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Supplementary Material Available: Tables of final atomic parameters, anisotropic thermal parameters, and hydrogen parameters (4 pages); tables of structure factors (7 pages). Ordering information is given on any current masthead page.

Manzamine A, a Novel Antitumor Alkaloid from a Sponge

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In our quest for antitumor activity in marine organisms occurring in Okinawan waters, we discovered a sponge[1,2] which gave an extract inhibiting the growth of P388 mouse leukemia cells. Subsequent purification afforded a compound having an IC_{50} of 0.07 μg/mL, which proved to be a novel alkaloid. We now describe the isolation of manzamine A hydrochloride (**1**) and the determination of its absolute configuration by X-ray.

A sample (735 g, wet weight) of the sponge, collected off Manzamo, Okinawa, in April 1985, was steeped in acetone. Evaporation gave an aqueous suspension which on extraction with ethyl acetate furnished an oil (13.0 g). A portion (10.7 g) was chromatographed over silica gel[3] by eluting with *n*-heptane–ethyl acetate–isopropyl alcohol (5:10:1). The biologically active fraction was purified over silica gel by successive elution with chloroform and acetone. The acetone eluate gave manzamine A hydrochloride (**1**, 100 mg) as colorless crystals after recrystallization from methanol: mp > 240 °C dec, $[\alpha]^{20}$ +50° (*c* 0.28, $CHCl_3$).

The molecular formula of the free base of **1** was deduced as $C_{36}H_{44}N_4O$ from HREIMS (*m/z* 548.3510, Δ 0.5 mmu) and by LRFABMS ($M^+ + 1$ at *m/z* 549).[4] The ^{13}C NMR spectrum[4] showed that all 36 carbons were different (17 sp^2- and 19 sp^3-hybridized atoms). The UV spectral data [MeOH λ_{max} 219 (ε 22 900), 236 (ε 18 600), 280 (ε 10 800), 290 sh (ε 9800), 346 (ε 5300), 357 nm (ε 5600)] were characteristic of the β-carboline chromophore.[5,6]

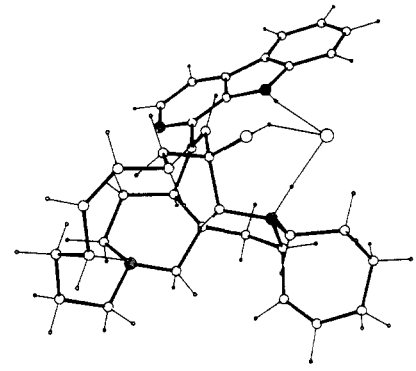

Figure 1. Perspective drawing of the absolute configuration of manzamine A hydrochloride (**1**). Nitrogen atoms are indicated by hatched spheres.

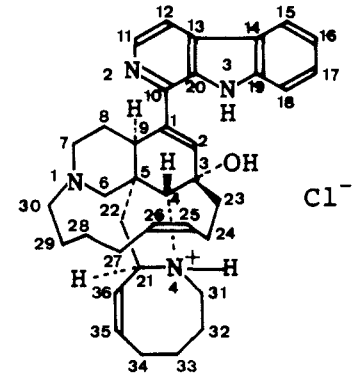

Figure 2. Numbering of the atoms of **1**.

The presence of two di- and one trisubstituted double bonds was revealed by the six olefinic carbon NMR signals and the splitting of the contiguous olefinic proton signals. However, these data only account for 12 of the required 17 sites of unsaturation. Consequently, besides the β-carboline ring, manzamine A must possess *five* rings containing two nitrogen atoms, as well as a single tertiary hydroxy group (IR, 1065 cm^{-1}).

As such complexity rendered conventional methods for structure determination impractical, a crystal of **1** was submitted to X-ray.[7] The resulting structure, shown in its absolute configuration, is unusual (Figure 1). Apart from the β-carboline substituent,[6,9] the molecule comprises a complicated array of 5-, 6-, 8-, and 13-membered rings (Figure 2). The piperidine and cyclohexene rings adopt chair and boat conformations, respectively, while the pyrrolidinium ring is an envelope. The conformation of the eight-membered cis-olefinic ring is as an envelope–boat P(0-++)[10] with a mirror plane passing through C(35) and C(31). The two six-membered rings bridged by a chain of nine carbon atoms constitute a 13-membered macrocycle which, unlike odd-membered macrocycles in general,[11] is perfectly ordered and rigid. Its

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(2) The sponge has been identified as *Haliclona sp.*

(3) Silica gel (230–400 mesh; 200 g) was stirred in a solution of heptane–ethyl acetate–isopropyl alcohol (5:10:1, 400 mL) containing aqueous ammonia (4 mL) and then packed into a column.

(4) Anal. Calcd for $C_{36}H_{44}N_4O$·HCl: C, 73.88; H, 7.75; N, 9.57; Cl, 6.06. Found: C, 73.80, H, 7.75; N, 9.44; Cl, 6.11. LREIMS, *m/z* 548 (4), 530 (100), 438 (19), 408 (66), 379 (26), 311 (55), 296 (27), 253 (23), 162 (46), 138 (27), 98 (32 rel %). IR (KBr) 3280, 3150, 3050, 3000, 2920, 2800, 2760, 2630, 2560, 1617, 1555, 1488, 1448, 1418, 1385, 1370, 1315, 1270, 1230, 1180, 1142, 1110, 1095, 1065, 1025, 820, 740, 725, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.76 (1 H, br s), 10.62 (1 H, br s), 8.34 (1 H, d, *J* = 5.2 Hz), 8.08 (1 H, d, *J* = 7.9 Hz), 7.85 (1 H, d, *J* = 5.1 Hz), 7.83 (1 H, d, *J* = 7.9 Hz), 7.52 (1 H, t, *J* = 7.9 Hz), 7.23 (1 H, t, *J* = 7.9 Hz), 6.52 (1 H, s), 6.29 (1 H, m), 5.57 (2 H, m), 5.39 (1 H, t, *J* = 9.9 Hz), 4.94 (1 H, m), 4.03 (1 H, m), 3.72 (1 H, d, *J* = 6 Hz), 3.27 (1 H, m). ^{13}C NMR ($CDCl_3$) δ 143.60 (s), 142.27 (d), 141.37 (s), 141.18 (s), 137.54 (d), 135.12 (d), 133.25 (s), 132.82 (d), 129.27 (s), 127.89 (d), 126.76 (d), 123.50 (d), 121.13 (s), 120.90 (d), 119.22 (d), 113.76 (d), 112.78 (d), 77.98 (d), 71.25 (s), 70.26 (t), 57.02 (d), 53.32 (t), 53.31 (t), 49.12 (t), 46.91 (s), 44.65 (t), 41.00 (d), 39.05 (t), 33.51 (t), 28.31 (t), 26.36 (t), 26.23 (t), 24.86 (t), 24.45 (t), 24.16 (t), 20.62 (t).

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(7) Crystal data for **1** ($C_{36}H_{44}N_4O$·HCl; *M* = 585.2): orthorhombic; space group $P2_12_12_1$; unit cell *a* = 12.989 (3) Å, *b* = 15.267 (5) Å, *c* = 15.890 (3) Å; *V* = 3151.0 Å^3; *Z* = 4, D_c = 1.234 g·cm^{-3}. The absolute configuration was determined by least-squares refinement of the absolute structure parameter x[8] (*x* = 0.01 (14)). The final *R* factor, based on 2447 reflections, was 0.046.

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conformation is quadrangular [1363][11] with the six bonds joining C(3) to C(29) forming a "convex side" and a pseudo mirror plane transfixing the double bond and the C(6) atom.

The chloride ion is held within the molecule by hydrogen bonding with two NH and one OH groups. The positive charge resides on the pyrrolidinium nitrogen atom as attested by the longer than usual bond lengths (~1.522 Å) of the attached α-carbon atoms.[12]

In summary, the structure of manzamine A hydrochloride is unprecedented in nature.[13] Moreover, its provenance is problematical as there appears to be no obvious biogenetic path.

Acknowledgment. We thank Prof. K. L. Rinehart, Jr., University of Illinois, for recording the mass spectra.

Supplementary Material Available: Tables of atomic coordinates, anisotropic displacement parameters, bond lengths, bond angles, and torsional angles (8 pages); table of structure factors (45 pages). Ordering information is given on any current masthead page.

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Catalytic Asymmetric Aldol Reaction: Reaction of Aldehydes with Isocyanoacetate Catalyzed by a Chiral Ferrocenylphosphine-Gold(I) Complex

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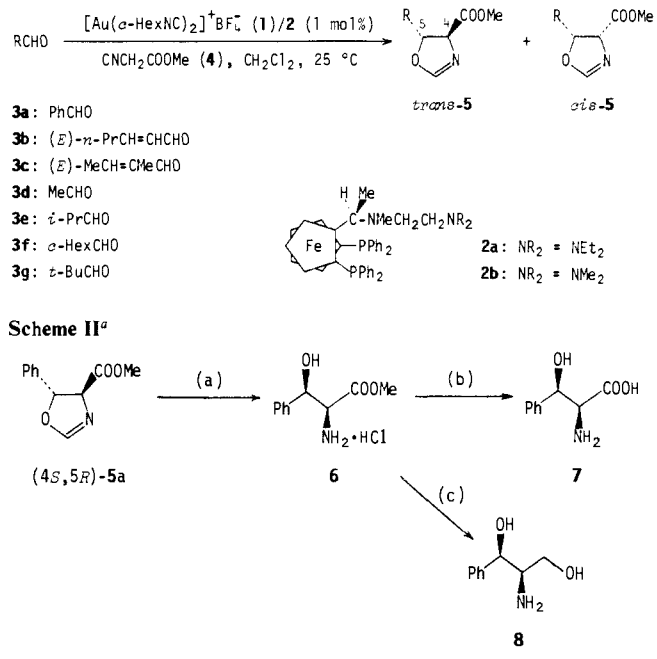
There has been great interest in the enantioselective aldol reactions of enolates with aldehydes to produce optically active β-hydroxycarbonyl compounds[1] and considerable efforts have been devoted to developing effective chiral enolates, e.g., boron enolates of chiral ketones[2] and imides[3] and tin enolates coordinated with chiral diamines.[4] Yet, there have been few reports on the use of chiral catalysts for such reactions.[5] Here we report that a chiral ferrocenylphosphine–gold(I) complex catalyzes the asymmetric aldol reaction of an isocyanoacetate with aldehydes,[6-8] producing optically active 5-alkyl-2-oxazoline-4-carboxylates with high enantio- and diastereoselectivity which are useful synthetic intermediates to optically active β-hydroxyamino acids and their derivatives.

Scheme I



Scheme II[a]

[a] (a) Concentrated HCl, MeOH, 50 °C, 3 h. (b) 6 N HCl, 80 °C, 6 h; amberlite IR-120B (H^+). (c) $LiAlH_4$/THF, reflux, 4 h; H_2O.

In numerous studies carried out in this laboratory, we have found that the gold complex generated in situ by mixing bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (**I**)[9] and (*R*)-*N*-methyl-*N*-[2-(dialkylamino)ethyl]-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine (**2**)[10,11] is an effective catalyst for the reaction of various types of aldehydes (**3**) with methyl isocyanoacetate (**4**) (Scheme I). A typical procedure is given for the reaction of benzaldehyde (**3a**). To a solution of the cationic gold complex **1** (27.5 mg, 0.055 mmol), the ferrocenylphosphine **2a** (39.7 mg, 0.056 mmol), and **4** (0.549 g, 5.54 mmol) in dry dichloromethane (5.5 mL) was added **3a** (0.642 g, 6.05 mmol), and the mixture was stirred under nitrogen at 25 °C for 20 h.[12] Evaporation of the solvent followed by bulb-to-bulb distillation (ca. 110 °C (0.3 mmHg)) gave 1.08 g (95% yield) of 4-(methoxycarbonyl)-5-phenyl-2-oxazoline (**5a**) (trans/cis = 89/11). The enantiomeric purities of *trans*-**5a** ($[\alpha]^{20}_D$ +297° (*c* 1.2, THF)) and *cis*-**5a** ($[\alpha]^{20}_D$ −80° (*c* 1.2, THF)), readily separated by column chromatography on silica gel (hexane/ethyl acetate = 1/2), were determined to be 96% ee and 49% ee, respectively, by ^1H NMR studies using Eu(dcm)$_3$.[13] The *trans*-**5a** was converted in high yields into known L-(−)-*threo*-β-phenylserine (**7**)[14] and (1*R*,2*R*)-(−)-1-phenyl-2-amino-1,3-propanediol (**8**)[15] via methyl phenylserinate (**6**) (Scheme II). Therefore, (+)-*trans*-**5a** has the

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