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ASYMMETRIC TOTAL SYNTHESIS OF INDOLMYCIN

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An asymmetric total synthesis of indolmycin was achieved via a key intermediate, α-indolmycenic acid ester. The ester was obtained by oxygenation of methyl (S)-3-(3-indolyl)butanoate which was prepared by asymmetric synthesis utilizing (2R,3S)-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione. (2S,3R)-N-[2-Hydroxy-3-(3-indolyl)-butanoyl]-N'-methylthiourea prepared from α-indolmycenic acid ester was treated with 2-chlorobenzoxazolium salt to give indolmycin in 93% optical purity.

Indolmycin (1) isolated from an African strain of Streptomyces albus[1] exhibits an antibacterial activity against Staphylococci[2]. It was shown by Schach von Wittenau and Els that indolmycin (1) is 5-1'-(3-indolyl)ethyl-2-methylamino-2-oxazolin-4-one[3] and the absolute configuration was also determined as 5S, 1'R by Chan and Hill[4]. Synthesis of optically active indolmycin (1) has been done employing resolution method by Preobrayhenskaya et al.,[5] but asymmetric synthesis of (1) has not yet been reported.

Previously we reported that highly optically active 3-substituted alkanoic acids are obtained by the reaction of (2R,3S)-6-alkyliden-3,4-dimethyl-2-phenyl-perhydro-1,4-oxazepine-5,7-dione with Grignard reagents[6].

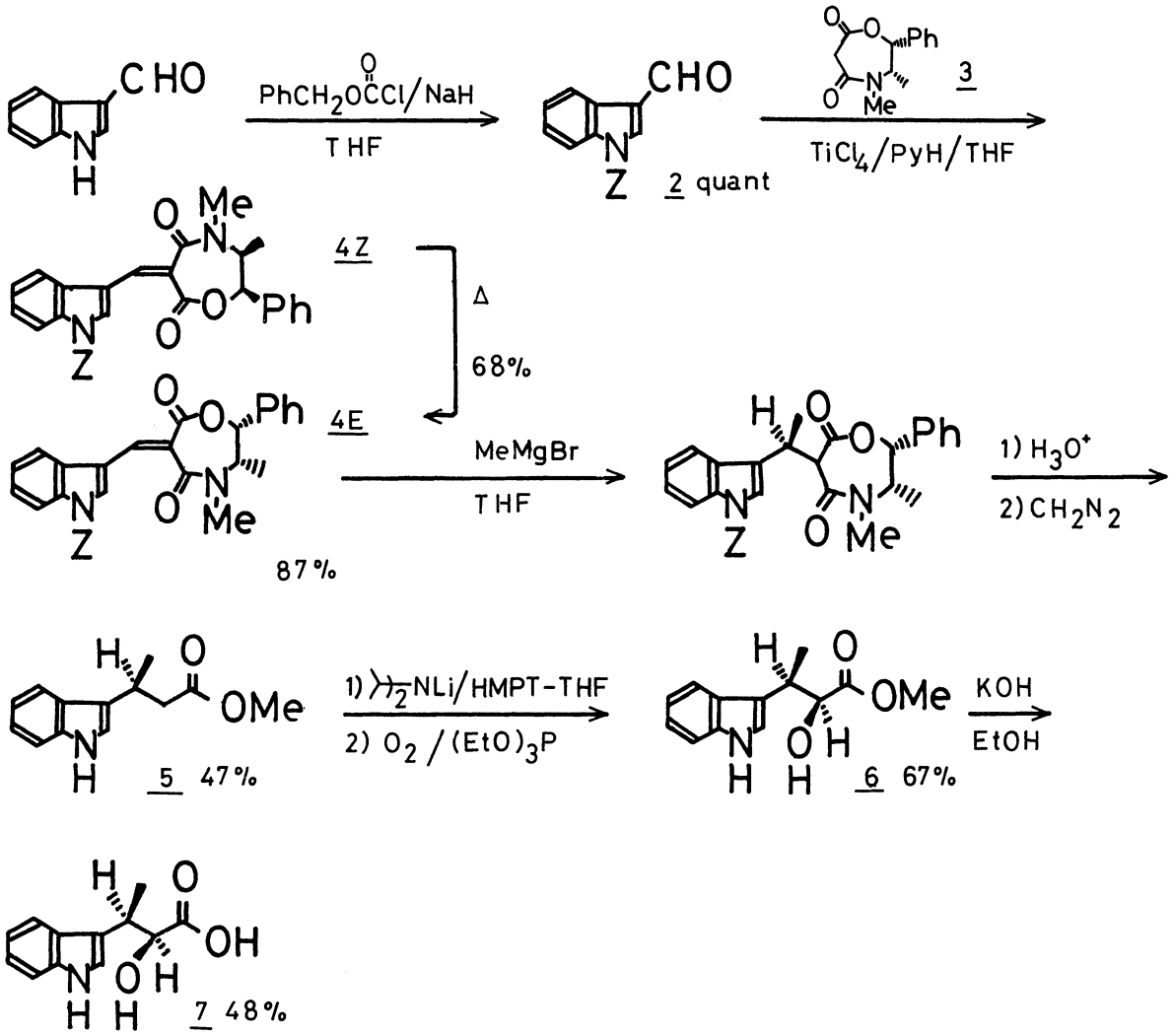
In this communication, we wish to report an asymmetric total synthesis of indolmycin (1) utilizing the above mentioned asymmetric reaction in the key step of the preparation of α-indolmycenic acid ester. The ester was in turn converted to (1) by the treatment with 2-chlorobenzoxazolium salt under mild conditions.

1-Carbobenzoxyindole-3-aldehyde (mp 70.5-71°)(2), prepared quantitatively by the reaction of indole-3-aldehyde with carbobenzoxychloride in THF using NaH as a base (0° to r.t., overnight), was treated with (2R,3S)-3,4-dimethyl-2-phenyl-perhydro-1,4-oxazepine-5,7-dione (3) in the presence of $TiCl_4$ and pyridine[7] to give the 6-(3-indolyl)methylene derivatives (4Z and 4E)[8] in 87% yield. The isomer ratio (4Z/4E) varied slightly with work-up procedure and the value of the ratio was approximately 1.5. The Z isomer (4Z) was thermally (160-70°, 1h) converted into the E isomer (4E) in 68% yield.

Methyl (S)-3-(3-indolyl)butanoate (5)[8] was obtained (47%) by the reaction of 4E with methylmagnesium bromide (1.1 equiv) in THF (-78°, 3h), followed by hydrolysis of the adduct (2:1 AcOH-6NH_2SO_4, reflux, 3h) and esterification of the acid with diazomethane. The ester (5) was treated with lithium diisopropylamide

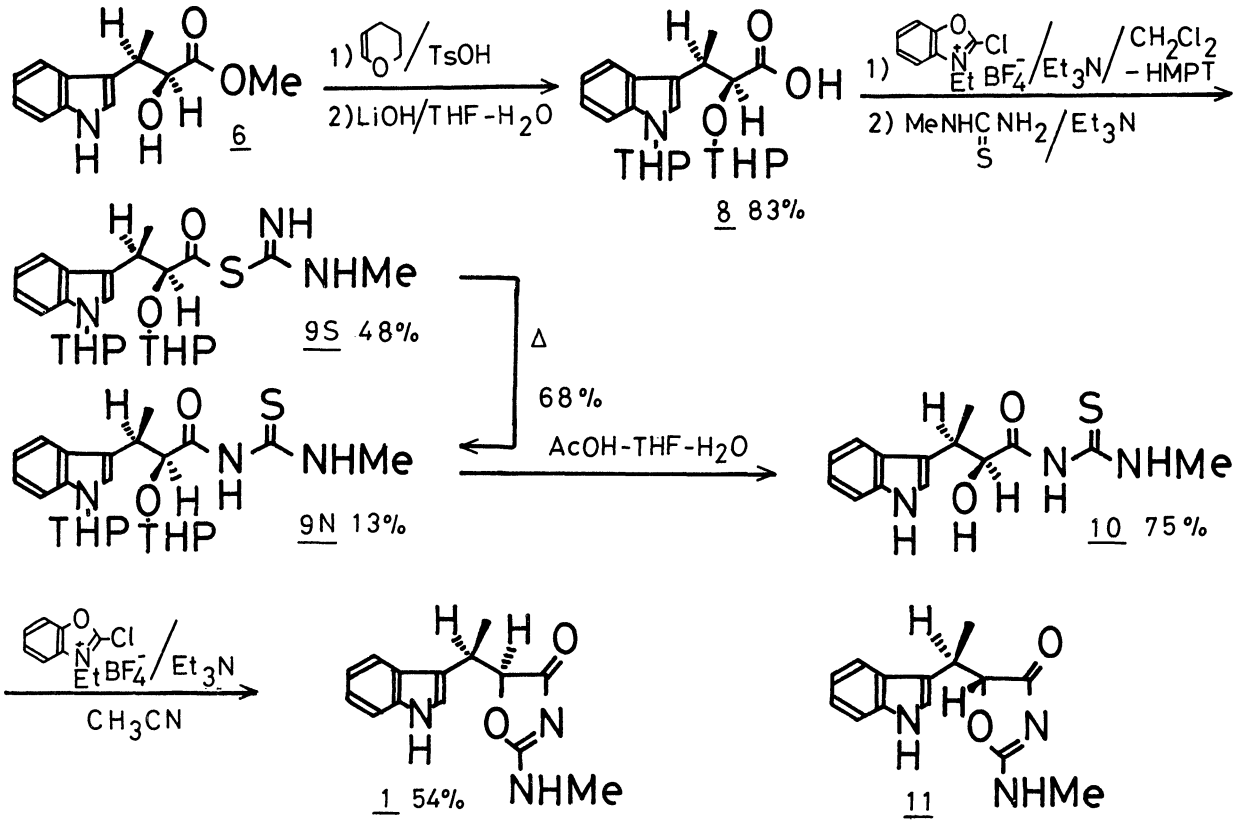
(2.2 equiv) in THF-HMPT at -78° to produce the corresponding enolate. α-Indolmycenic acid methyl ester (6)[8] was obtained by the oxygenation of the enolate in the presence of triethylphosphite (2.2 equiv) in 67% yield[9].

In order to confirm the structure of the ester, 6 was converted to α-indolmycenic acid (7)[10] (48%, mp 178-9°, $[\alpha]_D^{23}$ -9.5°(c 0.72 CH_3OH); natural 7, mp 181-2°, $[\alpha]_D^{25}$ -10°(c 2 CH_3OH)[3]) by hydrolysis (15% ethanolic KOH, reflux, 2h).



It is known that indolmycin (1) readily epimerizes in an alkaline medium to give its C_5-diastereoisomer, isoindolmycin (11), which has no antibacterial activity. Consequently, isoindolmycin (11) is produced as well as indolmycin (1) according to the conventional method of treating α-indolmycenic acid methyl ester and N,N'-dimethylguanidine hydrochloride with sodium methoxide[3].

In order to prevent the epimerization of 1 in the step of forming oxazoline moiety, the following synthetic route was devised. The epimerization of 1 can be minimized since the formation of 1 from the thiourea derivative (10) utilizing 2-chlorobenzoxazolium salt is completed under neutralization condition.



Methyl ester of α-indolmycenic acid (6) was treated with dihydropyrane (20 equiv) in the presence of a catalytic amount of p-toluenesulfonic acid in ether (r.t., 72h) to afford the tetrahydropyranyl derivative quantitatively. Then, the ester was hydrolyzed with LiOH (16 equiv) in THF-H_2O (5:4, 9ml/mmol) and the acid (8) was obtained in 83% yield.

The acid (8) was allowed to react with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (2 equiv) in CH_2Cl_2-HMPT (10:1, 5.5ml/mmol) at 0° for 2h in the presence of triethylamine (1.1 equiv). After addition of N-methylthiourea (2 equiv) to the solution, stirring was continued overnight at r.t.. The reaction mixture was treated with triethylamine (1.1 equiv) to give S-acylated thiourea (9S) and N-acylated thiourea (9N) in 48% and 13% yields, respectively. S-Acylated thiourea (9S) was successfully rearranged to produce 9N by refluxing in dioxane (25h, 68%). Deprotection (3:1:1 AcOH-H_2O-THF, reflux, 3h) of 9N gave N-[3-(3-indolyl)-2-hydroxybutanoyl]-N'-methylthiourea (10)[8] in 75% yield. The thiourea derivative (10) was treated with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (1.1 equiv) in acetonitrile (0°, 4h). After addition of triethylamine (2.2 equiv, 0°, 2h), indolmycin (1) was isolated by silica gel chromatography (19:1 Et_2O-CH_3OH) in 80% yield. Further it was purified by recrystallization (acetone) to give the pure product[10] (54%, mp 204-6°, $[\alpha]_D^{23}$-198°(c 2 CH_3OH); natural 1 , mp 212°, $[\alpha]_D^{25}$-214° (c 2 CH_3OH)[3]) in 93% optical purity.

References and Notes

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2) W. S. Marsh, A. L. Garretson, and E. M. Wesel, Antibiot. Chemother., 10, 316 (1960).
3) M. Schach von Wittenau and H. Els, J. Am. Chem. Soc., 83, 4678 (1961); 85, 3425 (1963).
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5) M. N. Preobrayhenskaya, E. G. Balashova, K. F. Turchin, E. N. Padeiskaya, N. V. Uvarova, G. N. Pershin, and N. N. Suvorov, Tetrahedron, 24, 6131 (1968).
6) T. Mukaiyama, T. Takeda, and M. Osaki, Chem. Lett., 1977, 1165; T. Mukaiyama, T. Takeda, and K. Fujimoto, Bull. Chem. Soc. Jpn., 51, 3368 (1978).
7) The experimental procedure for this reaction is noted in ref. 6). The isomers (E and Z) are easily separated each other by silica gel chromatography (1:1:1 AcOEt-n-hexane-CH_2Cl_2).
8) The physical and spectral data of these compounds are as follows;
4Z; mp 148-151° (reprecipitated with AcOEt and n-hexane), $[\alpha]_D^{16}$+26°(c 1.00 CH_2Cl_2); IR(KBr) 1740, 1640, 1220cm^{-1}; NMR($CDCl_3$) δ 1.22(3H,d,J=7Hz), 2.93 (3H,s), 4.07(1H,q,J=7Hz), 5.46(2H,s), 5.83(1H,s), 7.10-7.82(14H,m), 8.03-8.40(1H,m), 8.82(1H,s).
4E; mp 157-161°(reprecipitated with AcOEt and n-hexane) $[\alpha]_D^{19}$-205°(c 1.01 CH_2Cl_2); IR(KBr) 1740, 1640, 1230cm^{-1}; NMR($CDCl_3$) δ 1.30(3H,d,J=6Hz), 3.22 (3H,s), 3.77 (1H,q,J=6Hz), 5.48(2H,s), 6.13(1H,s), 7.14-7.77(13H,m), 7.98-8.43(2H,m), 8.47(1H,s).
5; bp 170-90°(bath temperature)/0.3mmHg, $[\alpha]_D^{19}$+ 10.9°(c 2.12 benzene); IR(neat) 3420, 3050, 2950, 1720, 1615cm^{-1}; NMR($CDCl_3$) δ1.33(3H,d,J=7Hz), 2.45(1H, dd, J=14Hz, 9Hz), 2.78(1H,dd,J=14Hz, 6Hz), 3.10-3.87(1H,m), 3.48(3H,s), 6.62 (1H,d,J=2Hz), 6.77-7.15(4H,m), 7.67-8.15(1H,br s).
6; mp 64.5-5.5°(ether-n-hexane), $[\alpha]_D^{24}$+4.3°(c 0.93 CH_3OH); IR(KBr) 3425, 3340, 2930, 1725, 1635cm^{-1}; NMR($CDCl_3$) δ1.28(3H,d,J=7Hz), 2.82(1H,d,J=5Hz), 3.23-3.83(1H,m), 3.63(3H,s), 4.35(1H,dd,J=5Hz,4Hz), 6.67-7.70(5H,m), 6.67-8.38 (1H,br s).
10; mp 194-5°(benzene); IR(KBr) 3510, 3400, 3310, 2920, 1675, 1635, 1560, 1495cm^{-1}; NMR(DMSO-d6) δ1.18(3H,d,J=7Hz), 2.97(3H,d,J=5Hz), 3.30-3.66(1H,m), 4.32(1H,dd,J=6Hz,4Hz), 6.07(1H,d,J=6Hz), 6.69-7.85(5H,m), 10.10-10.68(1H,br s), 10.14(1H,s), 10.68-11.12(1H,br s).
9) The reaction was carried out in accordance with the method reported by Konen et al.. D. A. Konen, L. S. Silbert, and P. E. Pfeffer, J. Org. Chem., 40, 3253 (1975).
10) The NMR and IR spectra of these compounds coincide with the spectra described in ref. 5).

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