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# Practical Syntheses of [*R*]- and [*S*]-1-Alkylamino-3-aryloxy-2-porpanols from a Single Carbohydrate Precursor[1)]

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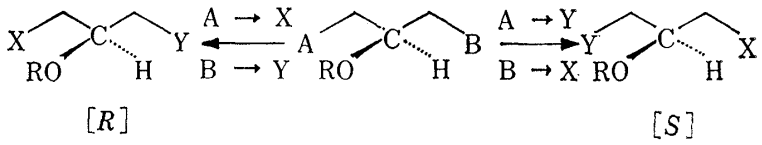
A practical synthetic route to optically active [2*R*]- and [2*S*]-1-alkylamino-3-aryloxy-2-propanols (β-blockers) from [2*R*]-2,3-O-isopropylideneglyceraldehyde ([*R*]-**1**) was developed. Synthesis of the [*S*]-isomers was carried out as follows. Borohydride reduction of [*R*]-**1** in the presence of excess alkylamine followed by alkoxycarbonylation, acid hydrolysis, and cyclization under $K_2CO_3$ catalysis gave [5*S*]-3-alkyl-5-hydroxymethyl-1,3-oxazolidin-2-ones, the tosylates of which were coupled with various phenols then hydrolyzed by alkali treatment to give [*S*]-(−)-β-blockers (*e.g.*, propranolol, carteolol) in satisfactory yields. [*R*]-, [*S*]-, and *rac*-pindolol were synthesized from the corresponding 3-isopropyl-5-(2-methyl-3-nitrophenoxymethyl)-1,3-oxazolidin-2-one by application of the Leimgruber-Batcho method.

**Keywords**——[*R*]- and [*S*]-1-alkylamino-3-aryloxy-2-propanols; optically active β-blockers; propranolol; carteolol; pindolol; carbohydrate precursor; [*R*]-2,3-O-isopropylideneglyceraldehyde; [5*S*]-3-alkyl-5-hydroxymethyl-1,3-oxazolidin-2-ones; Leimgruber-Batcho indole synthesis

Utilization of molecular symmetry is one of the basic strategies in organic synthesis, and is particularly important when the synthesis of an optically active compound is planned. If a compound is available that has intrinsic symmetry and its enantiotopic positions are differently substituted to produce a chiral molecule, it could represent a useful precursor to optically pure specimens of both the [*R*]- and [*S*]-isomers, since the operations A→X and B→Y, and A→Y and B→X schematically shown in Chart 1 would produce [*R*]- and [*S*]-isomer with respect to the original prochiral center, respectively.[2)] Some carbohydrates are economical sources of such a chiral precursor of latent symmetry. An example of such a precursor with a five carbon unit was discussed in the previous paper.[3)]




when RO>X>Y in sequence rule

Chart 1

One of the simplest examples of a right and left differentiated compound having prochiral centers is [2*S*]-2,3-O-isopropylideneglycerol ([*S*]-**2**) which is easily available from 1,2; 5,6-di-O-isopropylidene-D-mannitol by glycol cleavage followed by reduction.[4)] Conversion of [*S*]-**2** to [2*R*]-1-alkylamino-3-aryloxy-2-propanols (β-blockers) is a well-known procedure,[5–7)] which provides a practical route to β-blockers of [*R*]-configuration. Physiologically more active [*S*]-isomers[8)] can be obtained from the enantiomeric [2*R*]-2,3-O-isopropylideneglycerol ([*R*]-**2**) or its *p*-toluenesulfonyl ester ([*S*]-**3**),[6,7)] which were usually obtained by transformation of [*S*]-**2** to [*R*]-**2** or [*S*]-**3**.[6a,9)] However, this procedure is not straight forward, and has little practical value for synthesizing [*S*]-β-blockers.

One of the logical solutions to a practical synthesis of [*S*]-β-blockers from [*S*]-**2** or its precursor, [*R*]-2,3-O-isopropylideneglyceraldehyde ([*R*]-**1**), is readily apparent from a consideration of the scheme shown in Chart 1: first convert the aldehyde group to $-CH_2NHR$ then the protected primary hydroxyl to an aryloxy group. Here we present our approach to [*R*]- and [*S*]-β-blockers from [*R*]-**1** (or strictly from D-mannitol) on the above basis.

Our synthesis of [*R*]-isomers is essentially the same as the previously reported route[5–7] (Chart 2), but with slightly different reaction conditions (*e.g.*, the use of a dipolar aprotic solvent in the coupling reactions....see "Experimental") giving better yields. Thus, three [2*R*]-1-amino-3-aryloxy-2-propanol derivatives, [*R*]-(+)-propranolol ([*R*]-**7a**), [2*R*]-(+)-1-isopropylamino-3-(2-methyl-3-nitrophenoxy)-2-propanol ([*R*]-**7b**), and [*R*]-(+)-carteolol ([*R*]-**8c**) were prepared in 60—80% yields from [*S*]-**2** using 1-naphthol, 6-hydroxy-2-nitrotoluene, and 5-hydroxy-3,4-dihydrocarbostyril. Conversion of [*S*]-**6** to [*R*]-**7** and [*R*]-**8** might partly involve the epoxide intermediate **9**, in addition to direct substitution of the tosyloxy group by the amine, but even so, both reactions should give product of the same configuration.

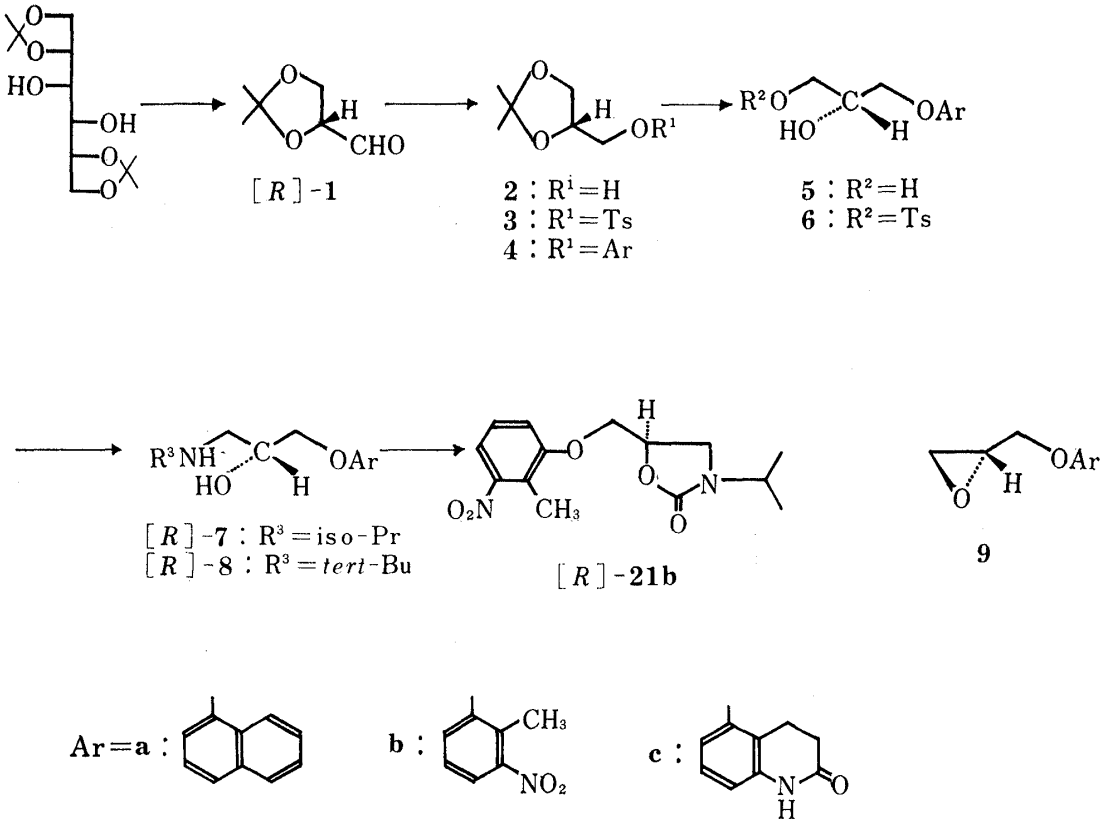



Chart 2. Synthesis of [*R*]-Isomers

For the synthesis of [*R*]-pindolol ([*R*]-**12**), we wished to avoid the use of 4-hydroxyindole as a coupling partner, since 4-hydroxyindole is sensitive to air oxidation, particularly under alkaline conditions.[10] A new route, conversion of [*R*]-**7b** to [*R*]-**12** was therefore exploited (Chart 3): *i.e.*, the indole ring was constructed after introducing the aminopropanol side chain, which acts as a protecting group for the phenolic hydroxyl at the same time. This was practically accomplished as follows. The hydroxyl and amino groups of the side chain in [*R*]-**7b** were first protected by conversion to the cyclic carbamate ([*R*]-**21b**).[11] Heating of [*R*]-**21b** with N,N-dimethylformamide dimethylacetal in N,N-dimethylformamide (DMF) followed by catalytic hydrogenation of the resulting aminostyrene derivative ([*R*]-**10**) over palladized charcoal afforded the indole derivative ([*R*]-**11**) in 72% yield. This procedure,

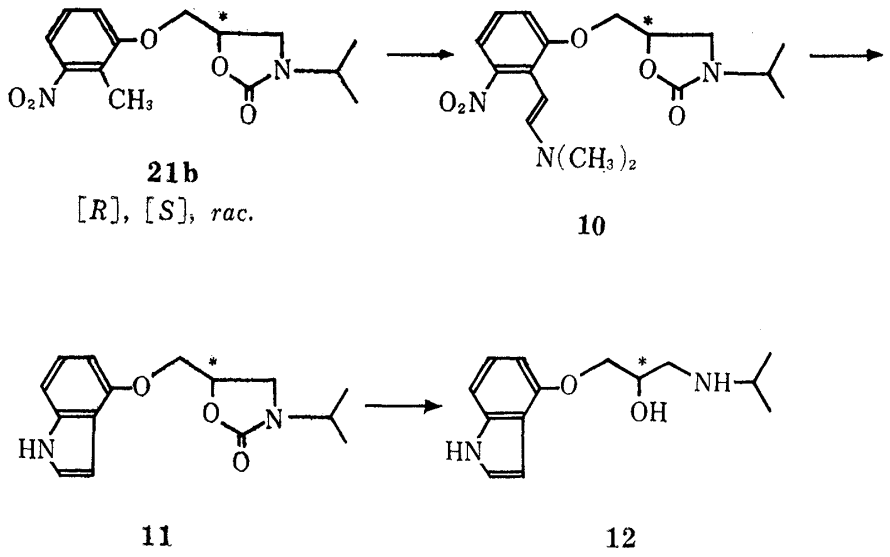



Chart 3. Synthesis of [*R*]-, [*S*]-, and *rac*-Pindolol

known as the Leimgruber-Batcho method,[12] was successfully applied recently in the synthesis of some 4-substituted indole derivatives.[13] The carbamate group was then hydrolyzed with ethanolic hydroxide to furnish [*R*]-(+)-pindolol ([*R*]-**12**). Similarly, transformation of racemic **7b**[14] by the same procedures resulted in racemic pindolol (*rac*-**12**) in 56% overall yield.

Synthesis of [*S*]-isomers was achieved as follows (Chart 4). 1,2; 5,6-Di-O-isopropylidene-D-mannitol was cleaved by the known procedure[4] and the unpurified product ([*R*]-**1**) was directly reduced with sodium borohydride in the presence of excess isopropylamine to provide [2*S*]-O-isopropylidene-3-isopropylamino-1,2-propanediol ([*S*]-**13**) in 70% yield. Conversion of this to the carbamate ([*S*]-**15**) with ethyl chloroformate followed by acid hydrolysis of the isopropylidene group, and treatment of the resulting diol ([*S*]-**17**) with $K_2CO_3$ in DMF, afforded [5*S*]-3-isopropyl-5-hydroxymethyl-1,3-oxazolidin-2-one ([*S*]-**19**) as a single product in 85% yield from [*S*]-**13**. Alternatively, the same compound ([*S*]-**19**) was obtained from [*S*]-**13** in lesser yield by acid hydrolysis followed by cyclization with diethyl (or dimethyl) carbonate. The IR (1715 $cm^{-1}$) and NMR ($\delta$ 3.22—4.70, 1H, $CH_2C\underline{H}(O-)CH_2$) spectral data of [*S*]-**19** were consistent with the structure shown. Formation of the oxazolidinone (**19**) should occur in preference to that of the alternative perhydrooxazinone (**27**) for well known stereochemical reasons.

Similarly, [5*S*]-3-*tert*-butyl-5-hydroxymethyl-1,3-oxazolidin-2-one ([*S*]-**22**) was obtained in 55% yield from 1,2; 5,6-di-O-isopropylidene-D-mannitol by borohydride reduction of [*R*]-**1** in the presence of excess *tert*-butylamine followed by alkoxycarbonylation, acid hydrolysis, and cyclization with $K_2CO_3$.

These optically active [5*S*]-oxazolidinones, [*S*]-**19** and [*S*]-**22**, are the common intermediates for various [*S*]-$\beta$-blockers. Conversion of [*S*]-**19** to the tosylate ([*S*]-**20**) followed by coupling with the sodium salts of phenols (ArONa) in DMF yielded the O,N-protected $\beta$-blockers of [*S*]-form, [*S*]-**21a** and [*S*]-**21b**, in 69% and 84% yields, respectively. Similarly the *tert*-butyl derivative ([*S*]-**22**), on reaction with the sodium salt of 5-hydroxy-3,4-dihydrocarbostryril, gave [*S*]-**24c** in 32% yield.

Alkaline hydrolysis of [*S*]-**21a** and [*S*]-**24c** gave the desired [*S*]-$\beta$-blockers, [*S*]-(—)-propranolol ([*S*]-**7a**) and [*S*]-(—)-carteolol ([*S*]-**8c**), respectively.

Conversion of [*S*]-**21b** to [*S*]-(—)-pindolol ([*S*]-**12**) was accomplished in a manner similar to that described for the [*R*]-isomer (Chart 3).

If the above coupling reaction proceeds through the intermediate **28**, the resulting product could racemize to some degree. However, the formation of such a quaternary carbamate

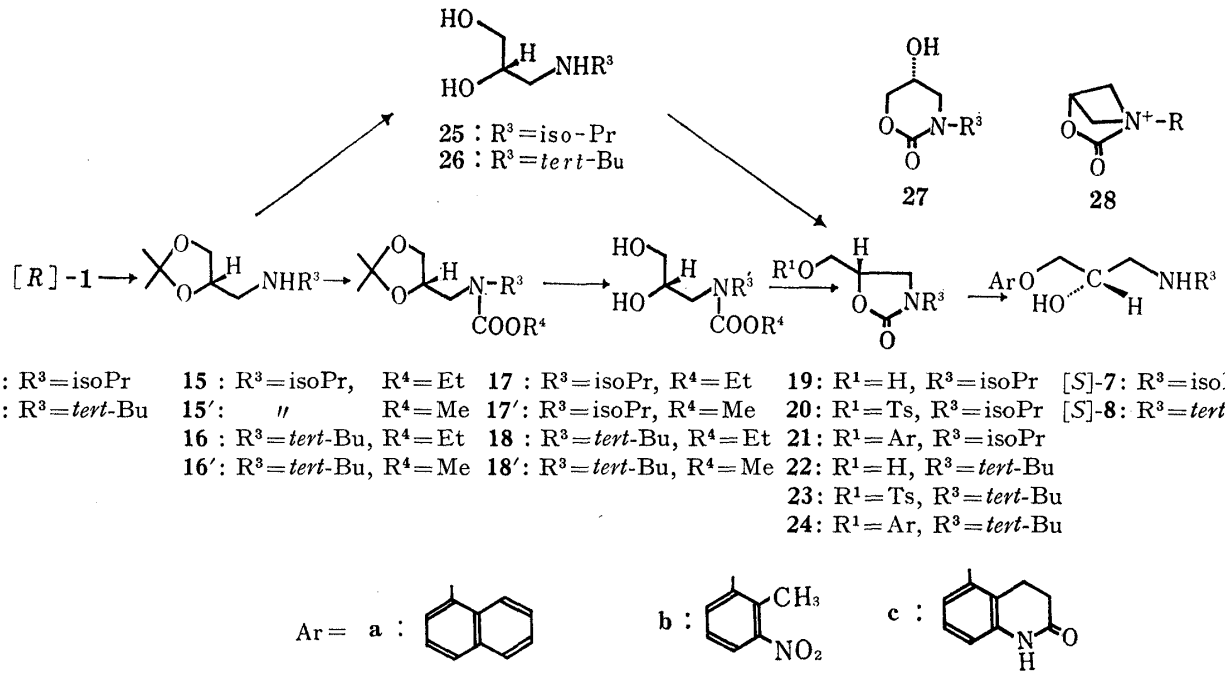



Chart 4. Synthesis of [*S*]-Isomers

seems highly improbable and the product obtained had sufficient optical activities, comparable in magnitude with those of the [*R*]-isomers but with different sign.

The pharmacological actions of the above synthesized [*R*]- and [*S*]-β-blockers are now under investigation by Prof. Gomi's group in our Faculty.

## Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage mp apparatus, and are uncorrected. Infrared (IR) spectra were taken in KBr discs with a Jasco IR-G spectrometer and are given in $cm^{-1}$. $^1H$-Nuclear magnetic Resonance (NMR) spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a JNM-PMX-60 (60 MHz, indicated in parentheses) or a JEOL FX-100 (100 MHz) spectrometer. Optical rotations were measured with a Jasco DIP-SL automatic polarimeter. High resolution mass spectra were taken with a Hitachi M-80 machine. Wakogel C-200 (silica gel) was used for column chromatography. For thin layer chromatography (TLC), Kieselgel $60F_{254}$ precoated plates were used and spots were observed by spraying 1% $Ce(SO_4)_2$ in 10% $H_2SO_4$ or Ehrlich reagent followed by heating at 100°C until coloration appeared. All organic extracts were dried over $Na_2SO_4$ before concentration. Identities were confirmed by TLC, IR, and NMR comparisons with appropriate authentic samples.

**[2*S*]-(+)-1,2-O-Isopropylideneglycerol (2)**——This was prepared from 1,2; 5,6-di-O-isopropylidene-D-mannitol in 50—60% yield by $Pb(OAc)_4$[4] or $NaIO_4$[15] oxidation followed by $NaBH_4$ reduction. Colorless liquid, bp 50°/3 mmHg. $[\alpha]_D^{17}$ +12.6° (neat, $d$=1.0588) (lit.[4b] $[\alpha]_D$ +13.9°).

**[2*R*]-(−)-3-Tosyloxy-1,2-propanediol Acetonide (3)**——This was prepared by tosylation of **2** in 87.7% yield. Colorless oil, $[\alpha]_D^{17}$ −3.5° ($c$=8.5, EtOH) (lit.[4b] $[\alpha]_D$ −4.6° ($c$=13, EtOH)).

**[2*R*]-3-(2-Methyl-3-nitrophenoxy)-1,2-propanediol (5b)**——6-Hydroxy-2-nitrotoluene (16.11 g) was dissolved in 1 N methanolic NaOMe (90.24 ml), then the solvent was evaporated off. The dried Na salt and [2*R*]-tosylate **3** (21.49 g) in DMF (50 ml) were heated at 140°C for 2 h under stirring. The cooled mixture was poured into water and the whole was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 2% NaOH and water, dried, and concentrated. The residue was passed in $CHCl_3$ through a short column of silica gel (4×5 cm) and the eluate was concentrated to give **4** as a gum. NMR (60 MHz) $\delta$: 1.38, 1.44 (each 3H, s, $CH_3$×2), 2.35 (3H, s, Ar–$CH_3$), 3.65—4.65 (5H), 6.80—7.50 (3H, Ar–H).

This gum was dissolved in EtOH (12 ml), and the solution was added in one portion to a warm (50°C) mixture of 1% HCl (5 ml) and EtOH (5 ml). The whole was stirred for 30 min at 50°C, then neutralized with Amberlite IRA-400 ($HCO_3^-$ form) and filtered. The resin was washed with EtOH. Concentration of the combined filtrates and crystallization of the residue from benzene gave the diol **5b**, mp 117.5—118°C as pale yellow needles (16.38 g, 96% from 3). $[\alpha]_D^{22}$ −16.0° ($c$=1.5, MeOH). IR: 3300, 1607, 1530. NMR ($CDCl_3$+DMSO-$d_6$, 60 MHz) $\delta$: 2.33 (3H, s, Ar–$CH_3$), 3.43—3.92 (3H), 3.92—4.26 (2H), 6.97—7.43 (3H,

Ar–H). *Anal.* Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.83; H, 5.78; N, 6.12.

**[2*R*]-3-(1-Naphthyloxy)-1,2-propanediol (5a)**——This was prepared from 1-naphthol (2.02 g) and [2*R*]-tosylate 3 (4.0 g) in 51% yield as described for **5b**. It crystallized in colorless prisms from EtOH, mp 115—116°C (lit.[6a] mp 109—111°C).

**[2*R*]-3-(2-Oxo-1,2,3,4-tetrahydro-5-quinolyloxy)-1,2-propanediol (5c)**——This was prepared from 5-hydroxy-3,4-dihydrocarbostyril and [2*R*]-tosylate 3 in 74% yield as described for **5b**. It crystallized in colorless needles from EtOH, mp 199—200.5°C (lit.[7] mp 191—192°C).

**[2*R*]-1-Isopropylamino-3-(2-methyl-3-nitrophenoxy)-2-propanol ([R]-7b)**——i) The monotosylate **6b**: *p*-TsCl (5.42 g) in $CH_2Cl_2$ (12 ml) was added slowly to a solution of the diol **5b** (4.32 g) in pyridine (25 ml) and $CH_2Cl_2$ (25 ml) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with $CH_2Cl_2$, then the organic layer was washed with 5% NaOH and water, dried, and concentrated. Chromatography of the residue with benzene gave the ditosylate (3 g), as pale yellow leaflets from *n*-hexane–$CH_2Cl_2$, mp 104—105°C. IR: 1600, 1525. NMR $\delta$: 2.09, 2.42, 2.44 (each 3H, s, Ar–C$\underline{H}_3\times3$), 4.13—4.27 (4H), 4.88—4.98 (1H), 6.86—7.79 (11H, Ar–H).

Further elution with $CH_2Cl_2$ gave the monotosylate **6b**, as a pale yellow gum, 5.19 g (71.7%). NMR (60 MHz) $\delta$: 2.17, 3.36 (each 3H, s, Ar–C$\underline{H}_3\times2$), 3.97—4.43 (5H), 6.79—7.86 (7H, Ar–H).

ii) The Isopropylamino Derivative **7b**: The monotosylate **6b** (5.10 g) and an excess of isopropylamine (10 ml) in toluene (7 ml) were heated in a sealed tube for 10 h at 130°C (bath temp.). The mixture was concentrated *in vacuo* and the brown residue was shaken with 1 N HCl and ether. The aqueous layer was made alkaline with 5 N NaOH and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give [*R*]-**7b**, mp 113—115°C, pale yellow prisms from EtOH (3.65 g, quantitative yield). $[\alpha]_D^{17}$ +5.26° ($c$=1.0, $CHCl_3$). IR: 3250, 1607, 1525. NMR (60 MHz) $\delta$: 1.08 (6H, d, $J$=6.8 Hz, –CH(C$\underline{H}_3$)$_2$), 2.33 (3H, s, Ar–C$\underline{H}_3$), 2.66—3.10 (3H), 3.83—4.17 (3H), 6.86—7.46 (3H, Ar–H). *Anal.* Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.07; H, 7.52; N, 10.23.

**[*R*]-(+)-Propranolol ([R]-7a)**——This was prepared from **5a** in 58.8% yield *via* the monotosylate **6a**, mp 128—131°C as described for **7b**. It crystallized in colorless needles from cyclohexane, mp 70—73°C. $[\alpha]_D^{15}$ +8.6° ($c$=1, EtOH). The hydrochloride crystallized in colorless needles from *n*-propanol, mp 201°C (lit.[6a] mp 188—189°C).

**[*R*]-(+)-Carteolol ([R]-8c)**——This was prepared from **5c** in 51.3% yield *via* the monotosylate **6c**, mp 120—122°C (lit.[7] 118—119°C), as described for **7b**, but with the use of *tert*-butylamine instead of isopropylamine. The hydrochloride crystallized in colorless needles from *n*-propanol, mp 243—245°C (dec.). $[\alpha]_D^{16}$ +13.9° ($c$=1, $H_2O$) (lit.[7] mp 238—240°C (dec.), $[\alpha]_D^{22}$ +11.6° ($c$=2.1 in $H_2O$).

**[5*R*]-3-Isopropyl-5-(2-methyl-3-nitrophenoxymethyl)-oxazolidin-2-one ([*R*]-21b)**——[*R*]-**7b** (1.6 g), dimethyl carbonate (0.8 g), and triethylamine (0.6 g) in DMF (4 ml) were heated in a sealed tube for 3 h at 130°C (bath temp.). The mixture was concentrated *in vacuo* and the residue was dissolved in benzene (15 ml). The solution was washed with 1 N HCl and water, dried, and concentrated. Crystallization of the residue from benzene–ether gave [*R*]-**21b**, mp 136—137°C, as colorless plates, 1.5 g (85% yield). IR: 1735, 1720. NMR (60 MHz) $\delta$: 1.13 (6H, d, $J$=6.8 Hz, –CH(C$\underline{H}_3$)$_2$), 2.25 (3H, s, Ar–C$\underline{H}_3$), 3.25—4.40 (5H), 4.52—5.06 (1H, m, –CH$_2$C$\underline{H}$(O–)CH$_2$–), 6.75—7.52 (3H, Ar–H).

***rac*-3-Isopropyl-5-(2-methyl-3-nitrophenoxymethyl)-oxazolidin-2-one (*rac*-21b)**——This was prepared from rac-**7b**[14] as described above, mp 107—111°C. IR: 1725 (broad). Its NMR spectrum was superimposable on that of [*R*]-**21b**.

**[2*S*]-O-Isopropylidene-3-isopropylamino-1,2-propanediol ([*S*]-13)**——Lead tetraacetate (36 g) was added slowly to a stirred solution of 1,2; 5,6-di-O-isopropylidene-D-mannitol (16 g) in AcOEt (200 ml) and the mixture was stirred overnight at room temperature. After decomposition of the excess reagent with ethyleneglycol (3—4 ml), the mixture was applied to a column of silica gel (5.5×8 cm) and eluated with $CHCl_3$. The combined AcOEt and $CHCl_3$ eluates, on concentration, gave crude [*R*]-**1**.

Isopropylamine (55 g) was added dropwise to a stirred solution of crude [*R*]-**1** in EtOH (50 ml) at 0°C. The mixture was stirred for 30 min, then $NaBH_4$ (2.9 g) was added portionwise under cooling. After standing for 12 h, the mixture was diluted with $CHCl_3$ (150 ml), applied to a short column of silica gel (4.5×5 cm) and eluted with $CHCl_3$. The combined eluates, on concentration, yielded a pale yellow oil. Vacuum distillation of this oil afforded [*S*]-**13** (14.6 g, 70%), bp 36.6°C/1 mmHg. $[\alpha]_D^{17}$ −2.05° ($c$=11.2, EtOH). IR (neat): 1660. NMR $\delta$: 1.06 (6H, d, $J$=6.8 Hz, –CH(C$\underline{H}_3$)$_2$), 1.35, 1.41 (each 3H, s, C(C$\underline{H}_3$)$_2$), 2.63—2.86 (3H), 3.52—3.70 (1H), 3.95—4.30 (2H). MS: Calcd for $C_7H_{13}NO_3$: 173.1414. Found: M$^+$ $m/z$ 173.1424.

**[2*S*]-O-Isopropylidene-3-*tert*-butylamino-1,2-propanediol ([*S*]-14)**——Method A: The *tert*-butylamino derivative was prepared in 65% yield in a manner similar to that described above, but using *tert*-butylamine instead of isopropylamine. It was a colorless oil, bp 53°C/1 mmHg. IR (neat): 1667. NMR: $\delta$ 1.10 (9H, s, –C(C$\underline{H}_3$)$_3$), 1.35, 1.41 (each 3H, s, C(C$\underline{H}_3$)$_2$), 2.62—2.72 (2H), 3.56—3.71 (1H), 3.93—4.24 (2H). MS: Calcd for $C_{10}H_{21}NO_2$: 187.1570. Found: M$^+$ $m/z$ 187.1563.

Method B: A mixture of 1,2; 5,6-di-O-isopropylidene-D-mannitol (18 g) in MeOH (100 ml), $NaIO_4$ (21.01 g) in $H_2O$ (100 ml), and 5% $NaHCO_3$ aq. (22.5 ml) was stirred at 0°C for 1 h, then *tert*-butylamine (75.37 g) was added and stirring was continued for a further 1 h. $NaBH_4$ (5.33 g) was added to the resulting solution and the mixture was stirred overnight at room temp. After dilution with MeOH (50 ml), the mixture was

filtered with the aid of Hyflo-Supercel and the filtrate was concentrated. Benzene was added to the residue and water was removed azeotropically by distillation. The residue was dissolved in ether. The solution was dried and concentrated, and the residue was distilled *in vacuo* to give [*S*]-**14** as a colorless oil (11 g, 42.8%). bp 60°C/5 mmHg. This was identical (IR and NMR) with the specimen obtained above.

**[5*S*]-5-Hydroxymethyl-3-isopropyl-oxazolidin-2-one** ([*S*]-**19**)——Ethyl chloroformate (2.08 g, 1.1 eq. mol), followed by $K_2CO_3$ (2.90 g, 1.2 eq. mol) in $H_2O$ (10 ml), was added dropwise at 0°C to a stirred solution of [*S*]-**13** (3.0 g) in $H_2O$ (6 ml) and the mixture was stirred for 1 h, then extracted with ether (150 ml). The ethereal layer was washed with sat. NaCl solution (50 ml×2) and water (50 ml×2), then concentrated to leave the N-ethoxycarbonyl derivative **15** as an oil (4.28 g, quantitative yield). IR ($CHCl_3$): 1675. NMR (60 MHz): $\delta$ 1.20 (6H, d, $J$=6.8 Hz, $-CH(CH_3)_2$), 1.27 (3H, t, $J$=6.8 Hz, $CH_2CH_3$), 1.37, 1.41 (each 3H, s, $C(CH_3)_2$), 3.17—4.40 (8H).

The ethyl carbamate **15** (4.25 g) in 80% AcOH (50 ml) was heated under reflux for 4 h. Removal of the solvent by evaporation *in vacuo* left the diol **17** as an oil.

The diol **17** and $K_2CO_3$ (0.3 g) in DMF (30 ml) were heated at 140°C for 6 h under an argon atmosphere, then concentrated *in vacuo*. Extraction of the residue with $CHCl_3$ and passage of the extract through a short column of a silica gel gave the oxazolidin-2-one [*S*]-**19**, mp 55—56°C, as colorless needles from ether (2.11 g, 76%). $[\alpha]_D^{21}$ +57.12° ($c$=1.17, $CHCl_3$). IR: 3370, 1715 (broad). NMR: $\delta$ 1.18 (6H, d, $J$=6.8 Hz, $-CH(CH_3)_2$), 3.30—4.20 (5H), 4.22—4.70 (1H). MS: Calcd for $C_7H_{13}NO_3$: 159.0894. Found: $M^+$ $m/z$ 159.0897.

**[5*S*]-5-Hydroxymethyl-3-*tert*-butyl-oxazolidin-2-one** ([*S*]-**22**)——Method A: Ethyl chloroformate (2.95 g), followed by $K_2CO_3$ (4.09 g) in water (5 ml), was added dropwise at 5°C to a stirred solution of the *tert*-butylamino derivative **14** (4.62 g) in acetone–water (1: 1, 6 ml), and the mixture was stirred vigorously for 30 min, then extracted with ether (50 ml×3). The ethereal layer was washed with sat. NaCl solution and water, dried, and concentrated to give the N-ethoxycarbonyl derivative **16** as an oil, bp 120°C/2 mmHg (5.49 g, 93%). IR ($CHCl_3$): 1680. NMR (60 MHz): $\delta$ 1.24 (3H, t, $J$=7 Hz, $-CH_2CH_3$), 1.33, 1.39 (each 3H, s, $C(CH_3)_2$), 1.40 (9H, s, $-C(CH_3)_3$), 4.07 (2H, q, $J$=7 Hz, $-CH_2CH_3$), 3.20—4.30 (5H).

A solution of **16** (3.24 g) in EtOH (3 ml) was added as a single portion to a mixture of 1% HCl (5 ml) and EtOH (5 ml) at 50°C, and the mixture was stirred for 5 min, then neutralized to pH~7 by adding Amberlite IRA-400 ($HCO_3^-$ form) and filtered. The resin was washed with EtOH. Concentration of the combined filtrate and washings gave the residue, from which water was completely removed azeotropically by distillation with benzene to leave the diol **18** as a colorless oil (2.34 g, 85.4%). IR ($CHCl_3$): 3350, 1680. NMR (60 MHz): $\delta$ 1.27 (3H, t, $J$=7 Hz, $CH_2CH_3$), 1.40 (9H, s, $C(CH_3)_3$), 3.30—4.40 (5H), 4.12 (2H, q. $J$=7 Hz, $-CH_2CH_3$).

The diol **18** (2.30 g) and $K_2CO_3$ (2.0 g) in DMF (50 ml) were heated at 120°C for 8 h under an argon atmosphere. The cooled mixture was filtered and the filtrate was concentrated to dryness to give the residue, which was chromatographed. Elution of the column with $CHCl_3$ and $CHCl_3$–MeOH (10: 1) gave the oxazolidin-2-one [*S*]-**22**, mp 83—84°C, colorless leaflets from ether–*n*-hexane (1.03 g, 57%). $[\alpha]_D^{16}$ +47.8° ($c$=1, $CHCl_3$). IR: 3400, 1725 (broad). NMR: $\delta$ 1.39 (9H, s, $C(CH_3)_3$), 3.43—3.94 (4H), 4.36—4.56 (1H, $-CH_2CH(O-)CH_2-$). *Anal.* Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.77; N, 8.07. Found: C, 55.48; H, 8.73; N, 8.09.

Method B: The amine **14** was converted to the N-methoxycarbonyl derivative **16′** in 95% yield in a manner similar to that described above, but with the use of methyl chloroformate. IR ($CHCl_3$): 1685. NMR (60 MHz): $\delta$ 1.44 (9H, s, $C(CH_3)_3$), 3.61 (3H, s, $COOCH_3$), 3.33—4.27 (5H).

Compound **16′** was hydrolyzed by 1% HCl–EtOH as described above to give the diol **18′** in quantitative yield.

Compound **18′** was converted to the oxazolidin-2-one [*S*]-**22**, mp 83—84°C, in 88.8% yield in a manner similar to that described in Method A. This product was identical (IR, NMR, and mixed mp) with the compound obtained in Method A.

**[5*S*]-3-Isopropyl-5-*p*-toluenesulfonyloxymethyl-oxazolidin-2-one** ([*S*]-**20**)——The oxazolidinone derivative [*S*]-**19** (1.54 g) and *p*-toluenesulfonyl chloride (1.2 eq. mol) in pyridine (15 ml)-$CH_2Cl_2$ (15 ml) were stirred overnight at room temperature. The mixture was poured into ice-water, extracted with $CHCl_3$, and the extract was washed with 10% $NaHCO_3$ and water, dried, and concentrated. Passage of the residue in $CH_2Cl_2$ through a short column (3×4 cm) of Florisil gave the O-tosyl derivative [*S*]-**20**, mp 79—80°C, as colorless leaflets from ether (2.99 g, 98.5%). $[\alpha]_D^{21}$ +40.8° ($c$=0.86, $CHCl_3$). IR: 1735. NMR: $\delta$ 1.15 (6H, d, $J$=6.8 Hz, $-CH(CH_3)_2$), 2.46 (3H, s, Ar–$CH_3$), 3.27—3.68 (2H, $-CH_2N$), 3.93—4.20 (3H, $CH(CH_3)_2$ and TsO–$CH_2-$), 4.55—4.74 (1H, m, $CH_2CH(O-)CH_2$), 7.37, 7.79 (each 2H, d, $J$=8.3 Hz, Ar–H). *Anal.* Calcd for $C_{14}H_{19}NO_5S$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.58; H, 6.39; N, 4.37.

**[5*S*]-3-*tert*-Butyl-5-*p*-toluenesulfonyloxymethyl-oxazolidin-2-one** ([*S*]-**23**)——The oxazolidinone [*S*]-**22** (252 mg) in pyridine (3 ml)–$CH_2Cl_2$ (6 ml) was tosylated with *p*-toluenesulfonyl chloride (229 mg) and worked up as described above to give the tosylate [*S*]-**23**, mp 97—98°C, colorless needles from ether (351 mg, 73.8%). $[\alpha]_D^{17}$ +27.5° ($c$=1, $CHCl_3$). IR: 1742, 1725, 1595. NMR: $\delta$ 1.36 (9H, s, $C(CH_3)_3$), 2.46 (3H, s, Ar–$CH_3$), 3.38—3.77 (2H, m, $-CH_2N$), 4.09—4.12 (2H, TsO–$CH_2-$), 4.30—4.70 (1H, m, $CH_2CH(O-)CH_2$), 7.36, 7.80 (each 2H, d, $J$=8.3 Hz, Ar–H). *Anal.* Calcd for $C_{15}H_{21}NO_5S$: C, 55.04; H, 6.47; N, 4.28. Found: C, 54.90; H, 6.52; N, 4.09.

**[5*S*]-3-Isopropyl-5-(1-naphthyloxymethyl)-oxazolidin-2-one** ([*S*]-**21a**)——1-Naphthol (0.375 g) was converted to the Na salt by treatment with 0.1 N NaOMe (0.14 g) in MeOH (11 ml). The dried Na salt and the

tosyl derivative [*S*]-**20** (0.626 g) in DMF (5 ml) were heated with stirring for 8 h at 120°C under an argon atmosphere. After cooling, the mixture was concentrated *in vacuo* and the residue was extracted with $CH_2Cl_2$. The extract was washed with 1 N NaOH and water, dried, and concentrated to give [*S*]-**21a**, mp 128—129°C, colorless leaflets from ether (400 mg, 70%). $[\alpha]_D^{17}$ +4.2° ($c$=0.75, $CHCl_3$). IR: 3040, 1730. NMR: $\delta$ 1.23 (6H, d, $J$=6.8 Hz, $-CH(C\underline{H}_3)_2$), 3.48—3.82 (2H), 4.00—4.34 (3H), 4.76—5.08 (1H), 6.72—8.24 (6H, Ar–H). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.53; H, 6.73; N, 4.95.

[*S*]-(−)-**Propranolol** ([*S*]-**7a**)——The carbamate [*S*]-**21a** (250 mg) and NaOH (0.5 g) in $H_2O$–EtOH (2: 1, 6 ml) were heated under reflux for 7 h. Evaporation of EtOH from the mixture and extraction with $CHCl_3$ yielded a gum after usual work-up. Crystallization of this product from *n*-hexane–ether gave [*S*]-(−)-propranolol [*S*]-**7a** as colorless needles, mp 72—73°C (200 mg, 88%). $[\alpha]_D^{15}$ −9.1° ($c$=1, EtOH). The IR and NMR spectra were superimposable on those of the [*R*]-isomer. The hydrochloride, mp 200—201°C, was obtained as colorless needles from *n*-propanol (lit.[6a] mp 188—190°C).

[5*S*]-**3-Isopropyl-5-(2-methyl-3-nitrophenoxymethyl)-oxazolidin-2-one** ([*S*]-**21b**)——6-Hydroxy-2-nitrotoluene (199 mg) was converted to the Na salt by treatment with an eq. amount of NaOMe in MeOH (5 ml). The dried Na salt and [*S*]-**20** (313 mg) in DMF (15 ml) were stirred at 120°C for 10 h and worked up as described above. Crystallization of the product from benzene–ether gave [*S*]-**21b**, mp 138—139°C, as colorless needles (250 mg, 85%). $[\alpha]_D^{19}$ +9.9° ($c$=1, $CHCl_3$). The IR and NMR spectra were superimposable on those of the [*R*]-isomer [*R*]-**21b** described above. *Anal.* Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.17; N, 9.52. Found: C, 57.40; H, 6.25; N, 9.65.

[5*S*]-3-*tert*-**Butyl-5-(2-oxo-1,2,3,4-tetrahydro-5-quinolyloxymethyl)-oxazolidin-2-one** ([*S*]-**24c**)——The tosylate [*S*]-**23** (351 mg) and the Na salt of 5-hydroxy-3,4-dihydrocarbostyril (1.3 mol eq.) in DMF (5 ml) were stirred at 110°C for 5 h, then concentrated to dryness, and the residue was dissolved in $CHCl_3$. The solution was washed with 1 N NaOH and water, dried, and concentrated. Crystallization of the residue gave the carteolol carbonate [*S*]-**24c**, mp 199—200°C, as colorless needles from ether (193 mg, 43%). $[\alpha]_D^{16}$ +12.2° ($c$=1, $CHCl_3$). IR: 1738, 1672, 1601. NMR: $\delta$ 1.42 (9H, s, $C(C\underline{H}_3)_3$), 2.46—2.68 (2H), 2.84—3.04 (2H), 3.48—3.88 (2H), 4.06—4.16 (2H), 4.52—4.90 (1H), 6.45, 6.54 (each 1H, d, $J$=8.0 Hz, Ar–H), 7.13 (1H, t, $J$=8.0 Hz, Ar–H). *Anal.* Calcd for $C_{17}H_{22}NO_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.05; H, 6.98; N, 8.71.

[*S*]-(−)-**Carteolol** ([*S*]-**8c**)——The carteolol carbonate [*S*]-**24c** (190 mg) was hydrolyzed as described for [*S*]-**7a**. The gummy product (120 mg, 67%) [IR: 3350, 3210, 1670, 1601; NMR: $\delta$ 1.13 (9H, s, $C(C\underline{H}_3)_3$)] was converted to the hydrochloride, which crystallized in colorless needles from *n*-propanol, mp 242—244°C, $[\alpha]_D^{16}$ −14.3° ($c$=1, $H_2O$) (lit.[7] mp 237—239°C, $[\alpha]_D^{22}$ −11.0°, $c$=2.0 in $H_2O$). The IR and NMR spectra of [*S*]-**8c** were superimposable on those of the [*R*]-isomer.

[5*R*]-**3-Isopropyl-5-(4-indolyloxymethyl)-oxazolidin-2-one** ([*R*]-**11**)——The oxazolidin-2-one [*R*]-**21b** (720 mg), N,N-dimethylformamide dimethylacetal (0.9 g), and triethylamine (2 drops) in DMF were stirred in a sealed tube at 130°C for 3 h. After cooling, the dark-red mixture was concentrated to dryness and the residue was dissolved in $CH_2Cl_2$ (60 ml). This solution was hydrogenated over 5% Pd-C (0.5 g) for 2 h, then the mixture was filtered, and the catalyst washed with $CH_2Cl_2$. The combined filtrate and washings were washed with 5% HCl and water, dried, and concentrated to give [*R*]-**11**, which crystallized in colorless prisms from AcOEt, mp 160—161°C. Yield, 470 mg, 70%. $[\alpha]_D^{17}$ −4.2° ($c$=1, $CHCl_3$). IR: 1732, 1720. NMR: $\delta$ 1.22 (6H, d, $J$=6.8 Hz, $-CH(C\underline{H}_3)_2$), 3.48—3.80 (2H), 3.96—4.32 (3H), 4.72—5.02 (1H, m, $CH_2C\underline{H}$-(O–)$CH_2$), 6.40—6.62, 6.92—7.13 (5H, Ar–H), 8.20—8.40 (broad s, NH). *Anal.* Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.55; H, 6.58; N, 10.26.

[5*S*]-**3-Isopropyl-5-(4-indolyloxymethyl)-oxazolidin-2-one** ([S]-**11**)——The [*S*]-oxazolidin-2-one [*S*]-**21b** was converted to [*S*]-**11** in a manner similar to that described above (yield, 73%), mp 159—161°C, colorless prisms from AcOEt. $[\alpha]_D^{17}$ +4.5° ($c$=1, $CHCl_3$). The IR and NMR spectra were superimposable on those of the [*R*]-isomer.

***rac*-3-Isopropyl-5-(4-indolyloxymethyl)-oxazolidin-2-one** (***rac*-11**)——The *rac*-oxazolidin-2-one *rac*-**21b** was converted to *rac*-**11** in a manner similar to that described for the [*R*]-isomer (yield, 75%). mp 181—182°C. IR: 1734, 1720. Its TLC behavior and NMR signals were identical with those of the [*R*]-isomer.

[*R*]-**4-(2-Hydroxy-3-isopropylamino-1-propyloxy)-indole** ([*R*]-(+)-**Pindolol**) ([**R**]-**12**)——The oxazolidone [*R*]-**11** (400 mg) was heated in $H_2O$–EtOH (2: 1, 6 ml) containing NaOH (0.5 g) under reflux for 8 h. The mixture was concentrated to 1/3 of the initial volume, and extracted with $CHCl_3$–MeOH (4: 1). The extract was washed with water, dried, and concentrated to dryness. Washing of the residue with $CH_2Cl_2$ left a white solid which was crystallized from benzene to give [*R*]-(+)-pindolol [*R*]-**12** (260 mg, 72%). It showed double mp 94—96°C and 168—170°C. $[\alpha]_D^{16}$ +4.9° ($c$=1, MeOH). IR: 3280, 1615, 1586. NMR (MeOH-$d_4$): $\delta$ 1.11, 1.12 (each 3H, d, $J$=6.1 Hz, $-CH(C\underline{H}_3)_2$), 2.54—3.08 (3H), 3.92—4.30 (3H), 6.40—6.58 (2H), 6.96—7.10 (3H). *Anal.* Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.76; H, 8.10; N, 11.35.

[*S*]-(−)-**Pindolol** ([*S*]-**12**)——The [*S*]-carbamate [*S*]-**11** was hydrolyzed and worked up as described above to yield [*S*]-(−)-pindolol [*S*]-**12**, double mp 95—97°C and 168—170°C. $[\alpha]_D^{16}$ −5.1° ($c$=1, MeOH). Its IR and NMR spectra were superimposable on those of the [*R*]-isomer.

***rac*-Pindolol** (***rac*-12**)——The *rac*-carbamate *rac*-**11** was hydrolyzed and worked up as described above

to give *rac*-pindolol *rac*-**12**, mp 175—176°C (lit.[16] mp 171—173°C). Its TLC behavior and NMR signals were identical with those of the [*R*]-isomer.

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