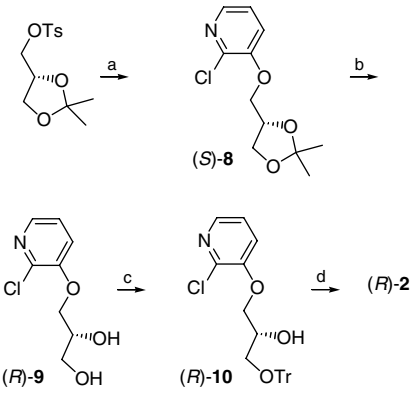


Scheme 1. Reagents and conditions: (a) trityl chloride, Et_3N, *t*-BuOH, 60 °C, 85%; (b) Mesyl chloride, Et_3N, DCM, −10 °C and then room temperature, 91%; (c) 2-Chloro-3-pyridinol, NaH, DMF, reflux, 100%; (d) 10% aq HCl, THF, reflux, 61%; (e) NaH, DME, reflux, 78%; (f) Cyclohexene, Pd/C, MeOH, MW (200 W), 120 °C, 240 s, 94%.

The 85% mean yield of the six synthetic steps resulted in an overall 35% yield of the whole synthesis. Only three of the six steps required chromatographic isolation of the reaction product, namely the tritylation, detritylation and intramolecular cyclization. A 99.3% enantiomeric excess could be attributed to (*R*)-**1** on the basis of the chiral HPLC analysis of the corresponding mesyl ester, quantitatively obtained by treatment of (*R*)-**1** with excess methanesulfonyl chloride and triethylamine in dichloromethane. These data were consistent with 99.7% enantiomeric excess determined for (*S*)-**3** by chiral HPLC analysis according to a previously reported method.[8]

The (*S*)-enantiomer of **1** was synthesized by the same strategy as illustrated in Scheme 1 but starting from (*S*)-1-benzylglycerol. Alternatively, the configuration of (*S*)-**4** was inverted displacing the mesylate by the acetate, hydrolyzing the resultant acetate and finally converting the liberated secondary alcohol into mesylate (*R*)-**4**. Such a three-step conversion was accomplished without purifying the two crude intermediate products; the overall yield was 75%.

As shown in Scheme 2, the reaction sequence for preparing (*R*)-**2** started from the tosyl ester of (*S*)-isopropylideneglycerol and consisted of the following steps: (a) displacement of tosylate by the sodium salt of 2-chloro-3-pyridinol to give (*S*)-**8**; (b) hydrolysis of the cyclic ketal; (c) tritylation of the primary hydroxyl group of the resultant diol (*R*)-**9**; (d) intramolecular cyclization of the secondary alcohol (*R*)-**10** immediately followed by detritylation.



Scheme 2. Reagents and conditions: (a) 2-chloro-3-pyridinol, NaH, DMF, reflux, 90%; (b) 10% aq HCl, 80 °C, 74%; (c) Trityl chloride, Et_3N, *t*-BuOH, reflux, 75%; (d) NaH, DME, reflux and then 10% aq HCl, EtOH, room temperature, 63%.

The 75% mean yield of the four synthetic steps resulted in 32% overall yield of the whole synthesis. One of the four steps, namely the acetonide hydrolysis, did not require chromatographic isolation of the reaction product.

The (*S*)-enantiomer of **2** was prepared by the same synthetic route as illustrated in Scheme 2 but using the tosyl ester of (*R*)-isopropylideneglycerol as a starting material.

In contrast with the previous case of the mesyl esters of (*R*)-**1** and (*S*)-**1**, attempts at determining the enantiomeric excess of (*R*)-**2** and (*S*)-**2** by chiral HPLC analysis of the respective mesylates were not successful. An almost complete, but not baseline resolution of the two enantiomers was achieved only under extreme direct phase HPLC conditions on silica gel coated with cellulose derivatives, such as very polar mobile phases (water saturated near 1:1 ethanol/hexane mixtures) at very low flow rates.[9] Conversely, ^{1}H NMR analysis (300 MHz) in the presence of chiral shift reagents or chiral solvating agents proved to be effective. Addition of Eu(hfc)$_3$ or, better still, of optically active trifluoroanthrylethanol split the CH_3 singlet into two peaks with a chemical shift difference of 4 and 18 Hz, respectively. On this basis, the absence of the methyl signal of the mesyl ester of (*R*)-**1** in the spectrum of the mesyl ester of (*S*)-**1** and vice versa led us to estimate the enantiomeric excess of the two mesylates higher than 98%.

3. Conclusion

In summary, we have reported the synthesis and enantiomeric excess assessment of the (*S*)- and (*R*)-forms of 2- and 3-hydroxymethyl substituted 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine **1** and **2**, important chiral building blocks for the preparation of several biologically active compounds. The new syntheses ensure the maintenance of the enantiomeric purity of the starting materials and, compared to the synthetic strategies already reported for the corresponding racemates, a very high regioselectivity thanks to the unequivocal course of the reactions of the intermediate glycerol mono-, di- and triethers. Further advantages are the efficiency (>30% overall yield), ready availability of the starting materials (1-benzylglycerol and isopropylideneglycerol tosylate) and reasonable number of synthetic steps. Finally, a new high melting chiral C_3 synthon, 1-benzyl-2-mesyl-3-tritylglycerol, distinguishes itself from the other intermediates of these syntheses by its potential due to stability, versatility, easy isolation by simple crystallization and possibility of inverting its configuration through a Walden inversion.

4. Experimental

Melting points were recorded on a Büchi Melting Point B-450 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Bruker 200 (200 MHz) instrument or on a Varian Gemini 300 (300 MHz) instrument. Optical rotations were measured in a 1 dm cell of 1 mL capacity using a Perkin–Elmer 241 polarimeter. HPLC analyses were performed on a Chiralcel OD column (250 × 4.6 mm i.d.) from *Daicel* using a Hitachi 7100 pump, a Hitachi L-7400 UV detector and a Hitachi D-7000 HPLC System Manager software. (*S*)- and (*R*)-glycerol acetonide were prepared by chemical resolution of the racemate as described in the literature[10] and successively transformed into the corresponding tosyl esters or 1-benzylglycerols according to standard procedures.

4.1. (*S*)-1-Benzyl-3-tritylglycerol (*S*)-3

(*R*)-1-Benzylglycerol was added to a stirred mixture of trityl chloride (59.6 g, 214 mmol), triethylamine (32 mL, 230 mmol) and *tert*-butanol (80 mL) at 60 °C under an N_2 atmosphere. After refluxing for 24 h, the mixture was concentrated and the resultant residue chromatographed on silica gel. Elution with cyclohexane/ethyl acetate (80:20) afforded 65.2 g (85%) of (*S*)-**3** as a white solid: mp 72 °C; $[\alpha]_D^{25} = -6.45$ (*c* 5, benzene); ee 99.7% (by HPLC on a Chiralcel OD column; hexane/ethanol/water 90.63:9.06:0.3, v/v/v; 0.2 mL/min; (*S*)-**3**: $k' = 1.05$; (*R*)-**3**: $k' = 0.92$); ^{1}H NMR ($CDCl_3$) δ 2.40 (br s, 1H), 3.20 (m, 2H), 3.58 (m, 2H), 3.98 (m, 1H), 4.55 (s, 2H), 7.20–7.45 (m, 20H).

4.2. (*S*)-1-Benzyl-2-mesyl-3-tritylglycerol (*S*)-4

Mesyl chloride (17.9 mL, 231 mmol) was added dropwise to a solution of (*S*)-**3** (75.6 g, 178 mmol) and triethylamine (34.5 mL, 248 mmol) at −10 °C. After stirring at rt for 3 h, the mixture was added with dichloromethane (100 mL), washed with 1 M HCl, dried and concentrated. The resultant oily residue (109 g) was crystallized from diisopropyl ether (500 mL) yielding 81.4 g (91%) of (*S*)-**4** as a white solid: mp 103 °C; $[\alpha]_D^{25} = -8.8$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.02 (s, 3H), 3.39 (m, 2H), 3.70 (m, 2H), 4.52 (s, 2H), 4.85 (m, 1H), 7.25–7.43 (m, 20H).

4.3. (*R*)-1-benzyl-2-(2-chloro-3-pyridinyl)-3-tritylglycerol (*R*)-5

A solution of 2-chloro-3-pyridinol (1.81 g, 14.0 mmol) in DMF (10 mL) was added to a suspension of 98% NaH (353 mg, 14.7 mmol) in DMF (20 mL) under an N_2 atmosphere. The mixture was heated at 60 °C, added with a solution of (*S*)-**4** (4.39 g, 8.7 mmol) in DMF (20 mL), refluxed for 24 h and concentrated. The residue was treated with water (15 mL) and extracted with cyclohexane (5 × 20 mL). The organic extracts were combined, washed with a saturated aqueous solution of sodium bicarbonate (10 mL) and then with brine (2 × 10 mL), dried and concentrated to give 5.85 g of crude (*R*)-**5**: ^{1}H NMR ($CDCl_3$) δ 3.42 (m, 2H), 3.79 (d, 2H), 4.55 (s, 2H), 4.45–4.62 (m, 1H), 7.10 (dd, 1H), 7.20–7.50 (m, 21H), 8.00 (dd, 1H).

4.4. (*S*)-1-Benzyl-2-(2-chloro-3-pyridinyl)glycerol (*S*)-6

A mixture of (*R*)-**5** (3.1 g, 5.8 mmol) and 10% HCl (20 mL) in THF (30 mL) was refluxed for 12 h. After cooling to room temperature, the precipitate was filtered off and THF evaporated. The acidic aqueous residue was washed with cyclohexane and this latter with 10% HCl. The aqueous phases were combined, made alkaline (pH 9) by the addition of sodium carbonate and extracted with ethyl acetate (2 × 50 mL). The organic extracts were dried and concentrated. The residue was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (60:40) afforded 1.07 g (61%) of (*S*)-**6** as a whitish wax: $[\alpha]_D^{25} = +7.3$ (*c* 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.16 (br s, 1H), 3.75 (d, 2H,

$J = 4.9$ Hz), 3.90 (m, 2H), 4.50 (m, 1H), 4.56 (s, 2H), 7.15 (dd, 1H, $J = 8.4$, 4.7 Hz), 7.30–7.37 (m, 5H), 7.43 (dd, 1H, $J = 8.4$, 1.6 Hz), 8.00 (dd, 1H, $J = 4.7$, 1.6 Hz).

4.5. (*R*)-2-Benzyloxymethyl-2,3-dihydro[1,4]dioxino-[2,3-*b*]pyridine (*R*)-7

A solution of (*S*)-**6** (5.6 g, 19 mmol) in DME (20 mL) was added to a suspension of 98% NaH (480 mg, 19 mmol) in DME (20 mL) under an N_2 atmosphere. The mixture was refluxed for 12 h, concentrated, added with water (100 mL) and extracted with dichloromethane (3×100 mL). The organic phases were combined, washed with water (20 mL), dried and concentrated. The resultant residue (5.8 g) was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (1:1) afforded 3.75 g (78%) of (*R*)-**7**: $[\alpha]_D^{25} = +24.9$ (*c* 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.68 (m, 2H), 4.26 (dd, 1H, $J = 11.3$, 7.3 Hz), 4.35 (m, 1H), 4.47 (dd, 1H, $J = 11.3$, 2.2 Hz), 4.60 (s, 2H), 6.86 (dd, 1H, $J = 7.7$, 4.8 Hz), 7.20 (dd, 1H, $J = 7.7$, 1.5 Hz), 7.33 (m, 5H), 7.81 (dd, 1H, $J = 4.8$, 1.5 Hz).

4.6. (*R*)-2-Hydroxymethyl-2,3-dihydro[1,4]dioxino-[2,3-*b*]pyridine (*R*)-1

A solution of (*R*)-**7** (1 g, 3.9 mmol) in methanol (3.5 mL) was added with 5% Pd/C (120 mg) and cyclohexene (1.5 mL) and irradiated for 4 min in a microwave oven at 200 W and 120 °C. The catalyst was removed by filtration and the filtrate concentrated, dissolved in dichloromethane (10 mL), washed with a saturated solution of sodium bicarbonate (2×10 mL), dried and concentrated again to give 610 mg (94%) of (*R*)-**1** as a viscous oil, which solidified upon standing: mp 91 °C; $[\alpha]_D^{25} = +32.6$ (*c* 0.5, EtOH); ee 99.3% (by HPLC of a sample of the mesyl ester on a Chiralcel OD column; hexane/2-propanol 60:40; 1 mL/min; mesyl ester of (*R*)-**1**: $k' = 7.8$; mesyl ester of (*S*)-**1**: $k' = 11.3$); ^{1}H NMR ($CDCl_3$) δ 3.01 (br s, 1H), 3.89 (m, 2H), 4.30 (m, 2H), 4.49 (m, 1H), 6.87 (dd, 1H, $J = 8.2$, 4.8 Hz), 7.19 (dd, 1H, 1H, $J = 8.2$, 1.7 Hz), 7.79 (dd, 1H, $J = 4.8$, 1.7 Hz).

4.7. (*R*)-1-Benzyl-3-tritylglycerol (*R*)-3

Prepared from (*S*)-1-benzylglycerol as described for (*S*)-**3**: mp 72 °C; $[\alpha]_D^{25} = +6.4$ (*c* 5, benzene); ee 99.6% (by HPLC under the conditions reported for (*S*)-**3**); ^{1}H NMR identical to that of (*S*)-**3**.

4.8. (*R*)-1-Benzyl-2-mesyl-3-tritylglycerol (*R*)-4

Method A: From (*R*)-**3**. The procedure was identical to that described for the conversion of (*S*)-**3** into (*S*)-**4**: mp 103 °C; $[\alpha]_D^{25} = +8.6$ (*c* 1, $CHCl_3$); ^{1}H NMR identical to that of (*S*)-**4**. *Method B*: From (*S*)-**4**. Potassium acetate (29.4 g, 0.3 mol) was added to a solution of (*S*)-**4** (10.7 g, 21.3 mmol) in isobutanol (150 mL). The mixture was refluxed for 20 h. The solvent was evaporated and the residue treated with dichloromethane and water. The organic phase was separated, dried and concentrated to give an oily residue, which was dissolved in acetone (70 mL) and added with 3 M KOH (7 mL). After stirring at room temperature overnight, the solvent was evaporated and the residue treated with dichloromethane and water again. The organic layer was separated, dried and concentrated to give 9.66 g of crude (*R*)-**3**. ^{1}H NMR analysis indicated that the product was unitary and could be directly mesylated without previous chromatographic purification as described for the conversion of (*S*)-**3** into (*S*)-**4**. Crystallization of the crude mesyl ester from diisopropyl ether afforded 8 g (75% of the starting (*S*)-**4**) of (*R*)-**4**: mp 103 °C; $[\alpha]_D^{25} = +8.7$ (*c* 1, $CHCl_3$); ^{1}H NMR identical to that of (*S*)-**4**.

4.9. (*S*)-1-Benzyl-2-(2-chloro-3-pyridinyl)-3-tritylglycerol (*S*)-5

Prepared from (*R*)-**4** as described for (*R*)-**5**: ^{1}H NMR identical to that of (*R*)-**5**.

4.10. (*R*)-1-Benzyl-2-(2-chloro-3-pyridinyl)glycerol (*R*)-6

Prepared from (*S*)-**5** as described for (*S*)-**6**: $[\alpha]_D^{25} = -7.0$ (*c* 0.5, EtOH); ^{1}H NMR identical to that of (*S*)-**6**.

4.11. (*S*)-2-Benzyloxymethyl-2,3-dihydro[1,4]dioxino-[2,3-*b*]pyridine (*S*)-7

Prepared from (*R*)-**6** as described for (*R*)-**7**: $[\alpha]_D^{25} = -24.0$ (*c* 0.5, EtOH); ^{1}H NMR identical to that of (*R*)-**7**.

4.12. (*S*)-2-Hydroxymethyl-2,3-dihydro[1,4]dioxino-[2,3-*b*]pyridine (*S*)-1

Prepared from (*S*)-**7** as described for (*R*)-**1**: $[\alpha]_D^{25} = -31.8$ (*c* 0.5, EtOH); ee 99.2% [by HPLC of a sample of the mesyl ester under the conditions reported for the mesyl ester of (*R*)-**1**]; ^{1}H NMR identical to that of (*R*)-**1**.

4.13. (*S*)-1-(2-Chloro-3-pyridinyl)-2,3-isopropylideneglycerol (*S*)-8

A solution of 2-chloro-3-pyridinol (10 g, 77.2 mmol) in DMF (40 mL) was added dropwise to a stirred suspension of 90% NaH (2.06 g, 77.2 mmol) under N_2 atmosphere. After 30 min, a solution of (*R*)-1-tosyl-2,3-isopropylideneglycerol (22.1 g, 77.2 mmol) was added dropwise. The reaction mixture was heated at 100 °C for 24 h. DMF was evaporated and the residue treated with dichloromethane (80 mL) and water (80 mL). The organic phase was separated, dried and concentrated and the residue purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (70:30) afforded 16.9 g (90%) of (*S*)-**9** as a colourless oil: $[\alpha]_D^{25} = +20.1$ (*c* 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.46 (s, 3H), 3.98–4.23 (m, 4H), 4.45–4.56 (m, 1H), 7.15–7.27 (m, 2H), 8.01 (dd, 1H, $J = 5.0$, 1.7 Hz).

4.14. (*R*)-1-(2-Chloro-3-pyridinyl)glycerol (*R*)-9

A stirred mixture of (*S*)-**9** (16.8 g, 69 mmol) and 10% HCl (100 mL) was heated at 80 °C for 2 h, cooled to

room temperature and, after adjusting the pH to 8 by the addition of 10% NaOH, submitted to continuous extraction with dichloromethane. The organic extract was dried and concentrated to give 10.4 g (74%) of (*R*)-**10** as a white solid: mp 125 °C; $[\alpha]_D^{25} = -3.8$ (*c* 0.5, EtOH); ^{1}H NMR (DMSO-d_6) δ 3.46 (t, 2H, $J =$ 5.7 Hz), 3.81 (m, 1H), 4.00 (dd, 1H, $J = 10.1$, 5.7 Hz), 4.10 (dd, 1H, $J = 10.1$, 5.7 Hz), 4.69 (t, 1H, $J =$ 5.7 Hz), 5.00 (d, 1H, $J = 5.1$ Hz), 7.36 (dd, 1H, $J =$ 8.1, 4.8 Hz), 7.57 (d, 1H, $J = 8.1$ Hz), 7.94 (d, 1H, $J = 4.8$ Hz).

4.15. (*R*)-1-(2-Chloro-3-pyridinyl)-3-tritylglycerol (*R*)-10

A mixture of (*R*)-**10** (5.13 g, 25.2 mmol), trityl chloride (9.8 g, 35 mmol), triethylamine (5.6 mL, 40 mmol) and *tert*-butanol (50 mL) was refluxed for 12 h under an N_2 atmosphere. The solvent was evaporated and the residue treated with ethyl acetate (50 mL) and water (20 mL). The organic phase was separated, washed with water (20 mL), dried and concentrated. The residue was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (60:40) afforded 8.4 g (75%) of (*R*)-**10** as a low melting solid: $[\alpha]_D^{25} = +11.7$ (*c* 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.55 (d, 1H), 3.35–3.50 (m, 2H), 4.10–4.30 (m, 3H), 7.10–7.50 (m, 17H), 8.00 (dd, 1H).

4.16. (*R*)-3-Hydroxymethyl-2,3-dihydro[1,4]dioxino-[2,3-*b*]pyridine (*R*)-2

A solution of (*R*)-**10** (8.2 g, 18.4 mmol) in DME (40 mL) was added to a suspension of 90% NaH (530 mg, 20 mmol) in DME (50 mL) under an N_2 atmosphere. The mixture was refluxed for 12 h and concentrated. The residue was added with 10% HCl (20 mL) and ethanol (25 mL) and the resultant mixture stirred at room temperature for 4 h, washed with dichloromethane (30 mL), made alkaline with 10% NaOH (25 mL) and extracted with ethyl acetate (3×30 mL). The organic extracts were combined, washed with water (30 mL), dried and concentrated. The residue was purified by chromatography on silica gel. Elution with dichloromethane/methanol (95:5) afforded 1.94 g (63%) of (*R*)-**2** as an oil: $[\alpha]_D^{25} = +28.1$ (*c* 0.5, EtOH); ee >98% (by ^{1}H NMR of a sample of the mesyl ester in $CDCl_3$ and in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol); ^{1}H NMR ($CDCl_3$+D_2O) δ 3.88 (dd, 1H, $J = 12.4$, 4.4 Hz), 4.00 (dd, 1H, $J = 12.4$, 4.4 Hz), 4.14 (dd, 1H, $J = 11.7$, 8.1 Hz), 4.33 (d, 1H, $J = 11.7$), 4.42 (m, 1H), 6.88 (dd, 1H, $J = 7.7$, 4.8 Hz), 7.20 (d, 1H, $J = 7.7$ Hz), 7.81 (d, 1H, $J = 4.8$ Hz).

4.17. (*R*)-1-(2-Chloro-3-pyridinyl)-2,3-isopropylideneglycerol (*R*)-8

Prepared from (*S*)-1-tosyl-2,3-isopropylideneglycerol as described for (*S*)-**8**: $[\alpha]_D^{25} = -19.5$ (*c* 0.5, EtOH); ^{1}H NMR identical to that of (*S*)-**8**.

4.18. (*S*)-1-(2-Chloro-3-pyridinyl)glycerol (*S*)-9

Prepared from (*R*)-**8** as described for (*R*)-**9**: mp 124 °C; $[\alpha]_D^{25} = +3.1$ (*c* 0.5, EtOH); ^{1}H NMR identical to that of (*R*)-**9**.

4.19. (*S*)-1-(2-Chloro-3-pyridinyl)-3-tritylglycerol (*S*)-10

Prepared from (*S*)-**9** as described for (*R*)-**10**: $[\alpha]_D^{25} = -11.1$ (*c* 0.5, EtOH); ^{1}H NMR identical to that of (*R*)-**10**.

4.20. (*S*)-3-Hydroxymethyl-2,3-dihydro[1,4]dioxino-[2,3-*b*]pyridine (*S*)-2

Prepared from (*S*)-**10** as described for (*R*)-**2**: $[\alpha]_D^{25} = -27.9$ (*c* 0.5, EtOH); ee >98% (by ^{1}H NMR of a sample of the mesyl ester under the conditions reported for the mesyl ester of (*R*)-**2**); ^{1}H NMR identical to that of (*R*)-**2**.

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