Tetrahedron Vol. 42, No 13, pp. 3405 to 3410, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00
Pergamon Journals Ltd

Synthesis of (-)-Fortamine and (+)-2-Deoxyfortamine From Resolved 3S,4S-N-Carbomethoxy-3-aminocyclohexen-4-ol

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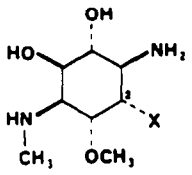
(*Received in USA* 13 *January* 1986)

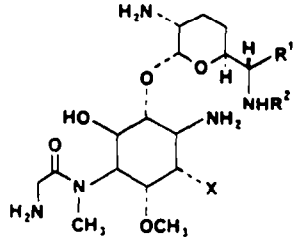
Abstract: A three step sequence (Scheme I) starting with racemic 3,4-epoxycyclohexene (**5**) and (S)-α-methylbenzylamine gave 3S,4S-N-carbomethoxy-3-aminocyclohexen-4-ol (**10**) with chromatographic removal of the undesired 3R,4R byproduct. The absolute configuration of **10** was established by x-ray crystallographic analysis of its precursor, **6** (as the HCl salt). Resolved **10** was converted to the aminocyclitols (-)-fortamine (**1**) and (+)-2-deoxyfortamine (**2**) by efficient routes which parallel those previously developed in the racemic series.

Fortamine (**1**) and 2-deoxyfortamine (**2**) are the aminocyclitol portions of the broad spectrum antibiotics fortimicin A (**3**) and istamycin A (**4**), respectively.[1,2] We recently reported the synthesis of racemic **1** and **2** from 3,4-epoxycyclohexene (**5**) using short, efficient, and sterocontrolled sequences.[3] In this paper we describe the resolution of an early intermediate, 3S,4S-N-carbomethoxy-3-aminocyclohexen-4-ol (**10**), the determination of its absolute configuration, and the conversion of **10** to optically pure **1** and **2**. Since natural **1** obtained by degradation of fortimicin A (**3**) has been converted back to **3**,[4] this work also constitutes the formal synthesis of that antibiotic.[5]



1, X = OH

2, X = H



3, X = OH, R^1 = CH_3, R^2 = H

4, X = H, R^1 = H, R^2 = CH_3

Results

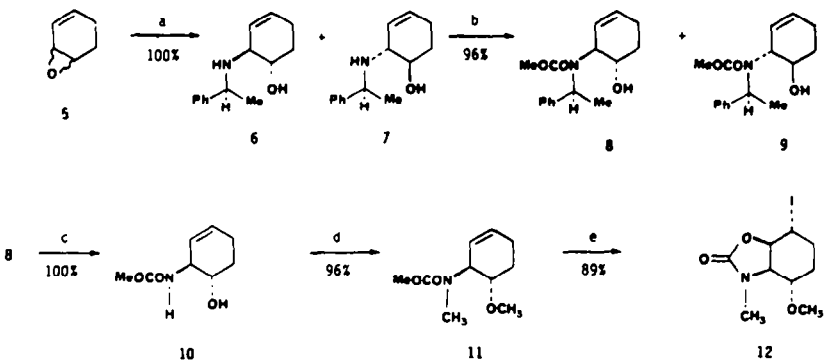
Racemic 3,4-epoxycyclohexene (**5**), which is available in 84% yield by mono-epoxidation of 1,3-cyclohexadiene[3], reacted with (S)-α-methylbenzylamine to give the diasteriomeric mixture of amino-alcohols **6** and **7** (Scheme I). A portion of the mixture was chromatographed on silica gel to give pure samples of both **6** and **7**. The high R_f isomer formed a hydrochloride salt, mp 226°C (dec), crystals of which were suitable for x-ray analysis. The crystallographic study revealed this compound to be **6** · HCl, that is, the "natural isomer", with the relative and absolute stereochemistry shown in Figure 1.

The separation of diasteriomers proved to be more efficient at the next stage. The mixture of 6 and 7 was converted to the N-carbomethoxy derivatives 8 and 9, which were cleanly separated by chromatography on silica gel. Basic hydrolysis of pure 8 and pure 9 gave pure (by TLC) 6 and 7, respectively, verifying the separation. From this point only the "natural" isomer 8 was carried through the synthesis, although 9 was available for exploratory experiments to work out reaction conditions.

Compound 8 was converted to 11, an intermediate in our racemic synthesis[3], by reductive removal of the phenethyl group, then N,O-bis-methylation. Because both methyl groups can be attached in a single operation (10 ⟶ 11), the synthesis of 11 in the optically active series adds only one step, and proceeds in 45% overall yield from 5, including the resolution, compared with 87% for racemic 11.[3]

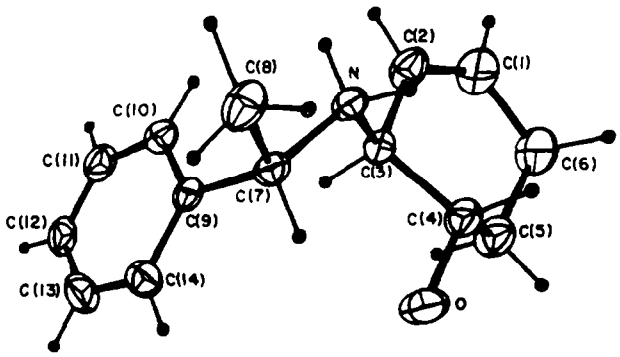
Although we had intersected with our published sequences for the synthesis of (±)-fortamine and (±)-2-deoxyfortamine[3], one further improvement was added. We had subsequently found[6] that halocyclization of unsaturated carbamates did not require the expensive reagent bromonium bis(collidine) perchlorate, but could be carried out more simply by using iodine as the electrophile.

Scheme I. [a]

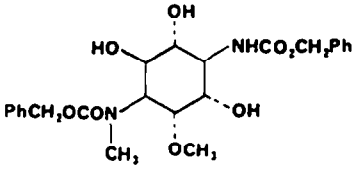


[a](a) $PhCH(CH_3)NH_2$, iPrOH, 80°C; (b) MeOCOCl, THF, Na_2CO_3; (c) Na, NH_3, THF; (d) KH, CH_3I. THF; (e) I_2. THF, aq $Na_2S_2O_3$.

Figure 1. ORTEP view of the cation $6 \cdot H^+$ showing the atom numbering scheme.



Thus **11** was converted to the iodide **12** in high yield. Conversion of **12** to **1** and **2** exactly parallels the remaining steps as previously published[3], and produced the aminocyclitols as their hydrochloride salts. Synthetic fortamine (**1**) was also characterized as its N,N'-bis(benzyloxycarbonyl) derivative **13**, its 1-N-benzyloxycarbonyl-4,5-cyclic carbamate derivative **14**, and its 4,5-cyclic carbamate derivative **15**, all of which were compared with authentic samples obtained by degradation of natural fortimicin B[7]. Synthetic **1**·2HCl showed [α] = +3.8 (H_2O), compared with the literature value of +4[8], and synthetic **13**–**15** gave rotations of +44°, -39.1°, and -62.5°, respectively, which matched those of the authentic materials (+46.2°, -38.2°, -65.7° in methanol).[8] Synthetic 2-deoxyfortamine (**2**) was characterized as its N,N'-diacetate derivative **16**, [α] = +89.3° (H_2O), lit. +103°[9] and 108°[10] (natural) and 90°[5d] (synthetic).



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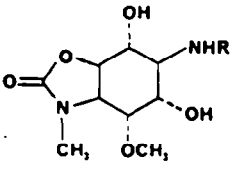
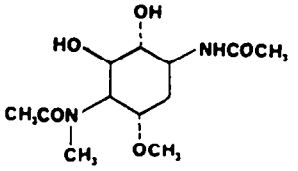


14, R = H

15, R = $PhCH_2OCO$



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Experimental

Apparatus and Reagents. Melting points were determined on an Electrothermal apparatus and are uncorrected. Infrared (IR) spectra were recorded by using a Perkin-Elmer Model 727B spectrophotometer (absorption maxima are in cm^{-1}). Proton nuclear magnetic resonance (NMR) spectra were obtained on deuteriochloroform solutions with a Varian Associates T-60 instrument. Chemical shifts are reported in parts per million downfield from tetramethylsilane, and coupling constants are in hertz. Elemental analyses were obtrained from Galbraith Laboratories (Knoxville, TN). Optical rotations [α] were taken using a Perkin-Elmer Model 141 polarimeter at 25°C, sodium D line, 1 dm path length.

Precoated silica gel plates (Baker Si250F) were used for analytical thin-layer chromatography (TLC). E. Merck silica gel 60 (230-400 mesh) was employed for column chromatography. Tetrahydrofuran (THF) was distilled from benzophenone ketyl. Other reagents were obtained commercially and used as received. Organic solutions were dried over anhydrous magnesium sulfate. All reactions were run under argon atmosphere.

3S,4S- and 3R,4R-3-[(S)-α-methylbenzylamino]-cyclohexen-4-ol (6 and 7). A mixture of 3.03 g (31.5 mmol) of epoxide 5[3], 3.90 g (31.5 mmol) of (S)-α-methylbenzylamine ([α] -42° as received from Aldrich Chemical Co.) and 10 mL of 2-propanol was heated in a sealed flask for 4 h at 80°C. Removal of the volatiles gave 7.75 g of crude product. This was dissolved in ether and caused to crystallize by the addition of hexane, giving 6.32 g (92% yield) of the mixture **6** and **7**. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.30; H, 8.81; N, 6.54. Found: C, 77.20; H, 8.57; N, 6.39. The product remaining in the mother liquors was carried on to **8** and **9** separately and then purified, bringing the yield for this step close to 100%. Although chromatography of the mixture of **6** and **7** was accompanied by much streaking, partial separation was achieved using 1:1 ether/petroleum ether as eluant (R_f's 0.44 and 0.33, respectively, with ether as eluant), and pure samples of each were obtained [hydrochlorides: mp 226°C (dec) and 260°C (dec), respectively].

3S,4S- and 3R,4R-N-Carbomethoxy-3-[(S)-α-methylbenzylamino] - cyclohexen-4-ol (8 and 9). A mixture of 0.478 g (2.2 mmol) of **6** and **7**, 0.462 g (4.4 mmol) of sodium carbonate and 10 mL of THF was treated with 0.36 mL (2.2 mmol) of methyl chloroformate in two portions. After 2 h at 23°, the reaction mixture was concentrated and partitioned between ether and water. The organic solution was concentrated and chromatographed using 1:2 petroleum ether/ether as eluant to give 0.264 g of **8**, 0.153 g of a mixture of **8** and **9**, and 0.167 g of **9**. A second chromatography completely separated the mixture, giving a total of 48% yield of each carbonate (R_f's 0.33 and 0.20, respectively). By separate but identical procedures pure **6** and **7** gave pure **8** and **9**, respectively. Likewise, basic hydrolysis (potassium hydroxide, methanol, 65°C) of **8** and **9** gave **6** and **7**, respectively, pure by TLC analysis. Compound **8**: mp 75-76°C (ether); NMR 7.3(br s, 5 H), 5.75 (br s, 1 H), 5.43 (app d, 1 H, J = 10), 4.93 (app d, 1 H, J = 6), 3.5 - 4.2 (m, 2 H), 3.60 (s 3 H), 1.4 - 2.4 (m, 5 H), 1.63 (d, 3 H, J = 7); [α] +70.46° (c = 1.07, methanol); Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.87; H, 7.81; N, 5.08. Compound **9**: mp 107 - 107.5°C (ether); NMR 7.3 (br s, 5 H), 5.67 (app d, 1 H, J = 8), 5.03 (app d, 2 H, J = 9), 3.8 - 4.2 (m, 2 H), 3.63 (s, 3 H), 1.5 - 2.4 (m, 5 H); 1.68 (s, 3 H); [α] -149.2° (c = 1.01, methanol).

3S,4S-N-Carbomethoxy-3-aminocyclohexen-4-ol (10). A solution of 0.134 g (2.92 mmol) of freshly cut sodium metal in 10 mL of anhydrous ammonia was stirred at -33°C. A solution of 0.404 g (1.46 mmol) of **8** in 5 mL of THF was added all at once. After 1 h at -33°C, the reaction was quenched by slow addition of 2 mL of aqueous saturated sodium bicarbonate solution. The ammonia was allowed to evaporate, water was added, and the resulting solution was extracted with dichloromethane (3 x 10 mL). Removal of the solvent gave 0.250 g (100%) of **10**, pure by TLC analysis. A portion crystallized from ethanol had mp 104 - 105°C, but in practice higher overall yields were obtained when **10** was taken on without crystallization. NMR 5.83 (br d, 1 H, J = 10), 5.36 br dd, 1 H, J = 10, 2), 4.6 - 5.1 (br s, 1 H), 3.8 - 4.3 (br s, 1 H), 3.1 - 3.8 (m, 1 H), 3.1 - 3.8 (m, 1 H) 3.66 (s, 3 H), 1.5 - 2.4 (M, 5 H); IR (KBr) 3375, 3260, 1680; [α] +121.8 (c = 1.02, ethanol); Anal. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.02, H, 7.74; N, 8.06.

3S,4S-N-Carbomethoxy-4-methoxy-3-methylamino-cyclohexene (11). A suspension of 252 mg (6.3 mmol) of oil free potassium hydride in 10 mL of THF and 1.77 mL (28.5 mmol) of iodomethane was stirred at 0°C. A solution of 493 mg (2.85 mmol) of **10** in 2 mL of THF was added, and the mixture was allowed to warm to 23°. After 4 h, the mixture was concentrated, 10 mL of water was added, and the aqueous solution was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried, concentrated, and chromatographed using 1:1 ether/petroleum ether as eluant to give 546 mg (96%) of dimethylated product **11** as an oil. NMR 5.80 (br d, 1 H, J = 9), 5.30 (br d, 1 H, J = 9), 3.70 (s, 3 H), 3.36 (s, 3 H), 3.2 - 3.6 (m, 1 H), 2.03 (s, 3 H), 1.8 - 2.4 (m, 4 H); IR (film) 1700; [α] +89.7 (c = 0.5, ether); Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60: N, 7.03. Found: C, 60.22; H, 8.65; N, 7.03.

7-Iodo-4-methoxy-3-methyl-3aα,4β,5,6,7β,7aα-hexahydrobenzoxazolidinone (12). A solution of 546 mg (2.74 mmol) of unsaturated carbamate **11** in 2 mL of THF was added to a solution of iodine (2.00 g, 7.88 mmol) in 15 mL of THF, and the reaction was kept overnight at 23°C. Saturated aqueous sodium thiosulfate was added dropwise until the iodine color discharged, then the reaction mixture was concentrated, and extracted using 2 mL of water and 3 x 5 mL of dichloromethane. The combined organic extracts were dried, concentrated, and chromatographed using 1:1 ether/petroleum ether as the eluant to give 759 mg (89%) of **12** as a white solid. A sample crystallized from ether had mp 137 - 138°C. NMR 4.80 (m, 1 H), 4.53 (m, 1 H), 3.3 - 3.8 (m, 2 H), 3.40 (s, 3 H), 2.93 (s, 3 H), 1.8 - 2.3 (m, 4 H); IR (KBr) 1760; [α] -30.4° (c = 1.41, ethanol); Anal. Calcd for $C_9H_{14}INO_3$: C, 34.75; H, 4.54; N, 4.50; I, 40.79. Found: C, 35.06; H, 4.54; N, 4.43; I, 40.50.

Degradation of Natural Fortimicin A. Fortimicin B, available by basic hydrolysis of **3**, was converted to N,N'-bis(benzyloxycarbonyl)-fortamine (**13**) by the published procedure.[7] A chilled solution of 112 mg (0.24 mmol) of **13** in 20 mL of THF was added to 5 mg (0.21 mmol) of oil free sodium hydride at 0°C, and the resulting mixture was stirred at 23°C for 14 h. Glacial acetic acid (0.2 mL) was added, then the solvents were removed. Chromatography of the residue using 4:1 hexane/acetone as the eluant gave 88 mg (97%) of the 4,5-cyclic carbamate **14**, mp 97-98°C (acetone/hexane), lit.[8] mp 94-97°C. NMR 7.35 (br s, 5 H), 5.12 (br s, 2 H), 4.2 - 4.7 (m, 1 H), 3.5 - 4.2 (m, 7 H), 3.45 (s, 3 H), 2.87 (s, 3 H); [α] -38.2 (methanol). Removal of the benzyloxycarbonyl group was accomplished as follows. A mixture of 72 mg (0.20 mmol)

of **14**, 3 mL of methanol, and 15 mg of 10% palladium on carbon was stirred under 40 psi of hydrogen at 23° for 4 h. The mixture was filtered and concentrated to give 46 mg (100%) of fortamine 4,5-cyclic carbamate **15** as a white solid, mp 128 - 132°, [α] -65.7 (methanol). NMR, IR, and TLC characteristics of **15** from degradation matched those of synthetic **15**. Treatment of natural or synthetic **15** with benzyl chloroformate in THF solution with sodium carbonate at 0°C gave **14** in 82% yield after chromatography.

Crystal Structure Determination. Details of the crystal structure determination of **6**·HCl are given in Table I. A clear, colorless prism, obtained from ethanol by slow evaporation, was mounted on the end of a glass rod. Diffractometer examination of the reciprocal lattice led to the unambiguous assignment of the space group as $P2_12_12_1$. Intensities were collected using MoKα radiation and corrected for Lorentz, polarization and absorption (empirical) effects.

The structure was solved by direct methods using the program MULTAN 82[11] and refined using full-matrix least-squres techniques. Except for the hydroxyl H atom, which could not be located with certainty, H atoms were found on a difference map or placed at positions calculated by assuming ideal bond geometry with C-H and H-H distances of 0.87 Å, respectively. Before the final refinement cycles, H atom temperature factors were set according to $B_H = B_N + 1$ where N is the atom bonded to H. H atom parameters were not refined. With all non-hydrogen atoms anisotropic (154 parameters), refinement converged with $R_{wF} = 0.043$ for the enantiomer reported and $R_{wF} = 0.044$ for the other enantiomer. Using Hamilton's R factor significance test[12], the hypothesis that the absolute configuration is correct is acceptable at the 99.5% confidence level. A view of the cation **6**·H^+ is shown in Fig. 1.

Table I. Crystal and Refinement Data for **6**·HCl

Formula	$C_{14}H_{20}ONCl$	fw	253.77
a,Å	9.8286(9)	b,Å	17.024(2)
c,Å	8.5760(7)	V,Å^3	1435.0(4)
space group	$P2_12_12_1$	Z	4
no. of refs used to determine cell constants	25	d_{calcd}, g/cm^3	1.174
d_{obsd}, g/cm^3	1.17(1)	λ(MoKλ),Å	0.71073
monochromator	graphite	linear abs coeff, cm^{-1}	2.5
crystal dimens, mm	0.16 x 0.19 x 0.4	rel trans factor range	0.99 < T < 1.00
diffractometer	Enraf-Nonium CAD-4	data collectiom method	θ-2θ
2θ range, deg	$2 \leq 2\theta \leq 45$	temp, K	297
scan range, deg	1.2 +0.35 tan θ	weighting scheme	$w = 4(Fo^2)/[\sigma(Fo^2)]^{2a}$
no. of std reflcns	3	% variation in std intens	±0.1
no. of unique data collected	1100	no. of data used in refinement	$863[F^2 \geq 3\sigma(F^2)]$
data: parameter ratio	5.6	final G.O.F.[b]	1.36
final R_F[c]	0.035	final R_{wF}[d]	0.043
systematic absences observed	h00, h = 2n+1; 0k0, k = 2n+1; 00l, l = 2n+1.	final largest shift/esd	<0.01
highest peak in final diff. map, e/A^3	0.23		

a. $[\sigma(fo)^2]^2 = [s^2(C + R^2B) + ((pFo^2)^2]/(Lp)^2$, where S is the scan rate, C is the total intergrated peak count, R is the ratio of scan to background counting time, B is the total background count, and p is a factor introduced to downweight intense reflections. For the present structure, p = 0.05.
b. Error in an observation of unit weight, equal to $[\Sigma w(|F_O|-|F_C|)^2/(NO-NV)]^{1/2}$ where NO is the number of observation and NV is the number of variables in the least-squares refinement.
c. $R_F = \Sigma/||F_O|-|F_C||/\Sigma|Fo|$.
d. $R_{wF} = [\Sigma w(|F_O|-|F_C|)^2/\Sigma wF_O{}^2]^{1/2}$.

Acknowledgement. This research was supported by grants from PHS (AI - 18703), the Merck Foundation, and Rutgers University (BRSG). We are grateful to Dr. James B. McAlpine, Abbott Laboratories, for a generous gift of fortimicin B, and to Prof. Harvey J. Schugar, Rutgers University, for assistance with the x-ray structure determination.

Supplementary Material. Listings of final atomic coordinates, anisotropic thermal parameters, bond distances, bond angles, and observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Center.

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