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Assignment of Absolute Configuration for Virantmycin and Synthesis of Its Antipode

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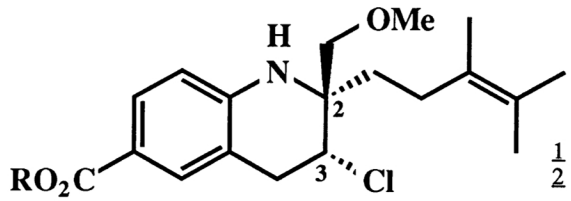
A total synthesis of antipodal virantmycin was accomplished starting from p-aminobenzoic acid. Absolute stereochemistry of the natural one was shown to be 2S, 3R.

The antibiotic virantmycin(1), isolated by one of us from Streptomyces nitrosporeus in 1981,[1] has been found to possess potent antiviral activity. The planar structure of 1 has been established by chemical and spectroscopic studies[2] and the synthesis of (±)-1 was reported by Raphael et al. in 1986.[3] However, the relative and absolute stereochemistry at C-2 and C-3 chiral centers has remained to be determined. In this communication we report the determination of the absolute configuration of virantmycin through the synthesis of its (+)-form.



1 R=H
2 R=Me

The Wittig reaction of hemi-acetal 3[4] with phosphorane 13[5] afforded (E)-α,β-unsaturated ester 4 (δ 6.57 ppm, 1H, t, J=7 Hz) and its (Z)-isomer (δ 5.60 ppm, 1H, t, J=8 Hz) with the ratio of ca. 30 : 1. The major ester 4 was led to allyl alcohol 5 by reduction of the ester group and protection of the sulfonamide group. The asymmetric epoxidation[6] of allyl alcohol 5 by the usual procedure using (L)-(+)-DET furnished optically active epoxy alcohol 6 (90%ee)($[\alpha]_D^{25}$ -14.9°, c 1.00, $CHCl_3$) in 98% yield, which was converted to allyl alcohol 7 (δ 4.96 ppm, 1H, br s ; δ 4.81 ppm, 1H, br s). The alcohol 7 was subjected to the metal catalyzed epoxidation[7] (TBHP, $VO(acac)_2/CH_2Cl_2$/0 °C/2.5 h) to give epoxy alcohol 8 as

a single diastereoisomer in 96% yield. The stereochemistry of 8 was deduced from the configuration of carboxylic ester 10 (vide infra). Treatment of the epoxide 8 with TFA in toluene at room temperature for 6 hours gave piperidine diol 9, which was converted into carboxylic ester 10[8] through protections, deprotections, stepwise oxidation, and monomethylation. The relative stereochemistry of 10 was determined by the ^{1}H-NMR data and NOE experiments. Observed J values between 3-H and 4-H_2 ($J_{3-4\alpha}$=6, $J_{3-4\beta}$=5) suggest an axial orientation of the hydroxyl group at C-3. Relative configuration between C-2 and C-3 substituents was confirmed by the presence of NOE between 17-H_2 and 4α-H as shown in Fig. 1. In the CD spectrum ($\Delta\varepsilon_{320}$=-33.9, $\Delta\varepsilon_{289}$=+17.1, in EtOH) of 4-dimethylaminobenzoate ester 14 (4-dimethylaminobenzoic acid, 2-chloro-1-methylpyridinium p-toluenesulfonate, ^{n}Bu$_3$N/toluene/reflux/4 h),[9] the negative sign of the first Cotton effect was corresponding to the negative chirality.[10] Thus, absolute configuration of 10 was assigned to be 2R, 3S as shown in Fig. 1. The configuration of C-3 to be S was consistent with the expected one from the Sharpless asymmetric epoxidation (5→6). Finally, the compound 10 was converted to chloro-ester 11 via an aziridine with double inversions at C-3.

All of spectroscopic data (NMR, IR, MS, UV) and chromatographic behavior of the synthetic chloro-ester 11 was completely identical with those of the methyl ester 2[2] prepared from natural virantmycin(1). The optical rotation of 11 was, however, observed as $[\alpha]_D^{26}$ +8.45° (c 0.250, $CHCl_3$) contrary to that of 2 ($[\alpha]_D^{26}$ -16.6°, c 0.425, $CHCl_3$).[11] Hydrolysis of the chloro-ester 11[3] yielded (+)-virantmycin(12) whose spectra and chromatographic behavior perfectly coincided with natural virantmycin(1). The optical rotation of 12 ($[\alpha]_D^{24}$ +11.2°, c 0.125, $CHCl_3$) was again different from that of 1 ($[\alpha]_D^{24}$ -11.1°, c 0.175, $CHCl_3$).[11] The stereochemistry of 12 was confirmed by NMR data (3α-H, δ 4.36, dd, J=6, 5 Hz) and NOE experiments (12a in Fig. 1).

Synthesis of antipodal virantmycin revealed that the absolute configuration of the natural product was shown to be 2S, 3R at the two chiral centers.

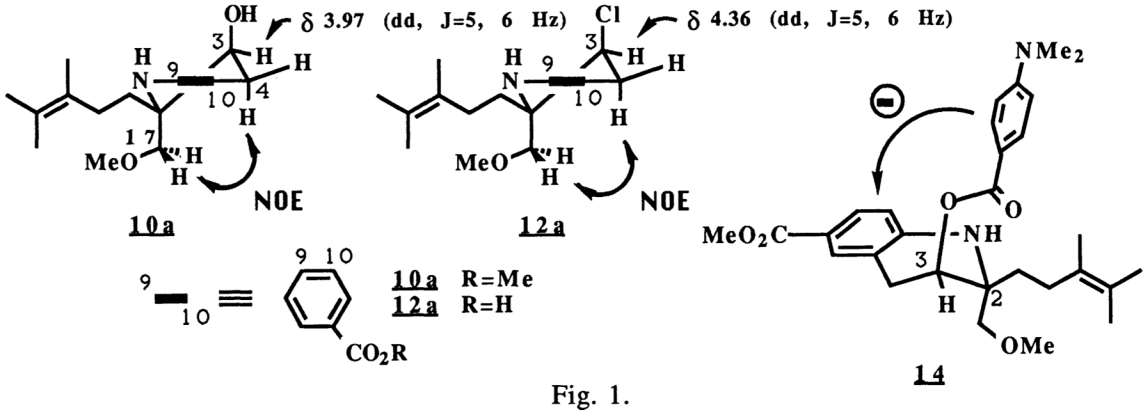
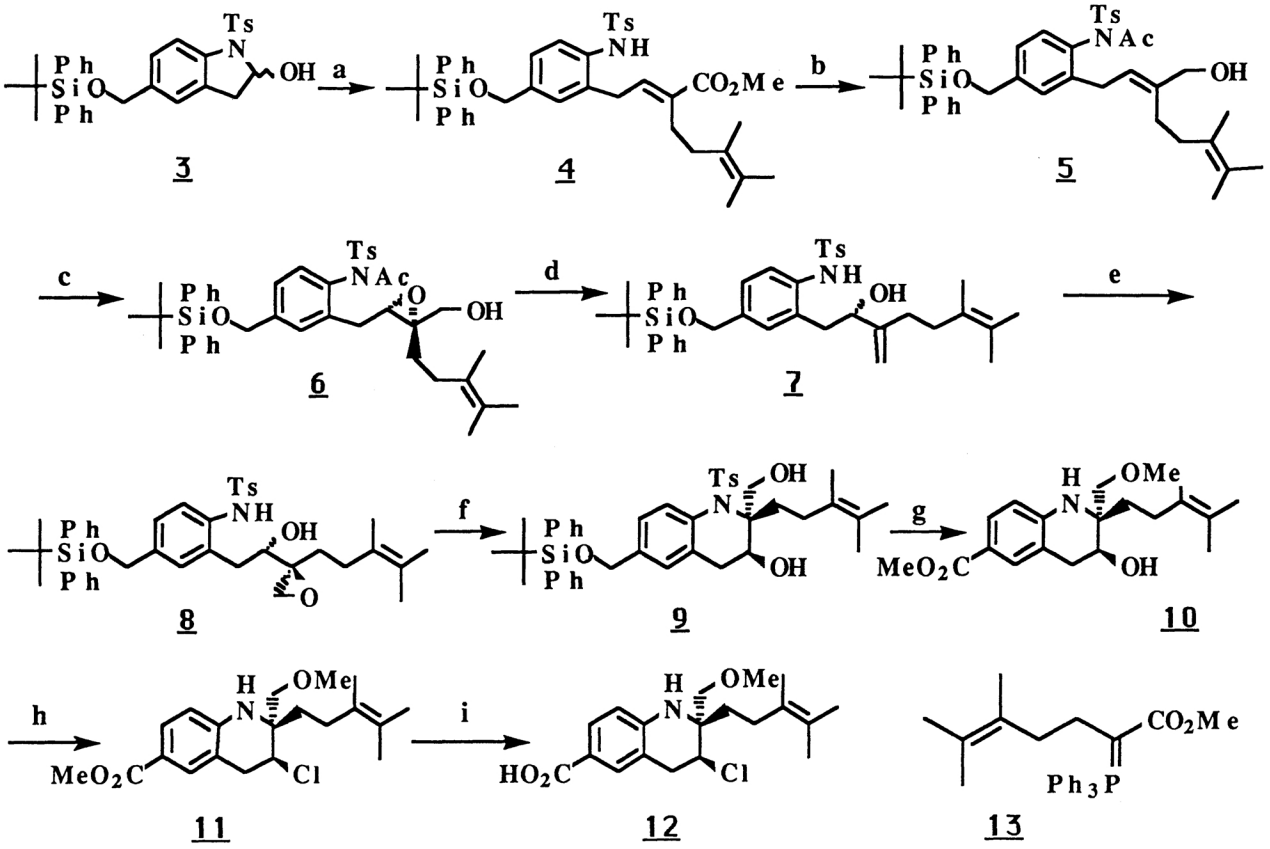


Fig. 1.



Reagents and Conditions

a. 13/CH_2Cl_2/rt/52 h (87%). **b.** 1) DIBAL/toluene/-15 °C/30 min (92%), 2) TMSCl, Et_3N/CH_2Cl_2, 3) AcCl, Et_3N/CH_2Cl_2, 4) citric acid/Et_2O, MeOH, H_2O (4:10:1)/rt/50 min (96%, 3 steps). **c.** (L)-(+)-DET, $Ti(O^iPr)_4$, TBHP/CH_2Cl_2/-20 °C/1.5 h (98%). **d.** 1) MsCl, Et_3N/CH_2Cl_2/0 °C/30 min (95%), 2) NaI(5 equiv.), Zn(2 equiv.)/DMF/100 °C/15 min (87%), 3) DIBAL/toluene/-15 °C/30 min (98%). **e.** TBHP, $VO(acac)_2/CH_2Cl_2$/0 °C/2.5 h (96%). **f.** TFA(2 equiv.)/toluene/rt/6 h (67%). **g.** 1) $Me_2C(OMe)_2$, CSA/acetone/rt/3 h (92%), 2) $^nBu_4NF$/THF/rt/15 h (99%), 3) PDC/CH_2Cl_2/rt/4 h,[12] 4) MnO_2, KCN, AcOH/MeOH, benzene (2:1)/rt/13 h,[13] 5) KOH/MeOH, Et_2O, H_2O (2:2:1)/rt/24 h (quant., 3 steps), 6) Na, naphthalene/DME/-15 °C/30 min (quant.), 7) CH_2N_2/MeOH/rt, 8) *p*-TsOH/MeOH, Et_2O (4:1)/rt/18 h (92%, 2 steps), 9) NaH, $^nBu_4NI$/THF/0 °C/30 min, then MeI(5 equiv.), HMPA(2 equiv.)/-15 °C/1.5 h (70%). **h.** 1) Ph_3P, DEAD/THF/rt/3 h (89%),[14] 2) Et_4NCl (20 equiv.), TFA/CH_2Cl_2/-15 °C/30 min (84%). **i.** LiOH/aq.CH_3CN (50%).[3]

Scheme 1.

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4) Hemi-acetal 3 was prepared from 2-(2-propenyl)4-carbethoxyaniline(15) through the following sequence of reactions; 1) TsCl, Py (quant.), 2) LAH (95%), 3) $^{t}BuPh_2SiCl$, imidazole/DMF/60 °C (82%), 4) OsO_4/THF, H_2O (1:1)/rt/30 min, then $NaIO_4$ (89%). For the preparation of 15, see; L. S. Hegedus, G. F. Allen, J. J. Bozell, and E. L. Warterman, J. Am. Chem. Soc., 100, 5800 (1978).

5) Phosphorane 13 was prepared from 1-bromo-2,3-dimethyl-2-butene(16) by the following sequence of reactions; 1) $NaCH(CO_2Me)_2$/THF (86%), 2) NaCl, H_2O/DMSO, 3) LAH, 4) MsCl, Et_3N/CH_2Cl_2 (86%, 3 steps), 5) NaI/DMF, 6) Ph_3P/benzene/reflux (89%, 2 steps), 7) $LiN(TMS)_2$/THF/0 °C/30 min, then $ClCO_2Me$/-78 °C/2 h (88%). For the preparation of 16, see; L. Ruzicka and H. Schinz, Helv. Chim. Acta, 23, 959 (1940).

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8) ^{1}H-NMR (500 MHz, in $CDCl_3$) data of compound 10.

δ 7.73 ppm (1H, d, J=2 Hz), 7.69 (1H, dd, J=8, 2), 6.49 (1H, d, J=8), 3.97 (1H, dd, J=6, 5), 3.84 (3H, s), 3.66 (1H, d, J=9), 3.48 (1H, d, J=9), 3.40 (3H, s), 3.10 (1H, dd, J=17, 5), 2.84 (1H, dd, J=17, 6), 2.06 (2H, m), 1.81 (1H, ddd, J=14, 12, 5), 1.62 (3H, s), 1.61 (6H, s), 1.57 (1H, ddd, J=14, 12, 5).

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11) The optical rotations of natural 1 and 2 were reexamined and these values were obtained.

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