Registry No. 1, 100-43-6; **2a**, 111-88-6; **2c**, 91-60-1; **2d**, 100-53-8; **3a**, 105163-65-3; **3b**, 105163-66-4; **3c**, 105163-67-5; **4b**, 105163-68-6; **6n**, 3079-27-4; **6o**, 934-72-5; **6p**, 35330-76-8; **7**·HCl, 6298-11-9; **8g** (X = Cl), 4548-45-2; **9a**, 105163-69-7; **9b**, 62237-49-4; **9c**, 105163-70-0; **9d**, 21070-67-7; **9d**·HCl, 21070-68-8; **9e**, 21181-90-8; **9e**·HCl, 21181-91-9; **9f**, 105163-71-1; **9g**, 105163-72-2; **9h**, 105163-73-3; **9i**, 105163-74-4; **10h**, 105163-75-5; **11n**, 3698-95-1; **12**·HCl (X = Cl), 85673-15-0; **13a**, 105163-76-6; **13b**, 105163-77-7; **14a**, 105163-78-8; **14b**, 90158-96-6; **16n**, 7560-60-3; **16p**, 35330-75-7; **16q**, 34008-69-0; **16r**, 7726-20-7; **18a**, 105163-79-9; **18b**, 14933-92-7; **18c**, 105163-80-2; **19a**, 822-27-5; **20l**, 28683-44-5; **21k**, 149-30-4; **21l**, 27410-87-3.

New Total Synthesis of (±)-Indolmycin

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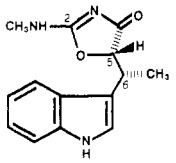
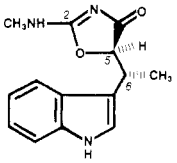
Received May 15, 1986

A convergent total synthesis of the antibiotic (±)-indolmycin (1) is presented. *N*-Carbobenzoxy-3-(1-chloroethyl)indole (12) is prepared in three steps from indole-3-carboxaldehyde (9). Alkylation of the lithium anion of 2-(dimethylamino)-4(5*H*)-oxazolone (4) with chloride 12 provides a mixture of the (±)-2-dimethylamino derivative of indolmycin (13) and its diastereomer (14) in a ratio of 2.2:1. Amine exchange is effected by treatment of 13 with methylamine, affording (±)-1 in five steps from commercially available 9. Efforts to extend this technology toward an asymmetric synthesis of (−)-1 are described.

Indolmycin (1), isolated from an African strain of *Streptomyces albus*,[1] exhibits an antibacterial spectrum that includes the pathogenic species *Pasteurella*, *Haemophilus*, and *Mycoplasma*,[2] which are responsible for many of the respiratory diseases in farm animals. It was shown by Schach von Wittenau and Els[3] that indolmycin (1) is 5-[1-(1*H*-indol-3-yl)ethyl]-2-(methylamino)-4(5*H*)-



(5*S*, 6*R*)-**1**
(−)-Indolmycin

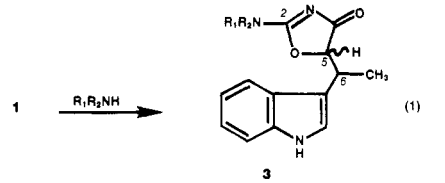


(5*R*, 6*R*)-**2**
(+)-Isoindolmycin

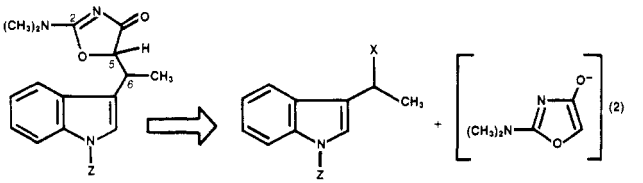
oxazolone, and the absolute configuration was later determined as 5*S*,6*R* by Chan and Hill.[4] In an alkaline medium indolmycin readily epimerizes at C-5 to afford isoindolmycin (2). In contrast to indolmycin, this unnatural diastereomer (5*R*,6*R*) possesses no antibacterial activity.[3] We wished to prepare a variety of analogues, related to indolmycin, and in particular some benzo-substituted compounds. Synthetic attempts were made using two published routes[3,5] for indolmycin itself, but these were found to be unacceptable when starting with the requisite substituted indoles (e.g., 5-methoxyindole, 5-fluoroindole, etc.).[6] Takeda and Mukaiyama[7] have reported a 14-step asymmetric synthesis of indolmycin that could be used for the preparation of certain analogues; however, we were interested in the development of a shorter sequence. In the present paper we report the successful use of the enolate anion derived from 2-(dimethylamino)-4(5*H*)-oxazolone (4) as a key intermediate in the synthesis of (±)-indolmycin. This new synthesis can also be readily adapted for the preparation of some compounds related to this antibiotic.

Results and Discussion

Shortly after we initiated work in the area of indolmycin chemistry, we found that a simple amine exchange reaction[8] affords 2-amino analogues of indolmycin in the manner illustrated below (eq 1). In principle, this reaction



could be used as the last step in a total synthesis of 1 (using methylamine), allowing facile manipulation of intermediates that do not possess an acidic hydrogen on the exocyclic nitrogen atom. The idea was conceived that the 2-(dimethylamino)-4(5*H*)-oxazolone ring could be constructed at an early stage in the synthetic sequence and then connected at C-5–C-6 by a displacement reaction with a suitably substituted 3-ethylindole nucleus, as shown retrosynthetically in eq 2. This new method, if successful,

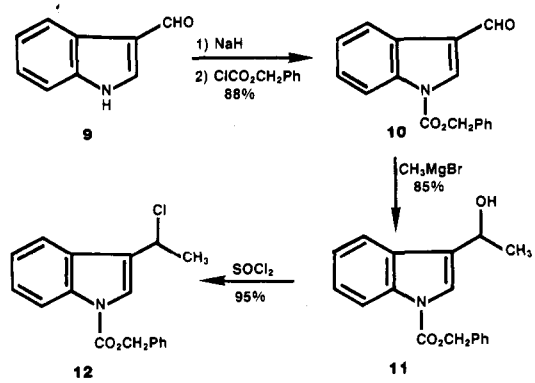


would circumvent some problems encountered in previous

(1) Rao, K. V. *Antibiot. Chemother. (Basel, 1954–70)* **1960**, *10*, 312.
(2) (a) Marsh, W. S.; Garretson, A. L.; Wesel, E. M. *Antibiot. Chemother. (Basel, 1954–70)* **1960**, *10*, 316. (b) Girard, A. E.; Pfizer Central Research, unpublished results.
(3) Schach von Wittenau, M.; Els, H. *J. Am. Chem. Soc.* **1961**, *83*, 4678; **1963**, *85*, 3425.
(4) Chan, T. H.; Hill, R. K. *J. Org. Chem.* **1970**, *35*, 3519.
(5) Preobrayhenskaya, M. N.; Balashova, E. G.; Turchin, K. F.; Padeiskay, E. N.; Uvarova, N. V.; Pershin, G. N.; Suvorov, N. N. *Tetrahedron* **1968**, *24*, 6131.
(6) (a) The electrophilic addition of ethyl *trans*-2,3-epoxybutyrate to various benzo-substituted indoles in the presence of a Lewis acid gave extremely low yields of the desired α-indolemycenic acid ethyl esters,[3] due to a competing indole dimerization reaction. In addition, our attempts to prepare requisite Mannich bases derived from benzo-substituted indoles and ethylideneisopropylamine were largely unsuccessful.[5] (b) The synthesis of a wide variety of indole-3-carboxaldehydes, key intermediates in the present work, derived from benzo-substituted indoles containing either an electron-withdrawing or an electron-donating group using a Vilsmeier-Haach formylation reaction, is well documented: Remers, W. A. In *The Chemistry of Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley: New York, 1979; Vol. 25; Part III, Chapter IX, pp 357–465.
(7) Takeda, T.; Mukaiyama, T. *Chem. Lett.* **1980**, 163.
(8) (a) Howell, C. F.; Quinones, N. Q.; Hardy, R. A., Jr. *J. Org. Chem.* **1962**, *27*, 1679. (b) Lindberg, U. H.; Pedersen, J. *Acta Pharm. Suecica* **1968**, *5*, 15.

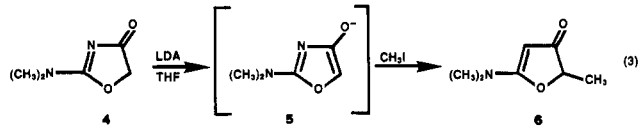
0022-3263/86/1951-4920$01.50/0

Scheme I



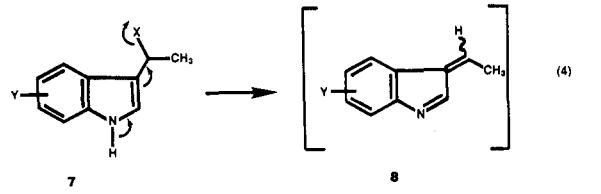
work in construction of the oxazolone ring at a late stage in the synthesis.[3,5] In addition, this approach would make possible the synthesis of benzo-substituted analogues not readily available via the published procedures, and would also allow preparation of 2-amino analogues of the parent antibiotic via the amine exchange reaction.

Total Synthesis of (±)-Indolmycin. 2-(Dimethylamino)-4(5*H*)-oxazolone (**4**) was conveniently prepared in one step from ethyl glycolate and dimethylcyanamide, in a manner analogous to that used previously for the synthesis of other 2-amino-4(5*H*)-oxazolones.[8a] Treatment of **4** with lithium diisopropylamide (LDA) followed by the addition of methyl iodide demonstrated that the desired enolate anion **5** could be formed and alkylated, as shown in eq 3. Various 3-(1-substituted-ethyl)indoles are known



(3)

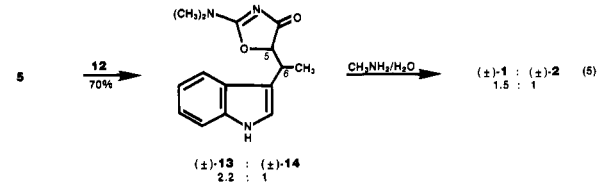
to be extremely labile in cases where the substituent "X" is a good leaving group. This is due to the rapid loss of HX from **7**, followed by polymerization of the resulting 3*H*-pseudoindole (**8**; eq 4).[9] For this reason we sought to



(4)

utilize some N-protected 3-(1-chloroethyl)indoles. Initially, compounds were synthesized with benzyl, *tert*-butyloxycarbonyl, and benzyloxycarbonyl protecting groups. Ultimately the latter group was chosen for this work due to its ease of removal under the reaction conditions. The desired *N*-carbobenzoxy-3-(1-chloroethyl)indole (**12**) was obtained as shown in Scheme I. Spectral data for **12** were consistent with the assigned structure, but attempts to further purify this material by column chromatography using silica gel were unsuccessful owing to its instability.

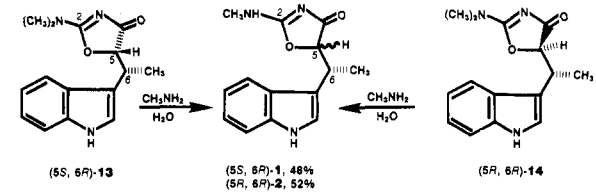
At this stage, both the oxazolone and the appropriately substituted indole were in hand, and we were in a position to attempt the construction of the C-5–C-6 bond in the manner described above (eq 2). Treatment of the enolate anion **5** (2 equiv.) with *N*-carbobenzoxy-3-(1-chloroethyl)indole (**12**, −78 °C → room temperature) indeed gave deprotected 2-dimethylamino derivatives of indolmycin in a 2.2:1 ratio of the (±)-natural and (±)-unnatural (iso) stereoisomers, **13** and **14**, in yields of 48% and 22%, respectively (eq 5).[10a] Initially, (±)-**13** and (±)-**14** were not



(5)

separated, and a mixture of both was allowed to react with 40% aqueous methylamine to afford (±)-indolmycin and (±)-isoindolmycin in a ratio of 1.5:1, respectively. Obviously, some epimerization takes place under these conditions. The racemic indolmycin and isoindolmycin could be readily separated by chromatography,[5] and the structures were confirmed by comparison with authentic samples.[3] Later, a method was developed for conducting the amine exchange reaction without epimerization, permitting pure (±)-**13** to be converted in quantitative yield to (±)-indolmycin (vide infra).

Although the epimerization of indolmycin (**1**) to isoindolmycin (**2**) is well known,[3,5] the ratio of these two diastereomers under thermodynamic conditions has not been previously determined. Starting from either the natural (5*S*,6*R*) or unnatural (iso, 5*R*,6*R*) 2-dimethylamino isomers **13** or **14**, respectively, an identical mixture of indolmycin and isoindolmycin (48:52, respectively) resulted from treatment with aqueous methylamine (eq 6). A



(6)

similar ratio was obtained upon kinetic deuteration of the lithium enolate derived from **13** with CD_3OD at −78 °C, affording a mixture of 5-deutero-2-(dimethylamino) derivatives of indolmycin and isoindolmycin. These studies emphasize the fortuitousness of the 2.2:1 predominance of the natural diastereomer in the alkylation reaction of the enolate anion **5** with the chloroethyl indole **12**.[10b,c]

Attempted Asymmetric Synthesis of Indolmycin

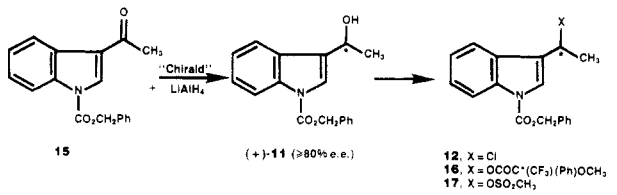
We next attempted the extension of the present technology to an asymmetric synthesis of indolmycin in order to allow relatively facile enantioselective production of analogues. Any asymmetric synthesis of indolmycin must address the problem of the rapid epimerization at C-5 that occurs in basic media. Indeed, Takeda and Mukaiyama[7] have developed an interesting asymmetric synthesis of indolmycin that requires a number of additional steps to overcome the problem of epimerization at C-5.

Although our work had shown that epimerization occurs during the aqueous amine exchange reaction, it was hoped

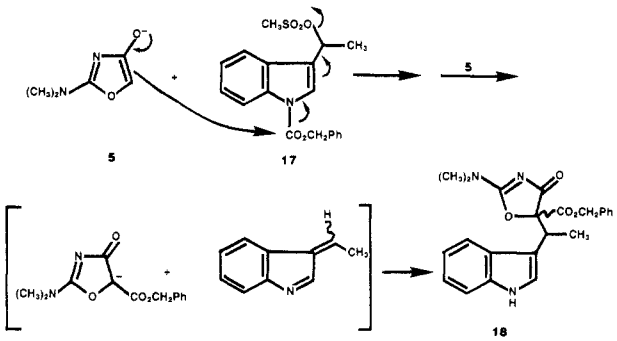
(9) Albright, J. D.; Snyder, H. R. *J. Am. Chem. Soc.* **1959**, *81*, 2239 and references therein.

(10) (a) Compounds (−)-**13** and (+)-**14** previously were prepared by reaction of (−)-**9** with dimethylamine (eq 1). The relative configurations about C-5 and C-6 were assigned by comparison of their NMR spectra and optical rotations with those of (−)-**1** and (+)-**2** (see Experimental Section). (b) Pure (±)-**14** can be converted to a 48:52 mixture of (±)-**1** and (±)-**2**, respectively. Therefore, quantitative conversion of (±)-**13** to (±)-**1** under nonepimerizing conditions (see text), along with quantitative conversion of (±)-**14** to (±)-**1** and (±)-**2** under epimerizing conditions, affords an overall yield of (±)-**1** from coupling precursors of 59% (i.e., 48% + 0.48 (22%)). (c) Comins and Stroud have recently reported a related nucleophilic substitution on a 3-alkylindole intermediate: Comins, D. L.; Stroud, E. D. *Tetrahedron Lett.* **1986**, *27*, 1869.

Scheme II



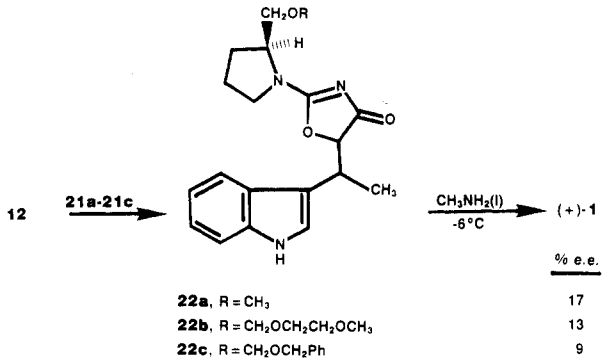
Scheme III



that conditions eliminating epimerization could be found. Attempts at amine exchange in various solvents led to the encouraging result that the 2-dimethylamino derivative of indolmycin, **13**, could be converted quantitatively to indolmycin within 1 h without significant epimerization in liquid methylamine under reflux (−6 °C). However, substantial epimerization took place if the reaction were allowed to proceed several hours. Gaseous methylamine in acetone was also found to afford indolmycin, without epimerization, in 24 h. Based on our initial work to prepare (±)-indolmycin, a possible method for an asymmetric synthesis of (−)-indolmycin appeared to be the use of chiral chloride **12**. Assuming that reaction of **12** with oxazolone anion **5** proceeds via S_N2 displacement, use of optically active **12** allows us to obtain complete stereocontrol at C-6. Obviously we are still forced to accept a mixture at C-5; in other words, this approach if successful gives rise to indolmycin and isoindolmycin, both optically active. We were able to prepare the requisite optically active alcohol (+)-**11** in ≥ 80% ee using LAH/Chirald complex[11] by reduction of ketone **15** (Scheme II).[12] The % ee was determined by the Mosher NMR method following conversion of the enantiomeric mixture to the corresponding diastereomeric esters **16** using α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[12a] However, all attempts to prepare the chiral chloride **12** from (+)-**11** (i.e., $SOCl_2$; $SOCl_2/TEA/Et_2O$; PPh_3/CCl_4) gave material of zero optical rotation, which was presumed to be racemic.[13]

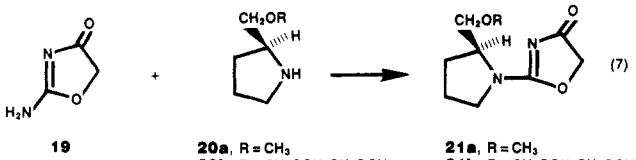
In a further effort to make an appropriate substrate derived from the optically active alcohol (+)-**11**, we considered the preparation of the optically active mesylate **17**. Model chemistry in the racemic series indicated that **17** is too unstable to be isolated, but it can be generated in situ from **11** in pyridine and used directly in the alkylation reaction with the enolate anion **5**. This reaction gives a totally unexpected result; namely, the formation of the 5-CO_2CH_2Ph derivatives **18** is observed. A plausible

Scheme IV



mechanism for their formation is illustrated in Scheme III.

Since the alkylation of (chloroethyl)indole **12** apparently proceeds through a planar achiral indolyl intermediate, we explored the incorporation of a chiral auxiliary into the oxazolone moiety. One likely prospect involved use of a chiral amine that could be added to the oxazolone by the amine exchange reaction with 2-amino-4(5*H*)-oxazolone[14] (**19**) and later be easily removed with methylamine. Proline derivatives were utilized, and it was hoped that these chiral oxazolone anions would be alkylated from one face only, thereby affording stereochemical control at C-5.[15] Any diastereoselection obtained in this reaction (i.e., formation of (5*S*,6*R*)-**1** in favor of (5*S*,6*S*-**2**) would be strictly fortuitous; however, we were hopeful that we would at least achieve the 2:1 predominance of the desired diastereomer that was observed in reaction of **5** with **12**. Owing to the relative abundance of potential low-energy conformations of the anion, as well as the question of the exact structure of the planar indolyl intermediate **8** (*E* or *Z*), it was not possible to predict, a priori, which enantiomer of the proline derivatives would be needed to give (−)-indolmycin. Since L-(−)-proline is the readily available natural form, we initiated our work with this material. Three 2-pyrrolidinyloxazolone derivatives, varying only in the side chain of the pyrrolidine ring, were easily prepared as shown in eq 7.



Alkylation of their respective anions with the (chloroethyl)indole **12** followed by amine exchange (methylamine in acetone, 24 h, room temperature), gave indolmycin (both diastereomers) as expected. In each case the natural diastereomer was isolated by chromatography, and its optical rotation was measured. The greatest enantiomeric excess obtained was 17% (see Scheme IV). In each case the material was enriched in the (+)-isomer, and thus a chiral auxiliary derived from D-(+)-proline would be required to obtain the desired natural (−)-indolmycin. However, due to the poor asymmetric induction observed, further experiments were not conducted. In summary, an efficient,

(11) Chirald [(2*S*,3*R*)-(+)-4-(dimethylamino)-1,2-diphenyl-3-methyl-2-butanol], Aldrich.

(12) (a) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870 and references therein. (b) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339.

(13) Racemization has been observed in a related *N*-methylindolyl system.[9] It was our hope that the electron-withdrawing nature of the carbobenzyloxy protecting group would obviate racemization in the present case.

(14) Traube, W.; Ascher, R. *Chem. Ber.* **1913**, *46*, 2077.

(15) (a) Seebach, v.-D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301. (b) Eichenauer, H.; Friedrich, E.; Lutz, W.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 206. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Ibid.* **1985**, *24*, 1 and references therein.

convergent synthesis of (±)-indolmycin has been completed that requires five linear steps and proceeds in an overall yield of 34%. The synthesis and biological evaluation of benzo-substituted and oxazolone analogues of indolmycin will be reported in future publications from these laboratories.

Experimental Section

General. Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. Nuclear magnetic resonance spectra (NMR) were recorded on a Varian Model T-60 or HA-100 spectrometer, and the chemical shifts are expressed in ppm downfield from tetramethylsilane. Data are presented in the order: number of hydrogens, multiplicity, coupling constant in hertz. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Mass spectra and exact mass determinations were obtained with a A.E.I. MS-30 spectrometer, at an ionizing potential of 70 eV. Elemental analyses were performed by the Pfizer Analytical Department. All evaporations were conducted in vacuo using either a water aspirator or a vacuum pump.

2-(Dimethylamino)-4(5*H*)-oxazolone (4). This compound was prepared in an analogous manner to that reported for the synthesis of some related 2-amino-4(5*H*)-oxazolones.[8a] To a stirred slurry of sodium hydride (0.48 g, 20 mmol, washed free of mineral oil) in toluene (100 mL) under nitrogen at room temperature was added ethyl glycolate (9.60 mL, 100 mmol). When hydrogen evolution ceased, dimethyl cyanamide (8.07 mL, 100 mmol) was added, and the mixture was heated at 87 °C for 1 h. It was then allowed to cool to room temperature, the solvent was evaporated, the residue was filtered (hot), and the filtrate was evaporated to afford 5.30 g (41%) of 4. Refluxing the insoluble material from above in ethyl acetate (100 mL), filtering, and evaporating the filtrate provided an additional 9% (1.15 g) of 4: mp 106–107 °C; NMR (Me_2SO-d_6) δ 3.03 (3, s), 3.10 (3, s), 4.62 (2, s). Anal. Calcd for $C_5H_8N_2O_2$: C, 46.92; H, 6.30; N, 21.89. Found: C, 47.04; H, 6.21; N, 21.79.

2-(Dimethylamino)-5-methyl-4(5*H*)-oxazolone (6). To 25 mL of THF in a flame-dried flask under nitrogen at 0 °C was added diisopropylamine (1.20 mL, 8.59 mmol), followed by *n*-butyllithium (3.74 mL, 2.3 M in hexane, 8.59 mmol). The mixture was cooled to −78 °C, and compound **6** (1.00 g, 7.81 mmol) was added as a finely ground solid. The mixture was allowed to warm to room temperature and was stirred for 105 min, then it was cooled to 0 °C, and methyl iodide (0.80 mL, 12.8 mmol) was added. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated, and the residue was stirred in ethyl acetate (50 mL) and filtered. The filtrate was evaporated, and comparison of its NMR spectrum with that of previously prepared **6**[8a] indicated formation of the desired product: NMR (Me_2SO-d_6) δ 1.13 (3, d, J = 7), 2.85 (3, s), 2.92 (3, s), 4.62 (1 q, J = 7).

***N*-Carbobenzoxyindole-3-carboxaldehyde (10).**[7] Sodium hydride (1.00 g, 41.4 mmol, washed free of mineral oil) was stirred in THF (50 mL) in a flame-dried flask at 0 °C under nitrogen. Indole-3-carboxaldehyde (5.00 g, 34.5 mmol) was added as a powder in small portions, and then the mixture was warmed to 40 °C and stirred for 30 min. The mixture was cooled to 0 °C, and benzyl chloroformate (4.92 mL, 34.5 mmol) was added. The mixture was allowed to warm to room temperature and was stirred overnight, after which it was poured into water (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with water (50 mL), dried with $MgSO_4$, filtered, and evaporated to 9.2 g (95%) of a gold-brown oil. Crystallization from hot hexane gave 8.47 g (88%) of white crystalline **10**: mp 70–71 °C (lit.[7] 70.5–71 °C); NMR (Me_2SO-d_6) δ 5.51 (2, s), 7.03–7.66 (7, m), 7.91–8.23 (2, m), 8.60 (1, s), 10.08 (1, s).

1-(*N*-Carbobenzoxyindol-3-yl)ethanol (11). To compound **10** (4.03 g, 14.4 mmol) in THF (50 mL) in a flame-dried flask under nitrogen at −78 °C was added methyl magnesium bromide (7.2 mL, 3.0M in ether, 21.7 mmol). The mixture was stirred for 2 h at −78 °C and was then quenched with 30 mL 10% NH_4Cl solution. The mixture was extracted with $CHCl_3$ (2 × 45 mL), dried with $MgSO_4$, filtered, and evaporated to afford 4.3 g (100%) of yellow oil. Purification by column chromatography on silica gel (20% ethyl acetate/$CHCl_3$) gave 3.62 g (85%) of white solid **11**: mp 78–80 °C; NMR ($CDCl_3$) δ 1.60 (3, d, J = 7), 1.88 (1, s), 5.08 (1 q, J = 7), 5.40 (2, s), 6.84–8.33 (10, m). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.29; H, 5.81; N, 4.75. Found: C, 73.28; H, 5.82; N, 4.70.

***N*-Carbobenzoxy-3-(1-chloroethyl)indole (12).** To a stirred solution of compound **11** (1.02 g, 3.45 mmol) in CH_2Cl_2 (20 mL) at −78 °C under nitrogen was added thionyl chloride (0.63 mL, 8.62 mmol). The mixture was allowed to warm to room temperature, was stirred for 2 h, and was then evaporated to a brown oil. The oil was dissolved in $CHCl_3$, treated with activated carbon and filtered through a pad of Super Cel; the filtrate was evaporated to afford 1.03 g (95%) of light brown oil: NMR ($CDCl_3$) δ 1.90 (3, d, J = 7), 5.26 (1, q, J = 7), 5.33 (2, s), 7.20–7.85 (9, m), 8.04 (1, m). This compound decomposed upon attempted purification by column chromatography (silica gel), and it was therefore used directly.

5-[1-(1*H*-Indol-3-yl)ethyl]-2-(dimethylamino)-4(5*H*)-oxazolone ((5*SR*,6*RS*)-13; (5*SR*,6*SR*)-14). To 20 mL of THF in a flame-dried flask under nitrogen at 0 °C was added diisopropylamine (0.94 mL, 6.70 mmol), followed by *n*-butyllithium (3.2 mL, 3.1 M in hexane, 6.70 mmol). The mixture was cooled to −78 °C, and compound **4** (0.86 g, 6.70 mmol) was added as a finely ground solid. The mixture was allowed to warm to room temperature and was stirred for 105 min, after which it was cooled to −78 °C and compound **12** (1.05 g, 3.35 mmol) was added in THF (5 mL). The mixture was allowed to warm to room temperature and was stirred overnight. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL), dried with $MgSO_4$, filtered, and evaporated. The crude product was subjected to medium-pressure liquid chromatography on silica gel (3% MeOH/$CHCl_3$), and the less polar component was collected to afford 0.44 g (48%) of (±)-**13**: NMR (Me_2SO-d_6) δ 1.36 (3, d, J = 7), 2.97 (3, s), 3.02 (3, s), 3.76 (1, m), 4.93 (1, d, J = 3), 6.77–7.75 (5, m), 8.37 (1, br s).

Further elution gave 0.20 g (22%) of the more polar diastereomer (±)-**14**: NMR (Me_2SO-d_6) δ 1.55 (3, d, J = 7), 2.89 (3, s), 3.67 (1, m), 4.83 (1, d, J = 3), 6.70–7.70 (5, m), 8.37 (1, br s).

Compounds (5*S*,6*R*)-(−)-**13** and (5*R*,6*R*)-(+)-**14** were prepared by stirring (5*S*,6*R*)-(−)-indolmycin (obtained from fermentation)[1] in 40% aqueous dimethylamine at room temperature overnight. The evaporated reaction mixture was subjected to medium-pressure chromatography on silica gel (2% MeOH/$CHCl_3$), and the separated diastereomers were recrystallized from ether/isopropanol. The NMR spectra of these compounds were identical with those of the racemic materials prepared above.

Compound (−)-**13**: mp 149–150 °C, $[\alpha]^{25}_D$ −175° (*c* 0.146, MeOH). HRMS calcd for $C_{15}H_{17}N_3O_2$ 271.1321, found 271.1332.

Compound (+)-**14**: mp 158–158.5 °C, $[\alpha]^{25}_D$ +25° (*c* 0.169, MeOH). Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.51. Found: C, 66.03; H, 6.33; N, 15.33.

Indolmycin (1). Methylamine (5 mL) was condensed into a flask (equipped with dry ice/acetone condenser) containing compound **13** (23 mg, 0.085 mmol) under nitrogen at −78 °C. The cold bath was removed, and the methylamine solution was allowed to warm to its boiling point (−6 °C) and was stirred for 1 h. The condenser was then removed, and the solvent was allowed to evaporate, leaving 22 mg (99%) of indolmycin. The spectral properties of this sample were identical with those of indolmycin from fermentation.[1]

Determination of Thermodynamic Equilibrium between Indolmycin (1) and Isoindolmycin (2). Samples of (5*S*,6*R*)-**13** and (5*R*,6*R*)-**14** (21 mg, 0.082 mmol) were each treated with 1 mL of 40% aqueous methylamine. After 3 days, the respective mixtures were evaporated and their optical rotations were measured. The fractions of **1** and **2** (represented by X_1 and X_2, respectively) in the mixtures were calculated from the formula: $[\alpha]^{25}_D$ $(X_1)(-214°) + (X_2)(+47°)$, where $[\alpha]^{25}_D$ of (5*S*,6*R*)-**1** −214° and $[\alpha]^{25}_D$ of (5*R*,6*R*)-**2** +47°, and $X_1 + X_2 = 1$. Starting from (5*S*,6*R*)-**13**, $[\alpha]^{22}_D$ −77°, or $X_1 = 0.48$. Starting from (5*R*,6*R*)-**14**, $[\alpha]^{25}_D$ −80°, or $X_1 = 0.49$.

***N*-Carbobenzoxy-3-acetylindole (15).** To a stirred slurry of sodium hydride (1.89 g, 78.6 mmol, washed free of mineral oil) in THF (30 mL) at 0 °C under nitrogen was added dropwise 3-acetylindole (10.0 g, 62.9 mmol) in THF (15 mL). The mixture was allowed to warm to room temperature and was stirred for 1 h, after which it was cooled to 0 °C and benzyl chloroformate

(8.97 mL, 62.9 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The excess sodium hydride was destroyed at 0 °C with 40 mL H_2O. The mixture was then extracted with $CHCl_3$ (3 × 40 mL), dried with $MgSO_4$, filtered, and evaporated to an off-white solid. Recrystallization from hexane afforded 15.9 g (86%) of **15**: mp 112–113 °C; NMR ($CDCl_3$) δ 2.57 (3, s), 5.49 (2, s), 7.13–7.67 (8, m), 8.10 (1, m), 8.17 (1, s). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.79; H, 5.16; N, 4.78. Found: C, 73.86; H, 5.29; N, 4.95.

(+)-1-(*N*-Carbobenzoxyindol-3-yl)ethanol (11). To a stirred slurry of lithium aluminum hydride (0.28 g, 7.29 mmol) in ether (25 mL at 0 °C under nitrogen) was added dropwise (2*S*,3*R*)-(+)-4-(dimethylamino)-1,2-diphenyl-3-methyl-2-butanol[11] (4.76 g, 16.9 mmol) in ether (10 mL), causing precipitation of a heavy white solid. After 3 min, the mixture was cooled to −78 °C and compound **15** (1.37 g, 4.68 mmol) was added slowly as a powder. After being stirred 2 h at −78 °C, the mixture was allowed to warm to room temperature and was stirred overnight. Excess hydride was destroyed at −78 °C by addition of water (5 mL). The mixture was allowed to warm to room temperature and was then washed with 2 N HCl (2 × 35 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated to afford 1.23 g (89%) of **18**: TLC data and the NMR spectrum of this material were identical with those of (±)-**13** as prepared above: $[\alpha]^{25}_D$ +15° (*c* 0.321, $CHCl_3$).

1-(*N*-Carbobenzoxyindol-3-yl)ethyl α-Methoxy-α-(trifluoromethyl)phenylacetate (16). To a stirred solution of compound (+)-**11** (110 mg, 0.40 mmol) in CCl_4 (5 mL) and pyridine (0.5 mL) at room temperature was added (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (200 mg, 0.79 mmol).[12] After 3 h, ether (10 ml) and water (1 mL) were added, and the mixture was washed successively with 2 N HCl (15 mL) and saturated bicarbonate solution (2 × 15 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated to a yellow oil. The ^1H NMR spectrum of the resulting oil indicated at least a 9:1 predominance of one diastereomer over the other.[12] Particularly separate peaks were δ 1.69 vs. 1.75 (3, d, *J* = 7), 3.42 vs. 3.53 (q, J_{CF_3} = 1), 6.41 vs. 6.45 (1, q, *J* = 7).

1-(*N*-Carbobenzoxyindol-3-yl)ethyl Methanesulfonate (17). To compound **11** (1.00 g, 3.39 mmol) in dry pyridine (15 mL) at room temperature under nitrogen was added methanesulfonyl chloride (0.39 mL, 5.08 mmol). The color darkened to a clear red within 5 min, and a light, white precipitate soon formed. The NMR spectrum of a small aliquot taken from the reaction mixture after 1 h indicated complete conversion to the desired product, although attempts to isolate it were unsuccessful due to rapid decomposition. NMR ($CDCl_3$, pyridine) δ 2.13 (3, d, *J* = 6), 2.90 (3, s), 5.46 (2, s); all other signals were obscured by pyridine. This material was used directly in the succeeding reaction.

5-Carbobenzoxy-5-[1-(1*H*-indol-3-yl)ethyl]-2-(dimethylamino)-4(5*H*)-oxazolone [18a (Less Polar Diastereomer) and 18b (More Polar Diastereomer)]. To 20 mL of THF in a flame-dried flask at 0 °C under nitrogen was added diisopropylamine (1.56 mL, 11.2 mmol), followed by *n*-butyllithium (4.42 mL, 2.3 M in *n*-hexane, 10.2 mmol). The mixture was cooled to −78 °C, and compound **4** (1.30 g, 10.2 mmol) was added as a finely ground solid. The mixture was then allowed to warm to room temperature and was stirred for 2 h, after which it was added dropwise to a pyridine solution of compound **17**, (1.26 g, 3.39 mmol) at −78 °C under nitrogen. The mixture was allowed to warm to room temperature and was stirred overnight. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (20 mL) and $CHCl_3$ (20 mL). The combined organic extracts were washed with 2 N HCl (3 × 20 mL), dried with $MgSO_4$, filtered, and evaporated to a yellow oil. The crude product was subjected to column chromatography on silica gel (3% MeOH/$CHCl_3$) to afford 0.37 g (27%) of **18a**: NMR ($CDCl_3$) δ 1.30 (3, d, *J* = 7), 3.10 (3, s), 3.13 (3, s), 4.30 (1, q, *J* = 7), 4.93 (2, s), 6.70–7.76 (10, m), 8.80 (1, br s).

Further elution gave 96 mg (7%) of the more polar diastereomer **18b**: NMR ($CDCl_3$) δ 1.52 (3, d, *J* = 7), 2.73 (3, s), 3.07 (3, s), 4.19 (1, q, *J* = 7), 5.30 (2, s), 6.51–7.84 (10, m), 8.67 (1, br s).

2(*S*)-(Methoxymethyl)pyrrolidine (20a), 2(*S*)-(((2-methoxyethoxy)methoxy)methyl)pyrrolidine (20b), and 2(*S*)-(((benzyloxy)methoxy)methyl)pyrrolidine (20c) were prepared according to the method of Seebach et al.[15a]

2-[2′(*S*)-(Methoxymethyl)-*N*-pyrrolidino]-4(5*H*)-oxazolone (21a), 2-[(2′(*S*)-(((Methoxyethoxy)methoxy)methyl)-*N*-pyrrolidino]-4(5*H*)-oxazolone (21b), and 2-[2′(*S*)-(((Benzyloxy)methoxy)methyl)-*N*-pyrrolidino]-4(5*H*)-oxazolone (21c). 2(*S*)-(Alkoxymethyl)pyrrolidine (**20a**, **20b**, or **20c**) and 2-amino-4(5*H*)-oxazolone[14] (**19**) (1.0 equiv) in EtOH (1 M) were heated under reflux for 8 h. The mixture was allowed to cool to room temperature, evaporated, and chromatographed on silica gel (5% MeOH/$CHCl_3$) to afford product as a yellow oil.

Compound **21a**: NMR ($CDCl_3$) δ 1.92–2.36 (4, m), 3.37 (3, s), 3.30–4.47 (5, m), 4.61 (2, m). HRMS calcd for $C_9H_{14}N_2O_3$ 198.1004, found 198.0999.

Compound 21b: NMR ($CDCl_3$) δ 1.68–2.32 (4, m), 3.40 (3, s), 3.33–4.45 (9, m), 4.55 (2, m), 4.73 (2, m). HRMS calcd for $C_{12}H_{20}N_2O_5$ 272.1372, found 272.1358.

Compound **21c**: NMR ($CDCl_3$) δ 1.52–2.62 (4, m), 3.25–5.01 (11, m), 7.02–7.61 (5, m). HRMS calcd for $C_9H_{13}N_2O_3$ (M−OCH_2Ph) 197.0929, found 197.0921.

5-[1-(1*H*-Indol-3-yl)ethyl]-2-[2′(*S*)-(alkoxymethyl)-*N*-pyrrolidino]-4(5*H*)-oxazolone (22a, Alkoxy = Methoxy; 22b, Alkoxy = (2-Methoxyethoxy)methoxy; 22c, Alkoxy = (Benzyloxy)methoxy)). To 20 mL of THF in a flame-dried flask under nitrogen at 0 °C was added diisopropylamine (0.78 mL, 5.56 mmol), followed by *n*-butyllithium (2.65 mL, 2.1 M in *n*-hexane, 5.56 mmol). The mixture was cooled to −78 °C, and compound **21a**, **21b**, or **21c** (5.05 mmol) was added in THF (5 mL). The mixture was then allowed to warm to room temperature and was stirred for 45 min, after which it was cooled to −78 °C and compound **12** (0.79 g, 2.53 mmol) was added in THF (5 mL). After being stirred at −78 °C for 1.5 h, the mixture was allowed to warm to room temperature and was stirred overnight. Water (25 mL) was added, and the mixture was extracted with ethyl acetate (2 × 25 mL), dried with $MgSO_4$, filtered, and evaporated. The resulting mixture of isomers was used directly in the succeeding reaction.

(+)-Indolmycin (1). Gaseous methylamine was bubbled into a solution of compound **22a**, **22b**, or **22c** in acetone for 1.5 h. The flask was sealed, and the reaction mixture was stirred for 24 h. The evaporated mixture was subjected to medium-pressure liquid chromatography on silica gel (3% MeOH/$CHCl_3$) to afford **1** (identical with authentic material by NMR and TLC). Indolmycin obtained from **22a** gave $[\alpha]^{25}_D$ + 36° (*c* 0.23, MeOH), or 17% ee; from **22b**, $[\alpha]^{25}_D$ +28° (*c* 0.24, MeOH), or 13% ee; and from **22c**, $[\alpha]^{25}_D$ +20° (*c* 0.28, MeOH), or 9% ee.

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