New, Concise Route to Indoles Bearing Oxygen or Sulfur Substituent at the 4-Position. Synthesis of (±)- and (*S*)-(−)-Pindolol and (±)-Chuangxinmycin

Hiroyuki ISHIBASHI,* Susumu AKAMATSU, Hiroko IRIYAMA, Kyoko HANAOKA, Takashi TABATA, and Masazumi IKEDA

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan.
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A new method for the synthesis of 4-alkoxy- and 4-[alkyl (or aryl)thio]indoles has been developed by using the indolone 3 as a common intermediate. The indolone 3 was prepared from *N*-(phenylsulfonyl)pyrrole (7) and the α-chlorosulfide 8 in four steps. Heating of a mixture of 3 and an appropriate alcohol in the presence of *p*-toluenesulfonic acid and cupric chloride afforded the 4-alkoxyindoles 11a—d. The method was applied to the synthesis of (±)-pindolol (19) and (*S*)-(−)-pindolol (20). Thiols also reacted with 3 in the presence of boron trifluoride to give 4-[aryl (or alkyl)thio]indoles 12, 21a, b, and 22a—d. The (indol-4-ylthio)acetate 22c was employed as a key intermediate for a concise total synthesis of (±)-chuangxinmycin (27).

Keywords 4-substituted indole; (±)-pindolol, (*S*)-(−)-pindolol; (±)-chuangxinmycin; α-chlorosulfide

Indoles bearing a substituent at the 4-position are of great interest as precursors in the synthesis of many therapeutically useful materials.[1] The preparation of 4-substituted indoles is, however, rather more difficult than that of other substituted indoles, and hence a number of methods have so far been examined for the construction of this class of compounds.[1,2] An attractive one is the use of 6,7-dihydroindol-4(5*H*)-ones **1** as intermediates.[3] The method, however, often gives unsatisfactory results due to the drastic conditions required for the oxidative aromatization. To overcome this problem, the 5-halo derivatives **2** have been designed as pre-oxidized molecules and applied to the synthesis of some 4-substituted indoles.[4] Our own interest in this area was stimulated by the prospect of designing a new entry to this class of compounds through a strategy that features aromatization of the 7-(arylthio)indolone **3**. The attack of nucleophiles on the carbonyl carbon atom of **3** provides the alcohols **4**, which are dehydrated to give, with concomitant elimination of thiol, the 4-substituted indoles **6**. Herein we report a new convenient synthesis of indoles bearing an oxygen or sulfur functionality at the 4-position by using the indolone **3** as a common intermediate. Applications of the method to the synthesis of (±)- and (*S*)-(−)-pindolol and (±)-chuangxinmycin are also presented.[5]

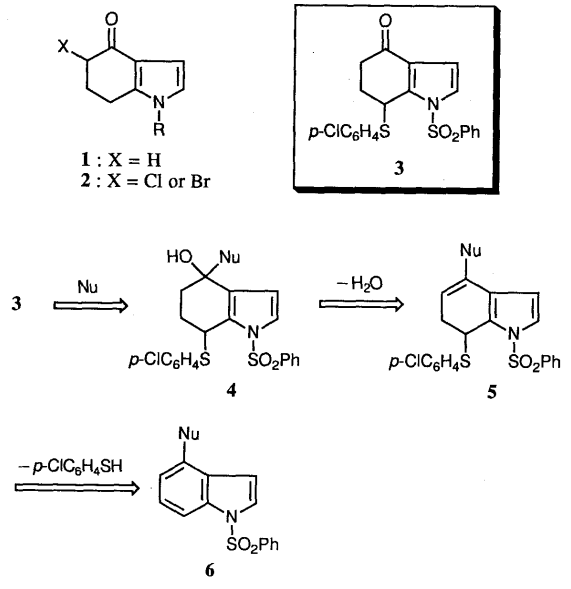


Chart 1

Synthesis of the Indolone 3 The indolone **3** was prepared from *N*-(phenylsulfonyl)pyrrole (**7**) in 4 steps. Thus, treatment of a mixture of an equimolar amount of **7** and ethyl 4-chloro-4-(4-chlorophenylthio)butanoate (**8**)[6] with four equivalents of $TiCl_4$ in CH_2Cl_2 at −78 °C gave the α-alkylation product **9** in 64% yield. Saponification of the ester moiety of **9** with LiOH in aqueous tetrahydrofuran (THF) followed by treatment of the resultant carboxylic acid with oxalyl chloride afforded the acyl chloride **10** in quantitative yield. The intramolecular Friedel–Crafts acylation of **10** was effected by treatment with an equimolar amount of $SnCl_4$ in CH_2Cl_2 at 0 °C to furnish the indolone **3** in 86% yield as colorless prisms (mp 113.5—114 °C).

Synthesis of 4-Alkoxyindoles: Applications to the Synthesis of (±)-Pindolol and (*S*)-(−)-Pindolol Treatment of the indolone **3** with 10 molar eq of *p*-toluene-

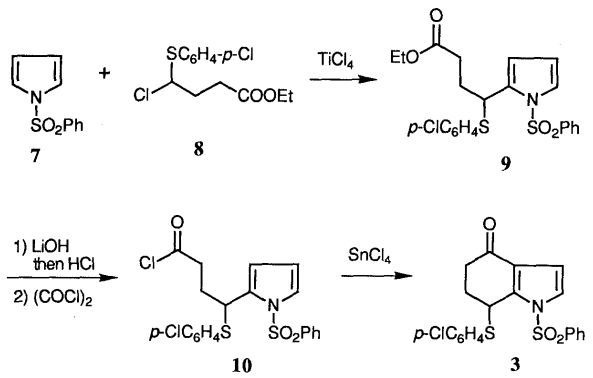


Chart 2

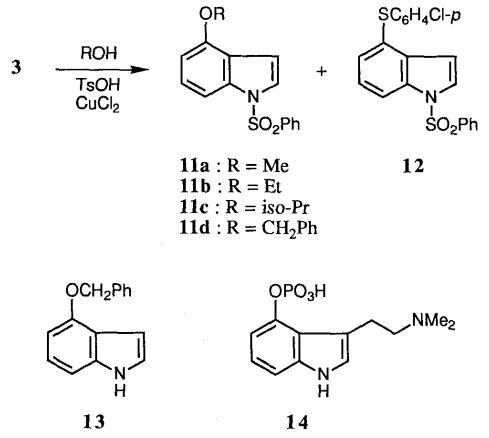


Chart 3

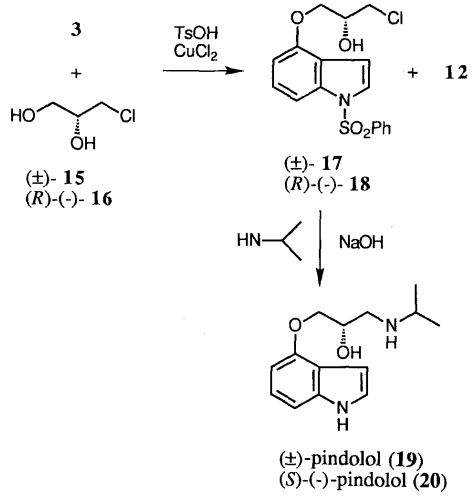


Chart 4

sulfonic acid (TsOH) in boiling methanol for 48 h gave 4-methoxy-1-(phenylsulfonyl)-1*H*-indole (**11a**) in 87% yield after purification by chromatography on silica gel. A careful examination of the ^{1}H-NMR spectrum of **11a**, however, showed it to contain a small quantity of the sulfur-substituted indole **12** (for the spectrum, see Experimental) as a by-product, which might arise from the reaction of **3** with *p*-chlorobenzenethiol formed during the course of the formation of **11a**. Though the mixture, when recrystallized from methanol, afforded **11a** as a pure form, we then examined a similar reaction in the presence of $CuCl_2$ (0.4 eq) as a thiol scavenger. These conditions gave **11a** in quantitative yield. Intriguingly, the reaction time was shortened to 6 h. Hydrogen chloride which was formed by reaction of *p*-chlorobenzenethiol with $CuCl_2$ might accelerate the reaction of **3** with methanol. The use of $CuCl_2$ alone (that is, without TsOH), however, did not effect the desired reaction. Similarly, the indolone **3** was heated in ethanol or isopropyl alcohol in the presence of TsOH (1 eq) and $CuCl_2$ (0.4 eq) to give **11b** (83%) and **11c** (92%), respectively.

The reaction of **3** with a high-boiling alcohol was performed by using benzene as a solvent. Thus, a mixture of **3** and benzyl alcohol (3 eq) was heated in boiling benzene in the presence of 0.2 eq of TsOH for 10 h to give the 4-(benzyloxy)indole **11d** in 67% yield, along with **12** (27%). When a similar reaction was carried out by adding $CuCl_2$ (0.5 eq), not only was the reaction time further shortened to 30 min, but also the product **11d** was obtained in high yield (82%). Subsequent deprotection of the *N*-sulfonyl group of **11d** with Mg–methanol in THF in the presence of NH_4Cl[7] gave, in 84% yield, 4-benzyloxy-1*H*-indole (**13**), a key intermediate for the synthesis of the hallucinogenic agent psilocibin (**14**).[8]

The above method was next applied to the synthesis of the *β*-adrenergic blocking agent (±)-pindolol (**19**), which has been widely used for the treatment of tachycardia and hypertension. Thus, a benzene solution of **3** and (±)-3-chloro-1,2-propanediol (**15**) (3 eq) was heated under reflux in the presence of TsOH (0.2 eq) and $CuCl_2$ (0.5 eq) for 1 h to give the 4-alkoxyindole **17** in 81% yield together with **12** (6%). The use of equimolar $CuCl_2$ in this reaction entirely prevented the formation of **12**, but nevertheless the yield of **17** was lowered to 77%. Compound **17** was then heated with a large excess of isopropylamine in the presence of NaOH in aqueous ethanol to give, with concomitant deprotection of the *N*-sulfonyl group, (±)-pindolol (**19**) (mp 172—173.5 °C, lit.[9] mp 171—173 °C) in 91% yield.

Pindolol has usually been employed as a recemic mixture, and has been synthesized *via* the reaction of 4-hydroxyindole with (±)-epichlorohydrin. The method, however, cannot be applied to the synthesis of (*S*)-(−)-pindolol (**20**), which exhibits higher activity than does the racemic mixture,[10] since the indol-4-yloxy anion attacks on the carbon *α* to the chlorine atom of (−)-epichlorohydrin to some extent, in competition with the requisite epoxide ring-opening, to bring about a decrease in optical purity.[11] Therefore, much effort has gone into the development of new methods for the synthesis of (*S*)-(−)-pindolol without the use of 4-hydroxyindole as an intermediate.[12]

A similar sequence of the reactions to that described above for the preparation of (±)-pindolol provided ready access to (*S*)-(−)-pindolol (**20**) in 65% overall yield from **3** and (*R*)-(−)-3-chloro-1,2-propanediol (**16**), *via* the intermediate **18**. In the present method, the alcohol **16** attacks on the carbonyl carbon atom of **3** with complete retention of its optical activity, and hence gives optically pure (*S*)-(−)-pindolol (**20**) [mp 94—95 °C (lit. mp 95—97 °C,[12a] 93.5—95 °C[12c]), $[\alpha]_D^{24}$ −4.9° (*c*=1, MeOH) (lit. $[\alpha]_D$ −5.1°,[12a] −4.6°[12c])].

Synthesis of 4-[Aryl (or Alkyl)thio]indoles. Application to the Synthesis of (±)-Chuangxinmycin As noted above, the reaction of **3** with alcohols gave the sulfur-substituted indole **12** as a by-product. This suggest that the reactions of **3** with thiols might provide a new synthesis of indoles bearing a sulfur substituent at the 4-position.

Indeed, a mixture of **3** and *p*-chlorobenzenethiol (3 eq) in benzene was heated under reflux in the presence of $BF_3 \cdot Et_2O$ to give **12** in 89% yield. Similar reactions of **3** with benzenethiol or *p*-toluenethiol gave the corresponding 4-(arylthio)indoles **21a** and **21b** in 98 and 97% yields, respectively. In these cases, no 4-chlorophenylthio compound **12** was formed. This may be ascribed to the higher nucleophilicity of benzenethiol or *p*-toluenethiol

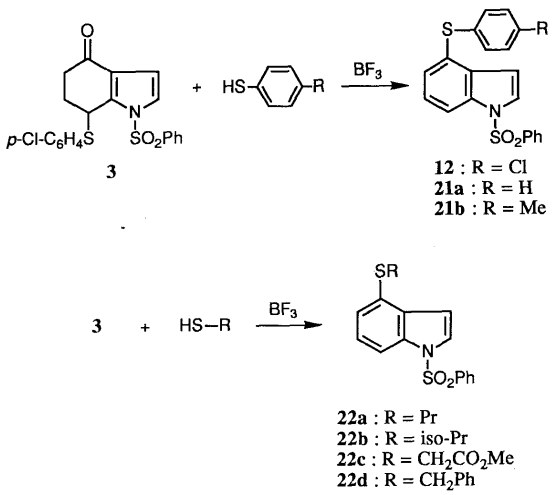


Chart 5

than that of *p*-chlorobenzenethiol formed during the course of the formation of **21a**, **b**.

The reactions of **3** with alkanethiols such as 1-propanethiol, 2-propanethiol, and methyl thioglycolate proceeded smoothly at room temperature to give the corresponding 4-(alkylthio)indoles **22a**, **22b** and **22c** in 97, 84 and 95% yields, respectively. The reaction with phenylmethanethiol required the use of refluxing conditions to afford the 4-(benzylthio)indole **22d** in 72% yield.

Chuangxinmycin (**27**), an antibiotic isolated from *Actinoplanes tsinanensis*,[13] is a unique indole alkaloid bearing a sulfur substituent at the 4-position, and is active against a number of gram-negative and gram-positive bacteria. Our attention was next turned to the synthesis of (±)-chuangxinmycin starting from the indole **22c**.

Friedel–Crafts acylation of **22c** with acetic anhydride in the presence of $AlCl_3$ gave the 3-acetyl derivative **23** in 91% yield. Treatment of **23** with piperidine and acetic acid in boiling benzene afforded the expected Knoevenagel condensation product **25** in 54% yield along with the carbinol **24** (44%) as a mixture of two diastereoisomers in a ratio of *ca.* 4 : 3. On the other hand, treatment of **23** with triethylamine in boiling benzene afforded quantitatively the carbinol **24**, which was then dehydrated with TsOH in boiling benzene to give **25** in 98% yield.

With the requisite tricyclic compound **25** so conveniently assembled, we then examined deprotection of the *N*-sulfonyl group of **25** with Mg–methanol in the presence of NH_4Cl. This, fortunately, also brought about reduction of the olefinic bond of the unsaturated ester moiety to give a mixture of chuangxinmycin methyl ester (**26a**) and its *trans*-isomer **26b** in a ratio of *ca.* 2 : 3 in 53% total yield. The structure determination of **26a**, **b** was made by comparing the ^{1}H-NMR spectral data (see Experimental) with the literature values.[14,15] Taking into account the results observed so far for the ester **26a**, **b** and their analogs,[14,17] we assumed that the product distribution of **26a** and **26b** (*ca.* 2 : 3) may reflect an equilibrium under the basic conditions employed. Thus, the obtained mixture of **26a**, **b** was hydrolyzed with NaOH in aqueous ethanol to afford quantitatively a mixture of chuangxinmycin (**27**) and its *trans*-isomer **28** in a ratio of *ca.* 2 : 3. As reported,[14]

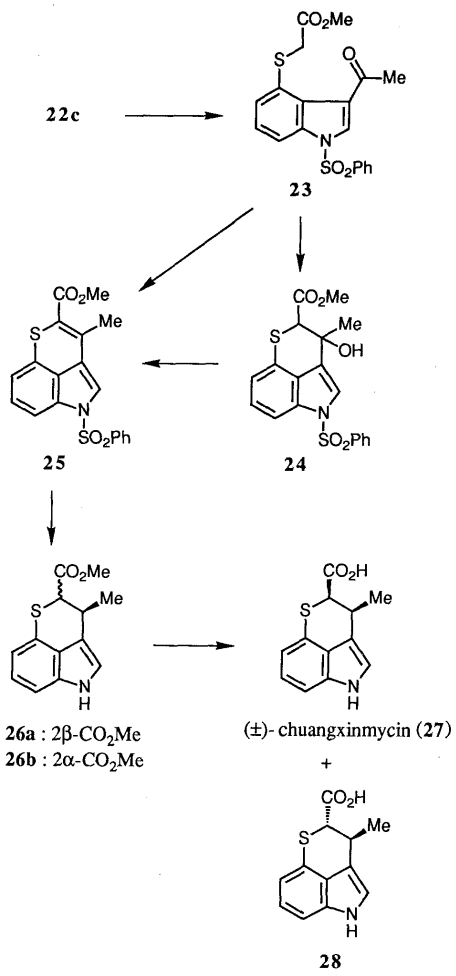
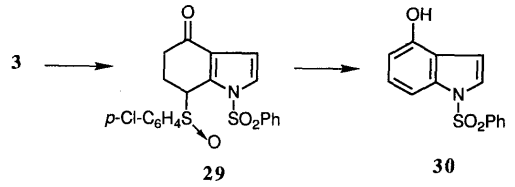


Chart 6

the isolation of **27** was easily accomplished by fractional crystallization of the mixture from CH_2Cl_2 and petroleum ether to give pure (±)-chuangxinmycin (**27**), mp 186—187 °C (lit. mp 181—184 °C,[16] 145—145.5 °C,[14] 190—191 °C[17]).

Finally, we also examined a transformation of **3** to the 4-hydroxyindole **30**. It was anticipated that the indolone **3**, on exposure to an appropriate acid, might provide **30**, through enolization of the carbonyl group of **3** and successive aromatization with release of *p*-chlorobenzenethiol. However, all attempts to prepare **30** by treatment of **3** with several acids such as TsOH, HCl, H_2SO_4, $BF_3 \cdot Et_2O$, and $SnCl_4$ under various conditions failed: the starting material **3** was recovered or a complex mixture of products was formed. Therefore, our attention was turned to the thermolysis of the sulfoxide **29** derived from **3**. The preparation of **29** was achieved by careful addition of *m*-chloroperbenzoic acid to a solution of **3** in CH_2Cl_2 to avoid the formation of the corresponding sulfone. The resultant sulfoxide **29** was then heated in refluxing benzene to give the desired **30** in 84% yield (based on **3**).

In conclusion, we have shown that the indolone **3** serves as a useful intermediate for the synthesis of indoles bearing an oxygen or a sulfur atom at the 4-position. Thus, we succeeded in concise syntheses of (±)- and (*S*)-(−)-pindolol and (±)-chuangxinmycin. An analogous reaction



29 30

Chart 7

of **3** with carbon nucleophiles such as Grignard reagents followed by dehydration of the resultant alcohols gives 4-alkylindoles. These results will be reported in the near future.

Experimental

Melting points are uncorrected. IR spectra were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM-PMX 60, JEOL JNM-EX 270, or Varian XL-300 spectrometer, and δ values are quoted relative to tetramethylsilane. Optical rotations were measured with a JASCO DIP-360 polarimeter. Exact MS determinations were obtained on a Hitachi M-80 instrument operating at 20 eV. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure.

Ethyl 4-(4-Chlorophenylthio)-4-(1-phenylsulfonyl-1*H*-pyrrol-2-yl)-butanoate (9) $TiCl_4$ (11 g, 6.4 ml, 58 mmol) was added to a solution of *N*-(phenylsulfonyl)pyrrole (**7**) (3 g, 14.5 mmol) and the α-chlorosulfide **8**[6] (5.1 g, 17.4 mmol) in CH_2Cl_2 (500 ml) at −78 °C, and the mixture was stirred at the same temperature for 2 h. Water was added to the reaction mixture, the organic layer was separated, and the organic phase was dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 9 : 1) to give **9** (4.3 g, 64%) as an oil. IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.20 (3H, t, J=7 Hz), 1.85—2.45 (4H, m), 4.05 (2H, q, J=7 Hz), 4.75 (1H, t, J=7 Hz), 5.9—6.3 (2H, m), 7.04 (4H, s), 7.15—7.85 (6H, m). *Anal.* Calcd for $C_{22}H_{22}ClNO_4S_2$: C, 56.95; H, 4.78; N, 3.02. Found: C, 56.91; H, 4.93; N, 2.97.

4-(4-Chlorophenylthio)-4-(1-phenylsulfonyl-1*H*-pyrrol-2-yl)butanoyl Chloride (10) A solution of $LiOH \cdot H_2O$ (2.8 g, 67.3 mmol) in water (16 ml) was added to a solution of **9** (7.8 g, 16.8 mmol) in THF (16 ml), and the mixture was stirred at room temperature for 48 h. Water (30 ml) was added to the reaction mixture, and the whole was acidified with 6 N HCl to pH 1, then extracted with Et_2O. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give the corresponding carboxylic acid (7.3 g, 100%). Pyridine (1.33 g, 16.8 mmol) and oxalyl chloride (6.4 g, 4.4 ml, 50.4 mmol) were added successively to a solution of the carboxylic acid in benzene (350 ml), and the mixture was stirred at room temperature for 30 min. The precipitated salts were removed by filtration and the filtrate was concentrated *in vacuo* to give the acid chloride **10** quantitatively as an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.9—2.4 (2H, m), 2.87 (2H, t, J=7 Hz), 4.67 (1H, t, J=7 Hz), 6.0—6.4 (2H, m), 7.0—7.9 (10H, m).

7-(4-Chlorophenylthio)-6,7-dihydro-1-(phenylsulfonyl)-1*H*-indol-4(5*H*)-one (3) $SnCl_4$ (5.6 g, 2.5 ml, 20.9 mmol) was added to a solution of **10** (3.16 g, 6.96 mmol) in CH_2Cl_2 (200 ml) at 0 °C and the mixture was stirred at the same temperature for 20 min. The reaction was quenched by addition of water and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 and the combined organic phase was dried over $MgSO_4$. The solvent was exaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 5 : 1) to give **3** (2.5 g, 86%), mp 113.5—114 °C (from MeOH). IR ($CHCl_3$): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 2.1—2.2 (1H, m), 2.27—2.47 (2H, m), 3.0—3.15 (1H, m), 5.16 (1H, t, J=2.8 Hz), 6.65 (1H, d, J=3.3 Hz), 7.25 (1H, d, J=3.3 Hz), 7.35 (2H, dt, J=8.3, 1.7 Hz), 7.48—7.56 (4H, m), 7.66 (1H, tt, J=7.3, 1.7 Hz), 7.88—8.04 (2H, m). ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ: 29.4, 33.0, 41.9, 109.0, 124.2, 125.6, 127.6, 129.5, 132.5, 134.2, 134.5, 134.6, 138.3, 140.9, 193.4. *Anal.* Calcd for $C_{20}H_{16}ClNO_3S_2$: C, 57.48; H, 3.86; N, 3.35. Found: C, 57.20; H, 3.85; N, 3.30.

General Procedure for the Preparation of 4-Alkoxyindoles 11a—c A mixture of **3** (100 mg, 0.24 mmol), $TsOH \cdot H_2O$ (45 mg, 0.24 mmol), and $CuCl_2 \cdot 2H_2O$ (17 mg, 0.1 mmol) in an appropriate alcohol (15 ml) was heated under reflux for 6 h. The excess alcohol was evaporated off, water (10 ml) was added to the residue, and the whole was extracted with CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 10 : 1) to give the following compounds. 4-Methoxy-1-(phenylsulfonyl)-1*H*-indole (**11a**), quantitative yield, mp 79—80 °C (from MeOH). IR (CCl_4): 1580, 1480, 1370, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 3.80 (3H, s), 6.58 (1H, d, J=7.5 Hz), 6.74 (1H, d, J=3.5 Hz), 7.0—7.6 (6H, m), 7.65—8.0 (2H, m). *Anal.* Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.51; H, 4.56; N, 4.93. 4-Ethoxy-1-(phenylsulfonyl)-1*H*-indole (**11b**), 83% yield, mp 114—115 °C (from hexane–AcOEt). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.42 (3H, t, J=7 Hz), 4.06 (2H, q, J=7 Hz), 6.61 (1H, d, J=7.5 Hz), 6.78 (1H, d, J=3.5 Hz), 7.05—7.6 (6H, m), 7.6—8.0 (2H, m). *Anal.* Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.54; H, 5.06; N, 4.83. 4-Isopropyloxy-1-(phenylsulfonyl)-1*H*-indole (**11c**), 92% yield, an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.33 (6H, d, J=6 Hz), 4.60 (1H, septet, J=6 Hz), 6.63 (1H, d, J=7.5 Hz), 6.77 (1H, d, J=3.5 Hz), 7.0—7.6 (6H, m), 7.6—8.0 (2H, m). *Anal.* Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.64; H, 5.56; N, 4.36.

4-Benzyloxy-1-(phenylsulfonyl)-1*H*-indole (11d) and 4-(4-Chlorophenylthio)-1-(phenylsulfonyl)-1*H*-indole (12) Method A: A mixture of **3** (200 mg, 0.48 mmol), benzyl alcohol (155 mg, 1.43 mmol), and $TsOH \cdot H_2O$ (18 mg, 0.1 mmol) in benzene (10 ml) was heated under reflux for 10 h. After completion of the reaction, the reaction mixture was washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 10 : 1). The first eluate gave **12** (53 mg, 27%), mp 110—111 °C (from hexane–AcOEt). IR ($CHCl_3$): 1370, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 6.68 (1H, d, J=3 Hz), 7.1—7.7 (11H, m), 7.8—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{14}ClNO_2S_2$: C, 60.07; H, 3.53; N, 3.50. Found: C, 60.11, H, 3.32; N, 3.49. The second eluate gave **11d** (117 mg, 67%), mp 130—131 °C (from hexane–AcOEt) (lit.[2b] mp 129.5—130.5 °C). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 5.10 (2H, s), 6.63 (1H, d, J=8 Hz), 6.82 (1H, d, J=4 Hz), 7.0—7.7 (11H, m), 7.7—8.0 (2H, m).

Method B: A mixture of **3** (150 mg, 0.36 mmol), benzyl alcohol (117 mg, 1.08 mmol), $TsOH \cdot H_2O$ (14 mg, 0.07 mmol), and $CuCl_2 \cdot 2H_2O$ (31 mg, 0.18 mmol) in benzene (10 ml) was heated under reflux for 30 min. Similar work-up to that described above afforded **11d** (108 mg, 82%).

4-(Benzyloxy)-1*H*-indole (13) A mixture of **11d** (93 mg, 0.26 mmol), magnesium powder (50 mg), and NH_4Cl (3 mg) in THF (5 ml) and MeOH (5 ml) was stirred at room temperature for 5 h. Since a portion of the starting material **11d** remained, additional magnesium (50 mg) was added and the mixture was stirred for 10 h. A saturated $NaHCO_3$ solution was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane–AcOEt, 10 : 1) to give **13**[18] (48 mg, 84%) as an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 5.16 (2H, s), 6.4—6.9 (2H, m), 6.9—7.6 (8H, m), 7.6—8.3 (1H, br).

(±)-1-Chloro-3-[(1-phenylsulfonyl)-1*H*-indol-4-yloxy]-2-propanol (17) A mixture of **3** (200 mg, 0.48 mmol), (±)-3-chloro-1,2-propanediol (**15**) (159 mg, 1.44 mmol), $TsOH \cdot H_2O$ (18 mg, 0.1 mmol), and $CuCl_2 \cdot 2H_2O$ (41 mg, 0.24 mmol) in benzene (10 ml) was heated under reflux for 1.5 h. After work-up similar to that described above for **11d**, the crude material was chromatographed on silica gel (hexane–AcOEt, 4 : 1). The first eluate gave **12** (11 mg, 6%). The second eluate gave **17** (141 mg, 81%) as an oil. IR ($CHCl_3$): 3590, 1580, 1485, 1360, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.83 (1H, br d, J=5 Hz, OH), 3.7—3.8 (2H, m, CH_2Cl), 4.15 (3H, br s, OCH_2, OCH), 6.5—6.8 (2H, m, H-3, 5), 7.0—7.6 (6H, m, aromatic protons), 7.6—8.0 (2H, m, aromatic protons). *Anal.* Calcd for $C_{17}H_{16}ClNO_4S$: C, 55.81; H, 4.41; N, 3.83. Found: C, 55.89; H, 4.51; N, 3.72.

(±)-Pindolol (19) A mixture of **17** (141 mg, 0.39 mmol) and isopropylamine (3.8 ml) in EtOH (2.5 ml) and 1 N NaOH solution (2.5 ml) was heated under reflux for 24 h. Water (10 ml) was added to the reaction mixture and the whole was extracted with CH_2Cl_2–MeOH (10 : 1). The organic phase was dried over $MgSO_4$ and the solvent was evaporated off to give (±)-pindolol (**19**) (90 mg, 93%), mp 172—173.5 °C (from ethanol) (lit.[9] mp 171—173 °C). ^{1}H-NMR (CD_3OD, 60 MHz) δ: 1.10 (6H, d, J=6.5 Hz, Me×2), 2.5—3.1 (3H, m, NCH_2, NCH), 4.0—4.3 (3H, m, OCH_2, OCH), 6.4—6.7 (2H, m, H-3, 5), 6.9—7.2 (3H, m, H-2, 6, 7). *Anal.* Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.41; H, 8.20; N, 11.24.

(*R*)-(−)-1-Chloro-3-[(1-phenylsulfonyl)-1*H*-indol-4-yloxy]-2-propanol (18) A mixture of **3** (150 mg, 0.36 mmol), (*R*)-(−)-3-chloro-1,2-propanediol (**16**) (119 mg, 1.08 mmol), $TsOH \cdot H_2O$ (14 mg, 0.07 mmol), and $CuCl_2 \cdot 2H_2O$ (31 mg, 0.18 mmol) in benzene (10 ml) was heated under reflux for 1.5 h. After work-up, the crude material was chromatographed on silica gel (hexane–AcOEt, 4 : 1). The first eluate gave **12** (5 mg, 4%). The second eluate gave **18** (101 mg, 77%) as an oil, $[\alpha]_D^{24}$ −2.7° (*c* = 0.43, $CHCl_3$). IR ($CHCl_3$): 3580, 1580, 1480, 1360, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 2.61 (1H, br s, OH), 3.7—3.9 (2H, m, CH_2Cl), 4.1—4.3 (3H, m, OCH_2, OCH), 6.66 (1H, dd, *J* = 7.9, 2.6 Hz, H-5), 6.74—6.79 (1H, m, H-3), 7.22 (1H, dt, *J* = 8.6, 2.0 Hz, H-6), 7.38—7.60 (4H, m, aromatic protons), 7.64 (1H, d, *J* = 8.3 Hz, H-7), 7.8—8.0 (2H, m, aromatic protons). *Anal.* Calcd for $C_{17}H_{16}ClNO_4S$: C, 55.81; H, 4.41; N, 3.83. Found: C, 55.70; H, 4.42; N, 3.67.

(*S*)-(−)-Pindolol (20) A mixture of **18** (266 mg, 0.73 mmol) and isopropylamine (7 ml) in EtOH (5 ml) and 1 N NaOH solution (5 ml) was heated under reflux for 24 h. After work-up, the crude material was chromatographed on silica gel ($CHCl_3$–MeOH–NEt_3, 10 : 1 : 1) to give (*S*)-(−)-pindolol (**20**) (142 mg, 79%), mp 94—95 °C (from benzene) (lit. mp 95—97 °C,[12a] 93.5—95 °C[12c]). $[\alpha]_D^{24}$ −4.9° (*c* = 1, MeOH) (lit. $[\alpha]_D$ −5.1°,[12a] −4.6°[12c]). IR ($CHCl_3$): 3600, 3490 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.10 (6H, d, *J* = 6.3 Hz, Me × 2), 1.6—2.4 (2H, br, OH, NH), 2.75—3.0 (3H, m, NCH_2, NCH), 4.08—4.20 (3H, m, OCH_2, OCH); 6.54 (1H, dd, *J* = 7.3, 1.0 Hz, H-5), 6.63—6.77 (1H, m, H-3), 7.0—7.15 (3H, m, H-2, 6, 7), 8.25 (1H, br s, indole NH). *Anal.* Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.60; H, 8.10; N, 11.17.

General Procedure for the Preparation of 4-Arylthio-1-(phenylsulfonyl)-1*H*-indoles 12, 21a, and 21b $BF_3 \cdot Et_2O$ (1 ml) was added to a solution of **3** (150 mg, 0.36 mmol) and *p*-chlorobenzenethiol, benzenethiol, or *p*-toluenethiol (1.08 mmol) in benzene (5 ml), and the mixture was heated under reflux for 8 h for **12** or for 4 h for **21a, b**. Water was added to the reaction mixture, the whole was extracted with benzene, and the organic phase was dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 15 : 1) to give the following compounds. The physical data of compound **12** (89% yield) have already been given above. 1-Phenylsulfonyl-4-(phenylthio)-1*H*-indole (**21a**), 98% yield, an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 6.73 (1H, d, *J* = 3.5 Hz), 7.0—7.7 (11H, m), 7.8—8.1 (3H, m). *Anal.* Calcd for $C_{20}H_{15}NO_2S_2$: C, 65.73, H, 4.14; N, 3.83. Found: C, 65.94; H, 4.12; N, 3.64. 4-(4-Methylphenylthio)-1-(phenylsulfonyl)-1*H*-indole (**21b**), 97% yield, mp 130—132 °C (from hexane–AcOEt). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.26 (3H, s), 6.69 (1H, d, *J* = 3.5 Hz), 6.9—7.6 (10H, m), 7.7—8.0 (3H, m). *Anal.* Calcd for $C_{21}H_{17}NO_2S_2$: C, 66.47; H, 4.52; N, 3.69. Found: C, 66.24; H, 4.54; N, 3.62.

General Procedure for the Preparation of 4-Alkylthio-1-(phenylsulfonyl)-1*H*-indoles 22a—d $BF_3 \cdot Et_2O$ (1 ml) was added to a solution of **3** (150 mg, 0.36 mmol) and 1-propanethiol, 2-propanethiol, methyl thioglycolate, or phenylmethanethiol (1.08 mmol) in benzene (5 ml), and the mixture was stirred at room temperature for 24 h, except for **22d** (heated under reflux for 22 h). Similar work-up to that described above for **21a, b** gave the following compounds. 1-Phenylsulfonyl-4-(propylthio)-1*H*-indole (**22a**), 97% yield, mp 103—105 °C (from hexane). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 0.96 (3H, t, *J* = 7 Hz), 1.1—2.0 (2H, m), 2.90 (2H, t, *J* = 7 Hz), 6.78 (1H, d, *J* = 3.5 Hz), 7.1—8.0 (9H, m). *Anal.* Calcd for $C_{17}H_{17}NO_2S_2$: C, 61.60; H, 5.17; N, 4.23. Found: C, 61.80; H, 5.24; N, 4.26. 4-Isopropylthio-1-(phenylsulfonyl)-1*H*-indole (**22b**), 84% yield, an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.26 (6H, d, *J* = 6 Hz), 3.36 (1H, septet, *J* = 6 Hz), 6.82 (1H, d, *J* = 3.5 Hz), 7.1—7.6 (6H, m), 7.7—8.0 (3H, m). *Anal.* Calcd for $C_{17}H_{17}NO_2S_2$: C, 61.60; H, 5.17; N, 4.23. Found: C, 61.94; H, 5.08; N, 4.13. Methyl [1-(phenylsulfonyl)-1*H*-indol-4-ylthio]acetate (**22c**), 95% yield, mp 135—136 °C (from hexane–AcOEt). IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 3.58 (2H, s), 3.60 (3H, s), 6.83 (1H, d, *J* = 3.5 Hz), 7.1—7.7 (6H, m), 7.7—8.0 (3H, m). *Anal.* Calcd for $C_{17}H_{15}NO_4S_2$: C, 56.49; H, 4.18; N, 3.88. Found: C, 56.23; H, 4.21; N, 3.80. 4-(Phenylmethylthio)-1-(phenylsulfonyl)-1*H*-indole (**22d**), 72% yield, mp 106—106.5 °C (from hexane). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 4.05 (2H, s), 6.70 (1H, d, *J* = 4 Hz), 7.1—7.6 (11H, m), 7.7—8.0 (3H, m). *Anal.* Calcd for $C_{21}H_{17}NO_2S_2$: C, 66.47; H, 4.52; N, 3.69. Found: C, 66.35; H, 4.54; N, 3.65.

Methyl [3-Acetyl-1-(phenylsulfonyl)-1*H*-indol-4-ylthio]acetate (23) A solution of **22c** (466 mg, 1.24 mmol) in 1,2-dichloroethane (2 ml) was added dropwise to a mixture of acetic anhydride (692 mg, 6.78 mmol) and $AlCl_3$ (1.79 g, 13.46 mmol) in 1,2-dichloroethane (12 ml), and the mixture was stirred at room temperature for 15 h. Water was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The organic phase was washed successively with saturated $NaHCO_3$ solution and brine, and then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **23** (466 mg, 94%) as an oil. IR ($CHCl_3$): 1730, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.60 (3H, s), 3.62 (3H, s), 3.66 (2H, s), 7.2—7.7 (5H, m), 7.7—8.0 (3H, m), 8.08 (1H, s). Exact MS *m/z*: Calcd for $C_{19}H_{17}NO_5S_2$: 403.0547. Found: 403.0557.

Methyl 2,3-Dihydro-3-hydroxy-3-methyl-5-phenylsulfonyl-5*H*-thiopyrano[4,3,2-*cd*]indole-2-carboxylate (24) A mixture of **3** (100 mg, 0.25 mmol) and triethylamine (0.1 ml) in benzene (5 ml) was heated under reflux for 15 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 4 : 1) to give **24** quantitatively as a mixture (*ca.* 4 : 3) of two diastereoisomers, an oil. IR (CCl_4): 3550, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.69, 1.74 (12/7H + 9/7H, both s, C_3-Me), 3.22 (4/7H, br s, OH), 3.60 (3H + 3/7H, s, OMe, OH), 3.75, 3.92 (4/7H + 3/7H, both s, H-2), 6.9—8.0 (9H, m, aromatic protons). Exact MS *m/z*: Calcd for $C_{19}H_{17}NO_5S_2$: 403.0546. Found: 403.0545.

Methyl 3-Methyl-5-phenylsulfonyl-5*H*-thiopyrano[4,3,2-*cd*]indole-2-carboxylate (25) Method A: A mixture of **24** (94 mg, 0.23 mmol) and $TsOH \cdot H_2O$ (44 mg, 0.23 mmol) in benzene (5 ml) was heated under reflux for 10 h. The reaction mixture was washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 4 : 1) to give **25** (88 mg, 98%), mp 172—173 °C (from benzene–MeOH). IR ($CHCl_3$): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.31 (3H, s), 3.81 (3H, s), 6.70 (1H, d, *J* = 7.5 Hz), 6.9—7.7 (6H, m), 7.7—8.0 (2H, m). *Anal.* Calcd for $C_{19}H_{15}NO_4S_2$; C, 59.21; H, 3.91; N, 3.63. Found: C, 59.13; H, 3.93; N, 3.57.

Method B: A mixture of **23** (82 mg, 0.2 mmol), piperidine (0.3 ml), and acetic acid (0.2 ml) in benzene (5 ml) was heated under reflux for 24 h. Water was added to the reaction mixture, the whole was extracted with benzene, and the organic phase was dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 4 : 1). The first eluate gave **24** (42 mg, 54%). The second eluate gave **25** (36 mg, 44%).

Methyl *cis*-2,3-Dihydro-3-methyl-5-phenylsulfonyl-5*H*-thiopyrano-[4,3,2-*cd*]indole-2-carboxylate (26a) and Its *trans*-Isomer (26b) Magnesium powder (100 mg) was added to a mixture of **25** (96 mg, 0.25 mmol) and NH_4Cl (5 mg) in dry THF (3 ml) and MeOH (3 ml), and the mixture was stirred at room temperature for 3 h. A saturated NH_4Cl solution was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give a mixture (*ca.* 2 : 3) of chuangxinmycin methyl ester (**26a**)[14,15] and its *trans*-isomer (**26b**)[15] (total 33 mg, 53%), an oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.35 (3H × 2/5, d, *J* = 6.9 Hz, C_3-Me for **26a**), 1.42 (3H × 3/5, d, *J* = 6.7 Hz, C_3-Me for **26b**), 3.60 (3/5H, d quintet, *J* = 1.1, 6.7 Hz, H-3 for **26b**), 3.73 (3H × 3/5, s, OMe for **26b**), 3.74 (3H × 2/5, s, OMe for **26a**), 3.75 (3/5H, d, *J* = 6.7 Hz, H-2 for **26b**), 4.19 (2/5H, d, *J* = 3.7 Hz, H-2 for **26a**), 6.92—6.99 (2H, m, aromatic protons), 7.09—7.13 (2H, m, aromatic protons), 8.03 (2/5H, s, NH for **26a**), 8.06 (3/5 H, s, NH for **26b**): the signal due to H-3 of **26a** overlapped with the signals between δ 3.73—3.75.

Chuangxinmycin (27) A mixture of **26a, b** (36 mg, 0.15 mmol) and NaOH (71 mg, 1.79 mmol) in water (1.3 ml) and EtOH (1.8 ml) was stirred at room temperature for 17 h. EtOH was evaporated off and the residue was washed with Et_2O. Et_2O (3 ml) was added to the aqueous layer and the whole was acidified with 10% HCl to pH 1. The organic phase was separated and the aqueous layer was further extracted with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a mixture of (±)-chuangxinmycin (**27**) and its *trans*-isomer **28** (total 33 mg, 100%). The mixture of **27** and **28** was then recrystallized from petroleum ether and CH_2Cl_2 to give pure (±)-chuangxinmycin (**27**) (6 mg, 18%), mp 186—187 °C (lit. mp 181—184 °C,[16] 145—145.5 °C,[14] 190—191 °C[17]). ^{1}H-NMR ($CDCl_3$–CD_3OD, 3 : 1, 270 MHz) δ: 1.36 (3H, d, *J* = 6.9 Hz, C_3-Me), 3.80 (1H, dq, *J* = 3.3, 6.9 Hz, H-3), 4.25 (1H, d, *J* = 3.3 Hz, H-2), 6.90 (1H, dd, *J* = 1.3, 6.9 Hz, H-8), 7.01 (1H, s, H-4), 7.09 (1H, dd, *J* = 6.9, 8.2 Hz, H-7), 7.14 (1H, dd, *J* = 1.3, 8.2 Hz, H-6). Exact MS *m/z*: Calcd for $C_{12}H_{11}NO_2S$: 233.0510. Found: 233.0519.

1-(Phenylsulfonyl)-1*H*-indol-4-ol (30) A solution of *m*-chloroperben-

zoic acid (80%) (51 mg, 0.24 mmol) in CH_2Cl_2 (5 ml) was added dropwise to an ice-cooled solution of **3** (100 mg, 0.24 mmol) in CH_2Cl_2 (35 ml) over a period of 30 min, and the mixture was stirred at room temperature for 15 h. The reaction mixture was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and then concentrated *in vacuo*. The resultant sulfoxide **29** was dissolved in benzene (5 ml) and the mixture was heated under reflux for 10 h. The solvent was removed by evaporation and the residue was chromatographed on silica gel to give **30** (55 mg, 84%), mp 130—131 °C (from hexane–AcOEt) (lit.[4a] mp 130.0—130.7 °C). IR ($CHCl_3$): 3600, 1370, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 6.0—6.3 (1H, br), 6.58 (1H, d, J=7.5 Hz), 6.75 (1H, d, J=4 Hz), 6.9—8.0 (8H, m).

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