Preparation of Alkyl-Substituted Indoles in the Benzene Portion. Part 7.[1] Synthesis of (±)- and (*S*)-(−)-Pindolol

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A new, short-step synthesis of a β-adrenergic blocking agent, pindolol, 1-(4-indolyloxy)-3-(2-propylamino)-2-propanol, is described. The acid-catalyzed indole cyclization reaction of 4-[1-(4-methylphenyl)sulfonyl-3-pyrrolyl]-4-oxobutanal (14) in the presence of (±)-3-chloro-1,2-propanediol (12) and (*R*)-1-*O*-[(4-methylphenyl)sulfonyl]glycerol (24) afforded (±)-1-chloro-3-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-2-propanol (15) and (*R*)-(−)-3-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-1-[(4-methylphenyl)sulfonyloxy]-2-propanol (25). Reaction of these with isopropylamine and removal of the protecting group at the indole nitrogen gave (±)- and (*S*)-(−)-pindolol (3 and 4), thus constituting an efficient three-step synthesis of 3 and 4 from the readily available aldehyde (14).

Keywords (±)-pindolol; (*S*)-(−)-pindolol; β-adrenergic blocking agent; indole synthesis; acid-induced indole cyclization

Pindolol, 1-(4-indolyloxy)-3-(2-propylamino)-2-propanol, is one of the most effective β-adrenergic blocking agents currently available, and is used for the treatment of hypertension and tachycardia.[2] The conventional methods for the synthesis of (±)-pindolol (**3**)[3] and pharmacologically more active (*S*)-(−)-pindolol (**4**)[4] have been based on the coupling reaction of 4-hydroxyindole (**2**)[5] with glycidol derivatives under basic conditions (Chart 1). These methods have been proved to be useful, but there are some disadvantages as follows. 4-Hydroxyindole (**2**), derived from 4-oxo-4,5,6,7-tetrahydroindole (**1**),[5] is known to be susceptible to air oxidation, particularly under alkaline conditions.[6] In the synthesis of the optically active (*S*)-isomer, the reaction of chiral (−)-epichlorohydrin (**5**) with **2** has been reported to result in a decrease of optical purity of **4**, due to the competitive reaction courses of path a and path b.[4,7] To overcome the latter disadvantage, some improvements have been reported in the cases of (*S*)-(−)-pindolol and other (*S*)-β-blockers by using (2*R*)-2,3-*O*-isopropylideneglycerol (**7**) prepared from (2*S*)-**6**[8] or L-ascorbic acid,[9] a chiral oxazolidinone derivative (**8**),[10] and (*R*)-glycidol (**9**).[11] However these are still modifications of the original Sandoz procedure. Some other improved synthetic methods for pindolol have also been developed.[10b,12]

We have devised a completely different pathway, in which 4-hydroxyindole (**2**) is not involved, for construction of the 4-substituted indole moiety, and report here our efficient and concise synthesis of (±)- and (*S*)-(−)-pindolol (**3** and **4**).

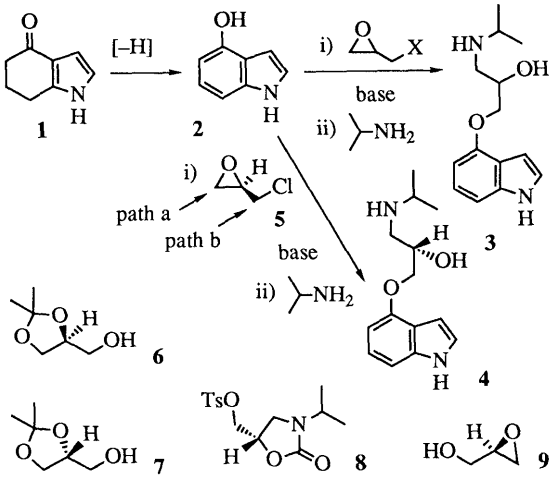


Chart 1

Synthesis of (±)-Pindolol (3) In the preceding paper,[1] we described the regioselective preparation of monoalkoxyindoles having their substituents on the benzene portion of the indole nucleus. For instance, 4-alkoxy-1-(arylsulfonyl)indole derivatives (**11**) were synthesized in good yields from readily accessible precursors, 1-[1-(arylsulfonyl)-3-pyrrolyl]-4,4-dialkoxy-1-butanones (**10**) in the presence of alcohols under acidic conditions (Chart 2). Here the 4-alkoxy groups were derived from the alcohols used as additives, and generally bifunctional alcohols such as 1,2-ethanediol and 1,3-propanediol afforded excellent yields of **11**. This meant that if commercially available 3-chloro-1,2-propanediol (**12**) could be successfully employed as an alcohol for this cyclization reaction, and incorporated suitably to afford an indole derivative (**11a**) bearing a 3-chloro-2-hydroxy-1-propoxy moiety at the 4-position, the process would provide a new synthetic pathway for (±)-pindolol (**3**), since the chloride (**11a**) would be easily converted into **3** by reaction with isopropylamine and removal of the protecting group at the indole nitrogen. So we initiated a study to assess the feasibility of this approach.

We examined the acid-catalyzed cyclization reaction of 4,4-dialkoxy-1-[1-(4-methylphenyl)sulfonyl-3-pyrrolyl]-1-butanones (**13a, b**)[1] and 4-[1-(4-methylphenyl)sulfonyl-3-pyrrolyl]-4-oxobutanal (**14**)[1] in the presence of 3-chloro-1,2-propanediol (**12**) (Table I). The desired compound (**15**) was produced in preference to a regioisomer, 3-chloro-2-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-1-propanol (**16**), irrespective of the reaction conditions.

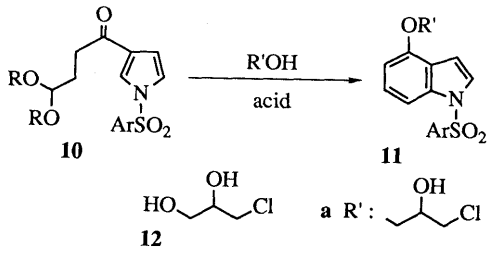
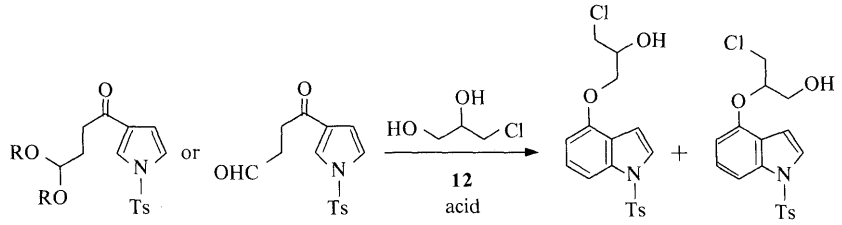


Chart 2

TABLE I. Preparation of 4-Alkoxyindole Derivatives (**15**, **16**) from **13a**, **b** and **14**

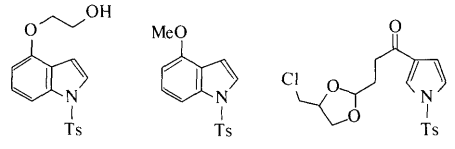


13a, b **14** **15** **16**

a: R = $-CH_2CH_2-$ **b**: R = Me

Run	Starting material	**12**	Acid	Conditions[a]		Products (% yield)[b]		
		eq	(eq)	Solvent	Time (h)	**15**	**16**	By-product
1	**13a**	20	*p*-TsOH (0.29)	PhMe	4	69	7.5	**17** (2.5)
2	**13b**	8	*p*-TsOH (0.19)	PhMe	5	70	10	
3	**13b**	5	*p*-TsOH (0.19)	PhMe	7	60	10	
4	**13b**	8	H_2SO_4 (0.43)	$CHCl_3$	1	69	10	
5	**13b**	8	H_2SO_4 (0.45)	CH_2Cl_2	3	64	5	**18** (15)
6	**14**	8	H_2SO_4 (0.47)	CH_2Cl_2	4	76	5	
7	**14**	8	H_2SO_4 (0.51)	$Cl(CH_2)_2Cl$	1	64	15	
8	**14**	8	H_2SO_4 (0.47)	$ClCH=CCl_2$	1.75	65	11.5	
9	**14**	8	$BF_3 \cdot OEt_2$ (4.0)	CH_2Cl_2	24	65	6	
10	**14**	8	$SnCl_4$ (4.0)	CH_2Cl_2	17	0	0	**19** (75)

a) Reactions were carried out under reflux using a Dean-Stark apparatus, except for runs 9 and 10, where the reactions were conducted at 0 °C. *b*) Isolated yield.



17 **18** **19**

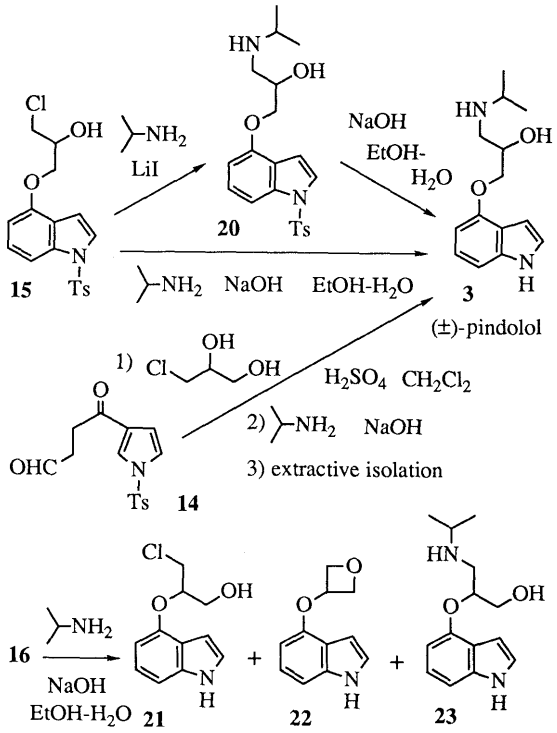
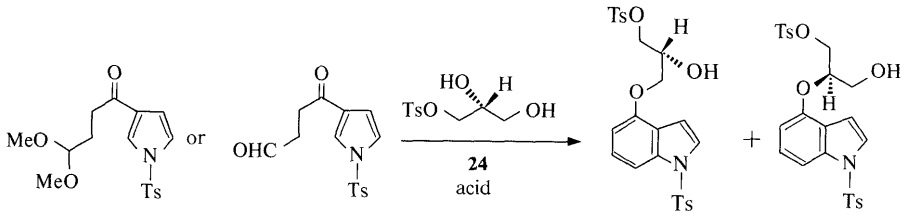


Chart 3

When **13a** or **13b** was refluxed with **12** in the presence of a catalytic amount of *p*-toluenesulfonic acid, the product ratio, **15**/**16** was 6—9.2 (runs 1—3). In run 1, the reaction proceeded accompanied by the formation in 2.5% yield of 2-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-1-ethanol (**17**),[1] which would be formed by participation of ethylene glycol derived from **13a**. The reaction of **13b** in refluxing chloroform using a catalytic amount of sulfuric acid gave a similar **15**/**16** ratio of 6.9 (run 4), whereas the same reaction as above in a lower boiling solvent, dichloromethane, provided a better **15**/**16** ratio (12.8), but at the same time gave a significant amount of 4-methoxy-1-(4-methylphenyl)sulfonylindole (**18**,[1] 15%), which would be derived from methanol originating from the dimethyl acetal function of **13b** (run 5). To suppress the formation of **18**, we decided to use **14** as a starting substance. When **14** was treated with **12** under sulfuric acid catalysis in refluxing dichloromethane, the best result was achieved culminating in the **15**/**16** ratio of 15.2, and **15** and **16** were obtained in 76% and 5% yields, respectively, without any other by-products (run 6). In the reaction with boron trifluoride etherate as a Lewis acid, however, use of a large excess of the acid and prolonged reaction time were necessary for complete consumption of the starting material (run 9). The reaction employing tin(IV) chloride failed to give desired compound but gave only an acetal product (**19**) in 75% yield (run 10).

The compound (**15**) thus obtained was readily transformed into (±)-pindolol (**3**) by way of **20** by treatment with isopropylamine in the presence of lithium iodide, followed by alkaline hydrolysis,[12a] in 87% overall yield (Chart 3). Direct preparation of **3** was possible in 81% yield, when **15** was heated with isopropylamine in the

TABLE II. Preparation of 4-Alkoxyindole Derivatives (**25**, **26**) from **13b** and **14**



13b **14** **25** **26**

Run	Starting material	**24**	Acid	Conditions[a]		Products (% yield)[b]	
		eq	(eq)	Solvent	Time (h)	**25**	**26**
1	**13b**	2	*p*-TsOH (0.20)	PhMe	6	62	11
2	**13b**	3	*p*-TsOH (0.20)	PhMe	4	67	11
3	**13b**	4	*p*-TsOH (0.20)	PhMe	3	68	9
4	**14**	4	H_2SO_4 (0.50)	CH_2Cl_2	3	71	5.5

a) All reactions were carried out under reflux using a Dean-Stark apparatus. *b*) Isolated yield.

presence of caustic alkali in aqueous ethanol. On the other hand, a similar treatment of the by-product (**16**) afforded mainly neutral substances (**21** and **22**) in 30% and 64% yields, respectively, instead of a basic compound (**23**), which was isolated in 3.5% yield. These results could be easily understood by assuming that the amine substitution of **15** and **16** proceeded through an intermediary epoxide and an oxetane (**22**). The former epoxide instantaneously reacted with isopropylamine to give **20**, while the latter oxetane (**22**) mostly remained intact. These phenomena coincide well with the observation that the reaction rate for base-catalyzed hydrolysis of oxetanes is much slower than that of epoxides.[13]

This finding made it possible to develop a simple large-scale preparation of (±)-pindolol (**3**) from **14** without any chromatographic separation. The pyrrole derivative (**14**) was condensed with **12** as in run 6 of Table I. The reaction mixure containing **15** and **16** was directly treated with isopropylamine in the presence of sodium hydroxide, and the crude mixture of the reaction products, including **3**, **21**, **22**, and **23** was divided into neutral and basic portions by extraction with diluted hydrochloric acid. The basic fraction was passed through a short column of alumina to remove colored materials, and purification by recrystallization afforded (±)-pindolol (**3**) in 58% yield, calculated from **14**.

In our synthesis, it is noteworthy that the 3-chloro-2-hydroxy-1-propoxy substituent is introduced simultaneously with the formation of the indole nucleus, and therefore the present sequence never involves labile 4-hydroxyindole (**2**).

Synthesis of (*S*)-(−)-Pindolol For the synthesis of (*S*)-(−)-pindolol, we selected (*R*)-1-*O*-(4-methylphenyl)-sulfonylglycerol (**24**) as a diol in the acid-catalyzed cyclization reaction, since **24** is readily accessible from (*S*)-glycerol acetonide (**6**) and a readily crystallizable compound.[14] The results of the indole formation reaction with **24** are summarized in Table II. Using two equivalents of **24**, the reaction took about six hours for completion and the ratio of **25**/**26** was not satisfactory (5.64) (run 1). When the amount of **24** was increased, the reaction time required decreased and the above ratio became better

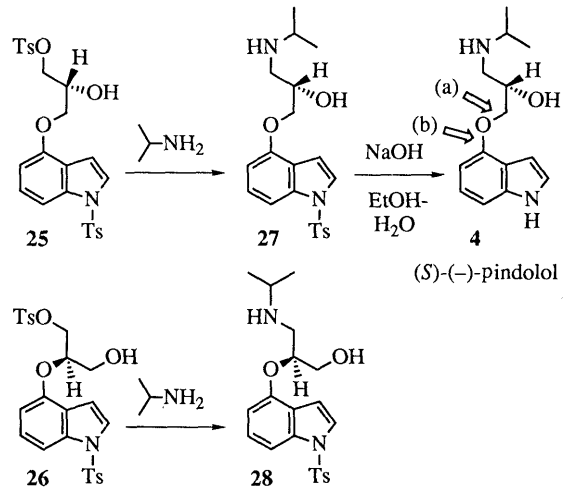


Chart 4

(runs 2, 3). Starting with the aldehyde (**14**), the usage of four equivalents of **24** in the sulfuric acid–dichloromethane system gave the best outcome (run 4), and the requisite compound (**25**) was obtained in 71% yield, accompanied by the undesired by-product (**26**) in 5.5% yield (**25**/**26** ratio: 12.9). Excess **24** was recovered by chromatography over silica gel. Aminolysis of **25** with isopropylamine (98%), followed by alkaline hydrolysis of **27** provided in 89% yield (*S*)-(−)-pindolol (**4**), whose specific rotaion $\{[\alpha]_D^{23}$ −4.6° (*c* = 1.01, MeOH)} showed good agreement with the reported value $\{[\alpha]_D^{16}$ −5.1° (*c* = 1, MeOH)}[12a] (Chart 4). Unlike the chloride (**16**), the tosylate (**26**) was easily transformed into (*S*)-3-(2-propylamino)-2-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-1-propanol (**28**) by aminolysis using isopropylamine in 91% yield. Probably the amino substitution takes place in the direct manner without intermediacy of the oxetane ring.

As already mentioned, condensation of 4-hydroxyindole (**2**) with chiral (−)-epichlorohydrin (**5**) is known to afford (*S*)-(−)-pindolol (**4**) possessing a decreased value of specific rotation, since the reaction involves bond formation between the oxygen atom and aliphatic carbon atom [bond (a)]. In our method, however, the bond between

the oxygen atom and aromatic carbon atom [bond (b)] was formed. Therefore partial racemization could not occur, keeping the optical purity the same as that of the initial reagent (**24**).

In conclusion, we have developed a new, efficient synthesis of both (±)-pindolol (**3**) and optically pure (*S*)-(−)-pindolol (**4**) by a three-step sequence from the readily available aldehyde (**14**) and diols (**12**) and (**24**) in 66% and 62% yields, respectively.

Experimental

Specific rotations were measured on a Perkin-Elmer polarimeter. For other general descriptions, see Part 5.[15]

Indole Cyclization Reaction with 3-Chloro-1,2-propanediol (12) Run 6 in Table I is described as a typical example among runs 1—8. A solution of the aldehyde (**14**) (75 mg, 0.246 mmol), 3-chloro-1,2-propanediol (**12**) (217 mg, 1.95 mmol), and 95% H_2SO_4 (12 mg, 0.116 mmol) in CH_2Cl_2 (5 ml) was refluxed using a Dean-Stark apparatus for 4 h, then cooled. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by preparative thin layer chromatography (PTLC) [hexane–EtOAc (4 : 1)] afforded 1-chloro-3-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-2-propanol (**15**) (71 mg, 76%) as a less polar compound and 3-chloro-2-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-1-propanol (**16**) (5 mg, 5%) as a more polar compound. **15**: Colorless syrup. HRMS Calcd for $C_{18}H_{18}ClNO_4S$: 379.0644, 381.0614. Found: 379.0625, 381.0630. ^{1}H-NMR δ: 2.24 (3H, s), 2.81 (1H, br s, OH), 3.52—3.88 (2H, m), 3.99—4.31 (3H, m), 6.56 (1H, d, J=8 Hz), 6.68 (1H, d, J=4 Hz), 7.09 and 7.66 (A_2B_2, J=8.5 Hz), 7.14 (1H, dd, J=8, 8 Hz), 7.40 (1H, d, J=4 Hz), 7.57 (1H, d, J=8 Hz). **16**: Colorless syrup. HRMS Calcd for $C_{18}H_{18}ClNO_4S$: 379.0644, 381.0614. Found: 379.0638, 381.0645. ^{1}H-NMR δ: 1.88 (1H, br s, OH), 2.30 (3H, s), 3.68 (2H, d, J=5.5 Hz), 3.94 (2H, br d, J=4 Hz), 4.43—4.71 (1H, m), 6.69 (1H, d, J=8 Hz), 6.71 (1H, d, J=4 Hz), 7.16 (1H, dd, J=8, 8 Hz), 7.16 and 7.71 (A_2B_2, J=8.5 Hz), 7.43 (1H, d, J=4 Hz), 7.61 (1H, d, J=8 Hz). Run 9: $BF_3 \cdot OEt_2$ (0.11 ml, 0.894 mmol) was added to a stirred solution of **14** (68 mg, 0.223 mmol) and **12** (198 mg, 1.78 mmol) in CH_2Cl_2 (4 ml) at 0 °C, and the mixture was stirred for 24 h at the same temperature. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [hexane–EtOAc (5 : 1)] gave **15** (55 mg, 65%) and crude **16**. The latter was further purified by PTLC [hexane–CH_2Cl_2 (2 : 3)] to afford **16** (5 mg, 6%). Run 10: $SnCl_4$ (70 μl, 0.598 mmol) was added to a stirred solution of **14** (45 mg, 0.147 mmol) and **12** (131 mg, 1.17 mmol) in CH_2Cl_2 (3 ml) at 0 °C, and the mixture was stirred for 17 h at the same temperature. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [hexane–EtOAc (2 : 1)] gave **19** (44 mg, 75%) as a diastereomeric mixture. **19**: Colorless syrup. MS m/z: 397, 399 (M^+). IR ($CHCl_3$) cm^{-1}: 1681. ^{1}H-NMR δ: 1.88—2.22 (2H, m), 2.40 (3H, s), 2.84, 2.87 (total 2H, t each, J=7 Hz), 3.27—4.43 (5H, m), 4.98, 5.10 (total 1H, dd each, J=4, 4 Hz), 6.64 (1H, dd, J=3, 1.5 Hz), 7.11 (1H, dd, J=3, 2 Hz), 7.30 and 7.78 (A_2B_2, J=8.5 Hz).

1-[1-(4-Methylphenyl)sulfonyl-4-indolyloxy]-3-(2-propylamino)-2-propanol (20) A solution of **15** (77 mg, 0.203 mmol) and LiI (82 mg, 0.613 mmol) in isopropylamine (2 ml) was refluxed with stirring for 22 h. After removal of isopropylamine by evaporation *in vacuo*, H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by Al_2O_3 PTLC (CH_2Cl_2) afforded **20** (77 mg, 94%) as a colorless syrup. HRMS Calcd for $C_{21}H_{26}N_2O_4S$: 402.1612. Found: 402.1616. ^{1}H-NMR δ: 1.02 (6H, d, J=6 Hz), 2.24 (3H, s), 2.53—2.99 (3H, m), 2.77 (2H, s, OH, NH), 3.87—4.18 (3H, m), 6.57 (1H, d, J=8 Hz), 6.72 (1H, d, J=4 Hz), 7.10 and 7.68 (A_2B_2, J=8.5 Hz), 7.14 (1H, dd, J=8, 8 Hz), 7.40 (1H, d, J=4 Hz), 7.56 (1H, d, J=8 Hz).

Reaction of 16 with Isopropylamine in an Alkaline Medium to Form 21, 22 and 23 A mixture of **16** (22 mg, 0.058 mmol), isopropylamine (0.8 ml), and 1 N NaOH (0.5 ml, 0.5 mmol) in EtOH (0.5 ml) was heated at 60—65 °C (bath temperature) with stirring for 13 h and further under reflux for 10 h. After cooling, the mixture was acidified with 2% HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$–H_2O and worked up as usual, affording 14 mg of a neutral material. Purfication of this material by PTLC [hexane–EtOAc (3 : 1)] gave 3-chloro-2-(4-indolyloxy)-1-propanol (**21**) (4 mg, 30%) as a more polar compound and 3-(4-indolyloxy)oxetane (**22**) (7 mg, 64%) as a less polar compound. The aqueous layer was made basic with saturated $NaHCO_3$, solid NaCl was added, and the whole was extracted thoroughly with 10% MeOH–containing CH_2Cl_2. Usual work-up afforded 1 mg of a basic material, which was purified by Al_2O_3 PTLC (0.3% MeOH–CH_2Cl_2) to give 2-(4-indolyloxy)-3-(2-propylamino)-1-propanol (**23**) (0.5 mg, 3.5%). **21**: Colorless syrup. MS m/z: 225, 227 (M^+). ^{1}H-NMR δ: 3.74 (2H, d, J=5.5 Hz), 4.00 (2H, br d, J=5 Hz), 4.46—4.82 (1H, m), 6.53—6.74 (2H, m), 6.95—7.19 (3H, m), 8.19 (1H, br s, NH). **22**: Colorless prisms, mp 116—117 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.80; H, 6.00; N, 7.40. MS m/z: 189 (M^+). ^{1}H-NMR δ: 4.73—5.11 (4H, m), 5.20—5.48 (1H, m), 5.93—6.17 (1H, m), 6.64 (1H, dd, J=3, 2.5 Hz), 6.87—7.17 (2H, m), 7.10 (1H, dd, J=3, 3 Hz), 8.20 (1H, br s, NH). **23**: Colorless syrup. MS m/z: 248 (M^+). ^{1}H-NMR δ: 1.08 (6H, d, J=6.5 Hz), 2.23 (2H, s, OH, NH), 2.68—3.14 (1H, m), 3.14 (2H, d, J=5 Hz), 3.97 (2H, d, J=4.5 Hz), 4.43—4.76 (1H, m), 6.54—6.74 (2H, m), 6.96—7.16 (3H, m), 8.17 (1H, br s, indole NH).

Synthesis of (±)-Pindolol (3) (a) According to Sakai's method,[12a] a solution of **20** (75 mg, 0.186 mmol) and 1 N NaOH (0.8 ml, 0.8 mmol) in EtOH (1.6 ml) was refluxed with stirring for 14 h. The reaction mixture was evaporated *in vacuo* and a crystalline residue was partitioned between 10% MeOH–CH_2Cl_2 and H_2O. The organic solution was worked up as usual and the resulting crude crystalline material was recrystallized from EtOH to afford (±)-pindolol (**3**) (43 mg, 93%) as colorless needles, mp 172—172.5 °C [lit.[16] mp 171—173 °C (EtOH)]. An admixture with an authentic sample[12a] of mp 172—173 °C showed mp 172—173 °C. *Anal.* Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.61; H, 8.10; N, 11.24. MS m/z (relative intensity): 248 (M^+, 11), 204 (7), 133 (97), 116 (13), 104 (18), 72 (100), 56 (11), 43 (12). ^{1}H-NMR [$CDCl_3$–CD_3OD (3 : 1)] δ: 1.10 (6H, d, J=6.5 Hz), 2.58—3.08 (3H, m), 3.91—4.36 (3H, m), 6.34—6.61 (1H, m), 6.54 (1H, d, J=3.5 Hz), 6.88—7.17 (2H, m), 7.08 (1H, d, J=3.5 Hz).

(b) A mixture of **15** (47 mg, 0.123 mmol), isopropylamine (1.2 ml), and 1 N NaOH (0.8 ml, 0.8 mmol) in EtOH (0.8 ml) was heated at 60—63 °C (bath temperature) with stirring for 12 h and further at 85 °C (bath temperature) for 12 h. After cooling of the mixture to room temperature, H_2O was added, then the mixture was extracted with 10% MeOH–CH_2Cl_2, and the extract was worked up as usual. Purification by Al_2O_3 PTLC (1% MeOH–CH_2Cl_2) gave crude crystals, which were recrystallized from EtOH to afford (±)-pindolol (**3**) (25 mg, 81%) as colorless needles, mp 171.5—172.5 °C.

(c) A mixture of **14** (179 mg, 0.586 mmol), **12** (521 mg, 4.67 mmol), and 95% H_2SO_4 (30 mg, 0.291 mmol) in CH_2Cl_2 (7 ml) was refluxed using a Dean-Stark apparatus with stirring for 4 h, then cooled to 0 °C. Saturated $NaHCO_3$–H_2O was added, and the mixture was extracted with CH_2Cl_2, and worked up as usual. The residual oil was diluted with EtOH (2.5 ml) and to this was added isopropylamine (2.5 ml) and 1 N NaOH (3.5 ml, 3.5 mmol). The resulting mixture was heated with stirring at 60—65 °C (bath temperature) for 13 h and further at reflux for 8 h. After removal of isopropylamine by evaporation *in vacuo*, the mixture was acidified by addition of 2% HCl–H_2O and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$–H_2O and worked up as usual to give 38 mg of the neutral component. The aqueous layer was made alkaline with saturated $NaHCO_3$–H_2O, solid NaCl was added, and the mixture was extracted with 10% MeOH–CH_2Cl_2. Usual work-up gave 124 mg of the basic component, which was passed through an Al_2O_3 column using 1% MeOH–CH_2Cl_2. Recrystallization of the eluate from EtOH gave (±)-pindolol (**3**) (85 mg, 58%) as colorless needles, mp 172—173 °C. Separation of the neutral part by PTLC [hexane–CH_2Cl_2 (1 : 3)] afforded, in increasing order of polarity, three products, crude **22** (6 mg), **21** (2 mg, 1.5%), and 3-ethoxy-1-(4-indolyloxy)-2-propanol (3.5 mg, 2.5%), colorless syrup, MS m/z: 235 (M^+), ^{1}H-NMR δ: 1.19 (3H, t, J=7 Hz), 2.59 (1H, br s, OH), 3.54 (2H, q, J=7 Hz), 3.58—3.79 (2H, m), 4.09—4.37 (3H, m), 6.51 (1H, dd, J=6, 2 Hz), 6.56—6.70 (1H, m), 6.91—7.19 (3H, m), 8.16 (1H, br s, NH). The crude **22** was purified by PTLC [hexane–EtOAc (5 : 1)] to give **22** as crystals (4.5 mg, 4%).

Indole Cyclization Reaction with (*R*)-1-*O*-(4-Methylphenyl)sulfonylglycerol (24) Run 4 in Table II is described as a typical example. A solution of the aldehyde (**14**) (80 mg, 0.262 mmol), the chiral diol [258 mg, 1.05 mmol, mp 60—61 °C, $[\alpha]_D^{23}$ −10.5±0.5° (c=1.01, MeOH)], prepared from D-mannitol,[14] and 95% H_2SO_4 (13.5 mg, 0.131 mmol) in CH_2Cl_2 (5 ml) was refluxed using a Dean-Stark apparatus for 3 h, then cooled to 0 °C. Saturated $NaHCO_3$–H_2O was added, then the mixture was extracted with 10% MeOH–CH_2Cl_2 and worked up as usual. The residue was separated by column chromatography over silica gel (20 g) using hexane–EtOAc (2 : 1) and then 3% MeOH–CH_2Cl_2, followed by purification by PTLC (CH_2Cl_2) for **25** and PTLC [hexane–EtOAc (1 : 1)]

for the recovery of **24** gave (*R*)-(−)-3-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-1-[(4-methylphenyl)sulfonyloxy]-2-propanol (**25**) (96 mg, 71%), (*R*)-(+)-2-[1-[(4-methylphenyl)sulfonyl-4-indolyloxy]-3-[(4-methylphenyl)sulfonyloxy]-1-propanol (**26**) (7.5 mg, 5.5%), and recovered **24** [153 mg, 59% recovery, $[\alpha]_D^{24}$ −9.7° (c=1.53, MeOH), pure enough to use repeatedly], which was recrystallized from Et_2O–hexane to give 147 mg of colorless needles, mp 59—60 °C. **25**: Colorless syrup. HRMS Calcd for $C_{25}H_{25}NO_7S_2$: 515.1071. Found: 515.1071. $[\alpha]_D^{23}$ −7.2° (c=0.91, $CHCl_3$). ^{1}H-NMR δ: 2.22 (6H, s), 3.09 (1H, br s, OH), 3.73—4.35 (5H, m), 6.44 (1H, d, J=8 Hz), 6.56 (1H, d, J=3.5 Hz), 6.97—7.26 (6H, m), 7.48—7.66 (1H, m), 7.66 (2H, $\underline{A_2}B_2$, J=8.5 Hz), 7.67 (2H, $\underline{A_2}B_2$, J=8.5 Hz). **26**: Colorless syrup. HRMS Calcd for $C_{25}H_{25}NO_7S_2$: 515.1071. Found: 515.1070. $[\alpha]_D^{23}$ +23.8° (c=0.80, $CHCl_3$). ^{1}H-NMR δ: 1.94 (1H, br s, OH), 2.31 (3H, s), 2.37 (3H, s), 3.83 (2H, br d, J=4.5 Hz), 4.24 (2H, d, J=4.5 Hz), 4.58 (1H, tt, J=4.5, 4.5 Hz), 6.59 (1H, d, J=8 Hz), 6.62 (1H, d, J=4 Hz), 7.00—7.29 (5H, m), 7.42 (1H, d, J=4 Hz), 7.58 (1H, d, J=8 Hz), 7.64 (2H, $\underline{A_2}B_2$, J=8.5 Hz), 7.71 (2H, $\underline{A_2}B_2$, J=8.5 Hz).

(*S*)-(−)-1-[1-(4-Methylphenyl)sulfonyl-4-indolyloxy]-3-(2-propylamino)-2-propanol (27) A mixture of **25** (97 mg, 0.188 mmol) and isopropylamine (3 ml) was refluxed with stirring for 26 h. After removal of isopropylamine by evaporation *in vacuo*, H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by Al_2O_3 PTLC (0.1% MeOH–CH_2Cl_2) gave **27** (74 mg, 98%) as a colorless syrup. HRMS Calcd for $C_{21}H_{26}N_2O_4S$: 402.1612. Found: 402.1607. $[\alpha]_D^{23}$ −5.39° (c=0.99, $CHCl_3$). ^{1}H-NMR δ: 1.01 (6H, d, J=6 Hz), 2.23 (3H, s), 2.53—3.01 (5H, m containing OH, NH), 3.86—4.20 (3H, m), 6.56 (1H, d, J=8 Hz), 6.71 (1H, d, J=4 Hz), 7.08 and 7.66 (A_2B_2, J=8.5 Hz), 7.11 (1H, dd, J=8, 8 Hz), 7.37 (1H, d, J=4 Hz), 7.55 (1H, d, J=8 Hz).

(*S*)-2-[1-(4-Methylphenyl)sulfonyl-4-indolyloxy]-3-(2-propylamino)-1-propanol (28) A mixture of **26** (24 mg, 0.047 mmol) and isopropylamine (2 ml) was refluxed with stirring for 38 h. After removal of isopropylamine, H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by Al_2O_3 PTLC (CH_2Cl_2) gave **28** (17 mg, 91%) as a colorless syrup. HRMS Calcd for $C_{21}H_{26}N_2O_4S$: 402.1612. Found: 402.1603. ^{1}H-NMR δ: 1.02 (6H, d, J=6 Hz), 2.30 (3H, s), 2.64 (2H, br s, OH, NH), 2.75 (1H, qq, J=6, 6 Hz), 3.04 (2H, d, J=4.5 Hz), 3.88 (2H, d, J=4.5 Hz), 4.44 (1H, tt, J=4.5, 4.5 Hz), 6.67 (1H, d, J=8 Hz), 6.72 (1H, d, J=3.5 Hz), 7.13 (1H, dd, J=8, 8 Hz), 7.18 and 7.69 (A_2B_2, J=8.5 Hz), 7.41 (1H, d, J=3.5 Hz), 7.56 (1H, d, J=8 Hz).

(*S*)-(−)-Pindolol (4) A solution of **27** (73 mg, 0.181 mmol) and 1 N NaOH (0.8 ml, 0.8 mmol) in EtOH (1.6 ml) was refluxed with stirring for 14 h, then cooled. Water was added and the mixture was extracted with 10% MeOH–CH_2Cl_2 and worked up as usual. The resulting crystalline product was purified by Al_2O_3 PTLC (1% MeOH–CH_2Cl_2), and recrystallization from benzene afforded (*S*)-(−)-pindolol (**4**) (40 mg, 89%) as colorless needles, mp 93.5—95 °C. *Anal.* Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.60; H, 8.14; N, 11.23. MS *m/z* (relative intensity): 248 (M^+, 17), 204 (9), 133 (100), 116 (14), 104 (19), 72 (99), 56 (11), 43 (7). ^{1}H-NMR δ: 1.07 (6H, d, J=6 Hz), 2.46 (2H, s, OH, NH), 2.59—3.06 (3H, m), 3.92—4.27 (3H, m), 6.48 (1H, dd, J=6, 2 Hz), 6.61 (1H, br d, J=3 Hz), 6.89—7.19 (3H, m), 8.38 (1H, br s, indole NH).

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