J. Org. Chem. **1990**, *55*, 5995–6000 **5995**

chromatographed by MPLC (25% EtOAc/hexanes) to give 329 mg (85%) of **12** as a light solid, which is recrystallized from $\mathrm{Et_2O}$/pentane: mp 98–100 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 10.36 (1, s, OH), 7.5–7.2 (m, 5, ArH), 7.07 (dd, 1, $J_{\mathrm{ortho}} = 9$ Hz, $J_{\mathrm{meta}} = 3$ Hz, ArH), 6.95 (dd, 1, $J_{\mathrm{ortho}} = 9$ Hz, $J_{\mathrm{H,P}} = 9$ Hz, ArH), 6.86 (dd, 1, $J_{\mathrm{meta}} = 3$ Hz, $J_{\mathrm{H,P}} = 17$ Hz, ArH), 5.71 (dd, 1, $J_{\mathrm{H4,H5}} = J_{\mathrm{H5,P}} = 5$ Hz, OCHAr), 3.9–3.8 (m, 1, $\mathrm{NC}\mathit{H}\mathrm{CH_3}$), 3.79 (s, 3, $\mathrm{OCH_3}$), 2.65 (d, 3, $J_{\mathrm{H,P}} = 10$ Hz, $\mathrm{NCH_3}$), 0.93 ppm (d, 3, $J_{\mathrm{H4,Me}} = 6$ Hz, $\mathrm{CHC}\mathit{H}_3$); ^{13}C NMR 157.6, 152.2, 135.7, 128.5 (2), 128.4, 126.1 (2), 121.7, 118.8, 115.3, 109.2 (d, $J_{\mathrm{C,P}} = 170$ Hz) (Ar), 83.5 (O*C*HAr), 59.4 (N*C*H$\mathrm{CH_3}$), 56.0 (O$\mathit{C}\mathrm{H_3}$), 28.5 (N$\mathit{C}\mathrm{H_3}$), 14.8 ppm (CH$\mathit{C}\mathrm{H_3}$). Anal. Calcd for $\mathrm{C_{17}H_{20}NO_4P}$: C, 61.26; H, 6.05; P, 9.29. Found: C, 61.19; H, 6.14; P, 9.27.

(2*S*,4*R*,5*S*)-2-(2,5-Dimethoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Oxide (13). To a solution of **12** (106 mg, 0.32 mmol) in dry THF (1.0 mL) is added dry DMF (0.10 mL), iodomethane (0.10 mL, 0.23 g, 1.6 mmol), and then granular NaH (15 mg, 0.62 mmol), and the mixture is stirred at reflux under a dry atmosphere ($\mathrm{CaSO_4}$ drying tube) for 1 h. The mixture is diluted with EtOAc (25 mL), and the excess NaH is destroyed by careful addition of water (10 mL), followed by saturated $\mathrm{NH_4Cl}$ (10 mL). The organic phase is worked up in the standard way to give 77 mg (70%) of a light crystalline solid **13**, which is recrystallized from $\mathrm{CH_2Cl_2}$/hexanes to give 55 mg (50%) of **13**: mp 133–135 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.56 (dd, 1, $J_{\mathrm{meta}} = 3$ Hz, $J_{\mathrm{C,P}} = 16$ Hz, ArH), 7.5–7.3 (m, 5, ArH), 7.02 (dd, 1, $J_{\mathrm{meta}} = 3$ Hz, $J_{\mathrm{ortho}} = 9$ Hz, ArH), 6.88 (dd, 1, $J_{\mathrm{ortho}} = J_{\mathrm{C,P}} = 9$ Hz, ArH), 5.63 (dd, 1, $J_{\mathrm{H4,H5}} = J_{\mathrm{H5,P}} = 7$ Hz, OC*H*Ar), 3.87 (s, 3, $\mathrm{OCH_3}$), 3.8 (m, 1, $\mathrm{NC}\mathit{H}\mathrm{CH_3}$), 3.79 (s, 3, $\mathrm{OCH_3}$), 2.59 (d, 3, $J_{\mathrm{H,P}} = 10$ Hz, $\mathrm{NCH_3}$), 0.82 (d, 3, $J_{\mathrm{H4,Me}} = 7$ Hz, $\mathrm{CHC}\mathit{H}_3$); ^{13}C NMR ($\mathrm{CDCl_3}$) 155.1, 153.4, 137.1, 128.2 (2), 128.0, 126.7 (2), 120.7, 119.9, ca. 116.0 (d), 112.4 (Ar), 82.4 (O*C*HAr), 68.6 (N*C*H$\mathrm{CH_3}$), 56.3 (O$\mathit{C}\mathrm{H_3}$), 55.9 (O$\mathit{C}\mathrm{H_3}$), 28.6 (N$\mathit{C}\mathrm{H_3}$), 15.4 ppm (CH$\mathit{C}\mathrm{H_3}$). Anal. Calcd for $\mathrm{C_{18}H_{22}NO_4P}$: C, 62.24; H, 6.38; P, 8.92. Found: C, 62.09; H, 6.48; P, 8.85.

(2*S*,4*S*,5*S*)- and (2*R*,4*S*,5*S*)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine 2-Oxide (14 and 15).[5,7] These compounds were prepared according to the procedure of Inch and co-workers. From pseudoephedrine (5.02 g, 30.4 mmol) was obtained 2.73 g (31%) of **15** as a white solid, 2.70 g (31%) of **14** as a yellow syrup, and 1.65 g (19%) of a mixture of both isomers.

Compound **15**: mp 150–153 °C (from EtOAc/hexane) [lit.[7] 124.6 °C (from EtOAc/EtOH)]; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.94–7.87 (m, 2, ArH), 7.57–7.36 (m, 8, ArH), 4.88 (dd, 1, $J_{\mathrm{H4,H5}} = 8$ Hz, $J_{\mathrm{H,P}} = 1$ Hz, OCHAr), 3.50 (dq, 1, $J_{\mathrm{H4,H5}} = 8$ Hz, $J_{\mathrm{H4,Me}} = 7$ Hz, $\mathrm{C}\mathit{H}\mathrm{CH_3}$), 2.66 (d, 3, $J_{\mathrm{H,P}} = 11$ Hz, $\mathrm{NCH_3}$), 1.28 ppm (d, 3, $J_{\mathrm{H4,Me}} = 7$ Hz, $\mathrm{CHC}\mathit{H}_3$). Anal. Calcd for $\mathrm{C_{16}H_{18}NO_2P}$: C, 66.89; H, 6.32; P, 10.78. Found: C, 66.95; H, 6.28; P, 10.67.

Compound **14**: ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.88–7.82 (m, 2, ArH), 7.59–7.40 (m, 8, ArH), 5.17 (d, 1, $J_{\mathrm{H4,H5}} = 9$ Hz, OCHAr), 3.56 (dq, 1, $J_{\mathrm{H4,H5}} = 9$ Hz, $J_{\mathrm{H4,Me}} = 6$ Hz, $\mathrm{C}\mathit{H}\mathrm{CH_3}$), 2.55 (d, 3, $J_{\mathrm{H,P}} = 10$ Hz, $\mathrm{NCH_3}$), 1.31 ppm (d, 3, $J_{\mathrm{H4,Me}} = 7$ Hz, $\mathrm{CHC}\mathit{H}_3$). Anal. Calcd for $\mathrm{C_{16}H_{18}NO_2P}$: C, 66.89; H, 6.32; P, 10.78. Found: C, 66.95; H, 6.28; P, 10.82.

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Supplementary Material Available: X-ray structural data (final atomic parameters) and an ORTEP stereodrawing for **15** as well as ^{13}C NMR spectra of **3**:**4** and **9** (12 pages). Ordering information is given on any current masthead page.

A Novel Ring Expansion Observed during the Lithium Aluminum Hydride Reduction of 13-Nitrooxyberberine

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An unusual ring expansion was observed in the course of studies on the synthesis of berberine linked to oligonucleotides at the 13-position. Nitration of oxyberberine (**1**) gave 13-nitrooxyberberine (**2**) as the major product. Lithium aluminum hydride reduction of **2** gave ring-expansion product **4** in addition to the expected primary amine **5**. The structure of **4**, a novel B/C-cis fused ring system, was solved by X-ray crystallography.

The placement of an amino group at the 13-position of a protoberberine would provide a useful functional group for the covalent attachment of oligonucleotides through linker chains. During the investigation of a synthesis of *cis*-13-aminotetrahydroberberine (**5**) by lithium aluminum hydride reduction of intermediate **2** (Scheme I), an unusual ring expansion reaction was observed which resulted in the formation of compound **4**. The present paper details the synthetic route leading to substance **4**, provides evidence in support of the assigned structure, and attempts to shed some insight into the mechanism of the transformation leading to this novel ring system. A conformational analysis of **4** is also presented.

Oxyberberine (**1**), prepared from berberine chloride by a combination of established methods,[1,2] was readily nitrated with aqueous nitric acid to give **2** and **3** in 91.3 and 0.8% yields, respectively. The structure of the expected major product **2** was readily confirmed by spectral data, while the structure of the minor dinitro product **3** was less obvious. The ^{1}H NMR spectrum of **2** contained an AB quartet at δ 7.39 and 7.26 ($J = 9.2$ Hz) corresponding to the D ring protons and singlets at δ 7.00 and 6.77 corresponding to the A ring protons. The spectrum of **3** contained singlets at δ 7.90, 6.79, and 6.78. The absence of ortho coupling in **3** demonstrated that the second nitro group must be at position 11 or 12. Comparison of the carbon spectra of **2** and **3** provided no additional insight

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[†] This paper is dedicated to Dr. Pennamuthiriar Chinnasamy, who performed the initial studies leading to the publication. He passed away unexpectedly on September 2, 1987.

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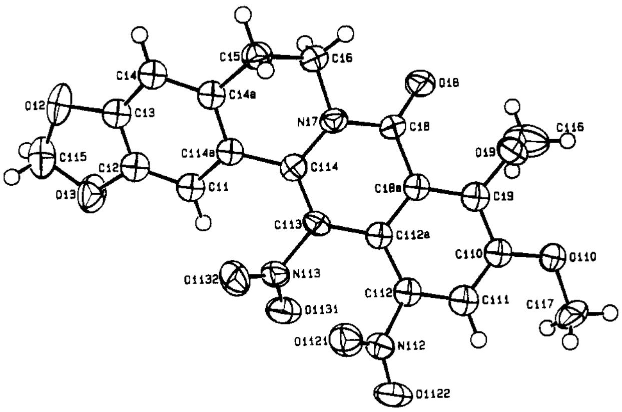


Figure 1. ORTEP plot of the X-ray structure of 3.

on this regiochemical problem, nor was any appreciable NOE observed between the aromatic proton at δ 7.90 and the methoxyl protons. The structure **3** was established by X-ray crystallographic analysis (Figure 1).

Lithium aluminum hydride reduction of **2** gave the unexpected ring expansion product **4** in addition to **5**, the desired intermediate for further synthesis. The stereochemistry of **5** was established spectroscopically, based on correlations with other 13-substituted tetrahydroprotoberberines. The trans orientation of the B/C ring fusion was determined, as in the case of several 13-hydroxytetrahydroprotoberberines, by the presence of Bohlmann bands near 2800 and 2750 cm^{-1} in both the solid and solution IR spectra.[3-5] These bands provide evidence of the interaction between the lone pair electrons of N-7 and at least two axial CH bonds which are antiperiplanar to the nitrogen lone pair.[6] The large difference in chemical shift (0.69 ppm) between the two protons at C-8 also indicates a B/C-trans ring fusion. Such chemical shift differences can be attributed to the selective deshielding of the 8-equatorial proton by the aromatic D ring, the lone pair of the oxygen atom adjacent to C-9, and the lone pair of the bridgehead nitrogen atom.[3,7-9] Takao and Iwasa observed a positive correlation between difference in chemical shifts of the two C-8 protons and the presence and/or intensity of solution IR Bohlmann bands among a series of 9,10-dimethoxy- or -(methylenedioxy)tetrahydroprotoberberines.[9] In the systems shown to be predominantly trans fused by IR data, only the 8-equatorial proton is deshielded by the nitrogen lone pair, while both protons are equally affected in the cis-fused system.

Coupling constants between H-13 and H-14 of 1.5 and 9.0 Hz were previously reported for the known compounds **11** and **10**, respectively, confirming the stereochemistries of these two diastereomers.[7] Analogously, the small $J_{13,14}$ value (2.3 Hz) observed in **5** demonstrates a cis orientation of these two protons. A dihedral angle near 55° is consistent with the Karplus equation.[8] Such a geometry would allow intramolecular hydrogen bonding between an amino proton and the bridgehead nitrogen atom. Solution IR data of **8**, **9**, and **12** demonstrated intramolecular hydrogen bonding between the hydroxyl proton and the lone pair of the nitrogen atom in the conformationally allowed cis isomers **9** and **12** having trans fused quinolizidine systems, but not in the trans isomer **8**, which has a cis fused quinolizidine system.[3-5]

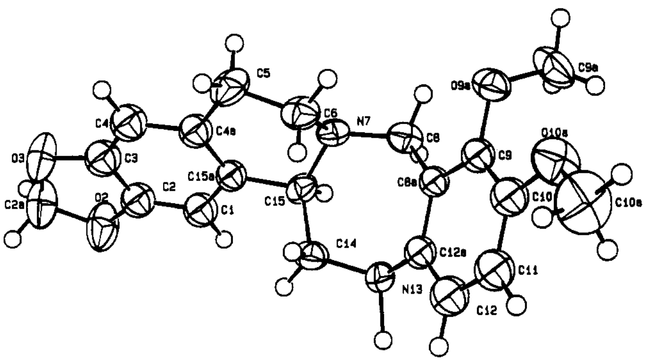


Figure 2. ORTEP plot of the X-ray structure of 4.

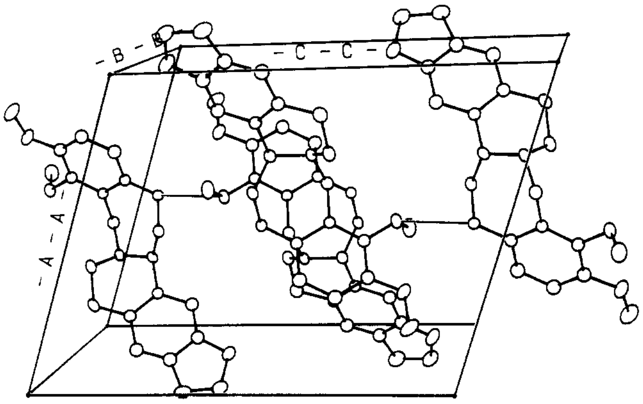


Figure 3. Unit cell diagram of the X-ray structure of 4.

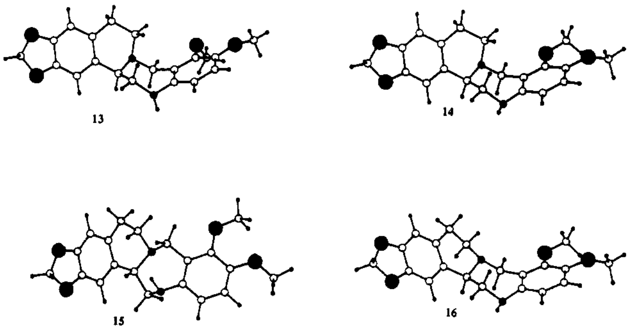
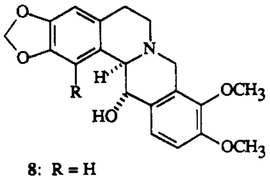
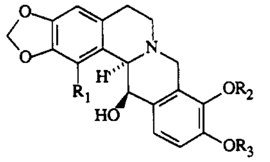


Figure 4. Computer-generated models of proposed conformations of 4.



8: R = H
10: R = OCH$_3$



9: R$_1$ = H, R$_2$ = R$_3$ = CH$_3$
11: R$_1$ = OCH$_3$, R$_2$ = R$_3$ = CH$_3$
12: R$_1$ = OCH$_3$, R$_2$ + R$_3$ = CH$_2$

The structure of diazepine **4** was solved by X-ray crystallographic analysis. The ORTEP plot (Figure 2) clearly shows a B/C-cis ring fusion. The intermolecular hydrogen

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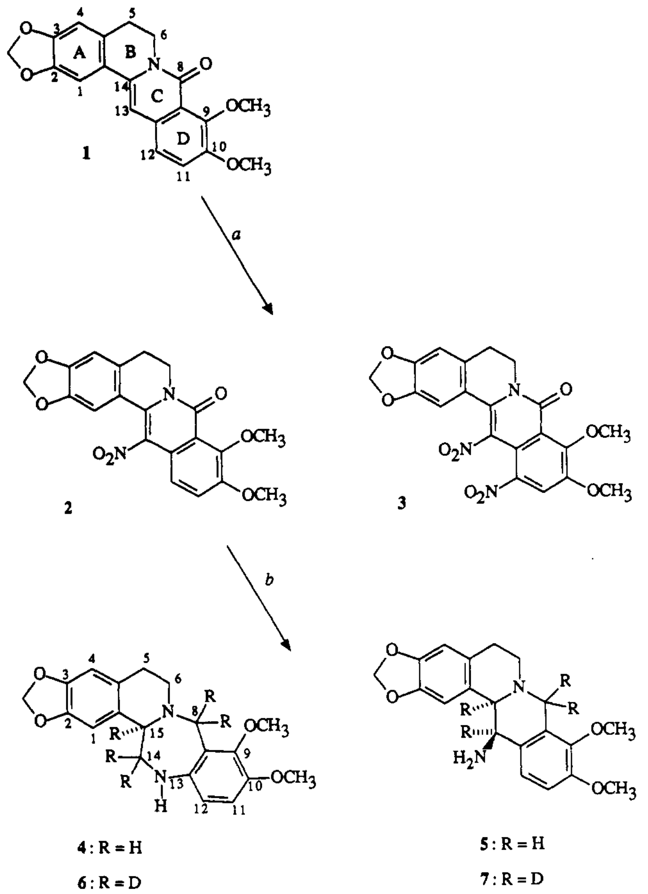
Table I. 500-MHz ^{1}H NMR Data for 4

δ	multiplicity	J, Hz	no. H's	position	basis of assignment
6.66	d	8.5	1	11	NOE with OCH_3
6.56	s		1	1	NOE with H-15
6.51	s		1	4	NOE with H-5
6.50	d	8.5	1	12	NOE with NH
5.86	dd	6.3, 1.4	2	OCH_2O	chemical shift, coupling
4.61	d	14.4	1	8_{eq}	deshielding by D ring, absence in spectrum of 6
4.10	dd	9.1, 4.1	1	15	spin simulation, absence in spectrum of 6
3.93	d	14.4	1	8_{ax}	NOE with H-15, absence in spectrum of 6
3.81	s		3	OCH_3	
3.80	s		3	OCH_3	
3.11	dd	13.5, 4.1	1	14	spin simulation, absence in spectrum of 6
3.10	dd	13.5, 9.0	1	14	spin simulation, absence in spectrum of 6
2.91	dt	16.1, 8.8	1	5	spin simulation
2.73	dd	8.8, 3.3	2	6	spin simulation, NOE with H-14_{ax} and H-8_{eq}
2.57	dt	16.2, 3.3	1	5	spin simulation, NOE with H-4
1.60	br s		1	NH	exchangeable with D_2O, NOE with H-12

Scheme I[a]



[a] (a) aqueous HNO_3, CH_2Cl_2, 25 °C (3 h); (b) $LiAlH_4$ (or $LiAlD_4$), THF, reflux (3 h).

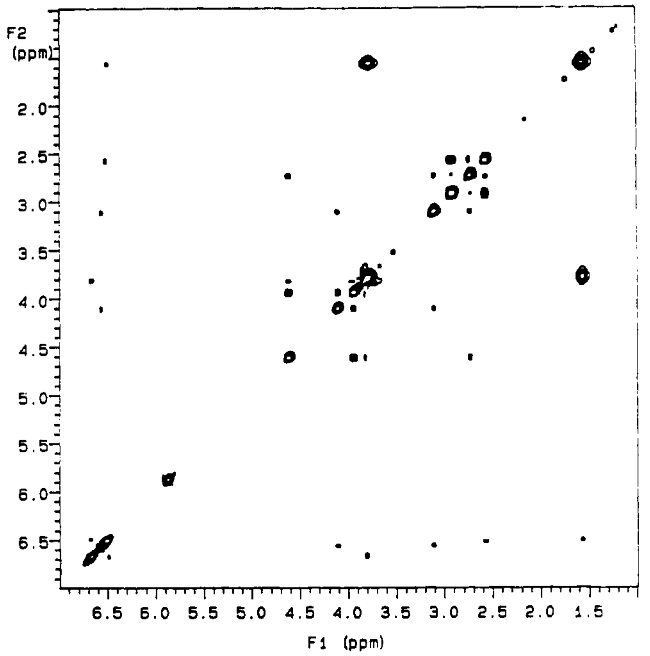


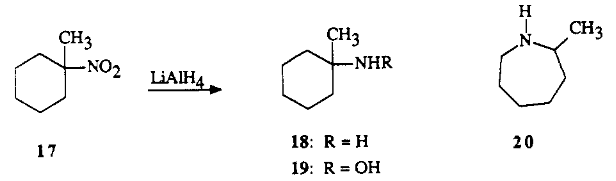
Figure 5. 500-MHz 2D NOESY spectrum of 4.

bond between the amino proton and one methoxyl oxygen atom (Figure 3) in the crystalline state accounts for the equatorial orientation of the amino proton and the spacial orientation of the methoxyl groups, which are altered by energy minimization (vide infra). The question at hand was whether the major conformation in solution is similar to that in the crystalline state.

A three-dimensional computer graphics model **13** of the molecule was constructed with QUANTA software using the coordinates of the X-ray structure (Figure 4). An equatorial NH proton is present in **13**. Energy minimization resulted in conformer **14**, in which the amino proton is now axial and the 9-methoxyl carbon atom lies nearly in the plane of the D ring. Modification of **13** by ring flipping or stereoinversion about N-7, followed by energy minimization, produced B/C-cis conformer **15** and B/C-trans conformer **16**, respectively. The energies of **13**–**16** calculated using CHARMm[9] were 208.10, 33.06, 36.99, and 34.87 kcal/mol, respectively. Thus, **14** is predicted to be more stable than **15** or **16**.

An unambiguous assignment of proton resonances of **4** was essential (Table I). A 2D NOESY experiment proved quite beneficial (Figure 5). The NOE between H-15 and the proton giving a singlet at δ 6.56 allowed the distinction of H-1 from H-4 (δ 6.51). Similarly, the NOE between H-15 and the proton giving a doublet at δ 3.93 distinguished the 8-axial and 8-equatorial (δ 4.61) protons. The cross-peak between a methoxyl signal and the doublet at δ 6.66 confirmed the assignments of H-11 and H-12 (δ 6.50). The assignments of the signals of methylene protons at positions 5, 6, and 14 were less straightforward, due to overlapping resonances and similar coupling constants. Very little precedent exists in the literature for distinguishing protons at the 5- and 6-positions of tetrahydroprotoberberines. The region between δ 2.5 and 3.2 of the NMR spectrum of **4** was virtually unchanged after D_2O exchange, ruling out the possibility of coupling between the amino proton and the C-14 protons. The 2D NOESY data suggested that the signals centered at δ 2.57 (1 H), 2.73 (2 H), and 3.10 (2 H), arise from protons at positions 5, 6, and 14, respectively, based upon the NOE's of these

Scheme II

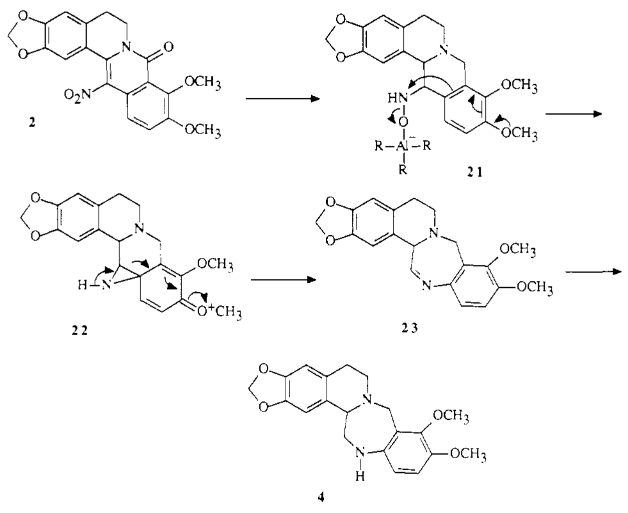


protons with H-4, H-8$_{\mathrm{eq}}$, and H-15, respectively. Spin simulation with the RACCOON program over the region of δ 2.5–3.2 was achieved by using the H-5, H-6, and H-14 assignments suggested by the NOE data and assigning the signal at δ 2.92 to the other H-5. The H-14 assignments of **4** were confirmed by the NMR spectrum of the deuterated analogue **6**, in which the AB quartet arising from the protons at position 8 and the ABX pattern of the signals at δ 4.10, 3.11, and 3.10 are absent.

Spectral data support a conformation similar to either **13** or **14** as the major solution conformation. The lack of Bohlmann bands in the solution IR spectrum gives evidence of a B/C-cis fusion. A difference in chemical shift of 0.68 ppm between the two C-8 protons initially appeared to suggest a B/C-trans fusion.[8,9] Dreiding models, however, show that the 8-equatorial proton of **4** lies nearly in the plane of the D ring, while the plane of the D ring of **5** lies within the H8$_{\mathrm{ax}}$–C8–H8$_{\mathrm{eq}}$ angle. Thus, the 8-equatorial proton of **4** is more strongly deshielded by the D ring and the lone pair of the oxygen atom adjacent to C-9 than is the homologous proton of **5**. Therefore in this molecule, the large chemical shift difference between the two C-8 protons is consistent with a B/C-cis fusion. Two important NOE's also support conformations **13** or **14**. The NOE observed between H-15 and H-8$_{\mathrm{ax}}$ is consistent with **13**, **14**, or **16**, but not **15**. The NOE observed between H-14$_{\mathrm{ax}}$ and H-6$_{\mathrm{ax}}$ is consistent with **13** or **14** but with neither **15** nor **16**.

A mechanism for the ring expansion to form **4** may be proposed on the basis of examples in the literature involving similar reductive rearrangements of nitro compounds and oximes in the presence of lithium aluminum hydride. Several nitrocycloalkanes have been reacted with lithium aluminum hydride to give ring expansion products in addition to the expected primary amines.[13] Interestingly, reduction of 1-methyl-1-nitrocyclohexane (**17**, Scheme II) gave the hydroxylamine **19** in addition to the primary amine **18** and the ring expansion product **20**.[13] Subsequent lithium aluminum hydride reduction of **19** gave **18** and **20**, suggesting the role of the hydroxylamine intermediate in the ring expansion process.[13] In addition, numerous examples have been reported of a similar rearrangement of aromatic and strained alicyclic oximes on treatment with lithium aluminum hydride.[14] However, the available evidence indicates that these reactions of oximes occur by reduction to a hydroxylamine derivative followed by aryl migration rather than by a Beckmann rearrangement of the oxime itself. For example, treatment of both *syn*- and *anti*-isobutyrophenone oxime with lithium aluminum hydride gives, in addition to the primary amine, *N*-isobutylaniline as the sole reductive rearrangement product under conditions that do not permit oxime isomerization, which is clearly inconsistent with a pathway involving Beckmann rearrangement of the oxime followed by reduction to the product.[14g] The proposed hydroxylamine intermediates in these reactions of oximes have been prepared and do in fact undergo reductive rearrangement in the presence of lithium aluminum hydride.[14g] Therefore, both nitro compounds and oximes appear to undergo reductive rearrangement through hydroxylamine intermediates. In the reductive rearrangement of oximes having both alkyl and aryl substituents, only the aryl group migrates, and the rearrangement is facilitated by electron-donating substituents on the aromatic ring.[14d] These results are consistent with an intramolecular electrophilic reaction of a hydroxylamine derivative to form an aziridine intermediate, which then undergoes ring opening and reduction to the product. Similar aziridine intermediates have been proposed for aryl migration during the Beckmann rearrangement.[15]

Scheme III



Based on a hydroxylamine intermediate, a proposed mechanism for the formation of **4** is shown in Scheme III. Reduction of the lactam and the nitro groups with lithium aluminum hydride would give the aluminate of the hydroxylamine **21**. Nucleophilic attack of the aromatic ring on the electrophilic nitrogen then leads to the intermediate aziridine **22**, which fragments to form the seven-membered ring of **23**. Reduction of the imine group of **15** affords the observed product **4**.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Chemagnetics A-200 MHz or a Varian VXR-500 MHz spectrometer. ^{13}C NMR spectra were recorded on a Chemagnetics A-200 spectrometer operating at 50 MHz or a Varian VXR 500 spectrometer operating at 125 MHz. NMR samples were dissolved in CDCl$_3$. IR spectra were recorded on a Beckman IR-33 or a Perkin-Elmer 1600 FTIR spectrometer. Analytical thin-layer chromatography was performed on Merck Kieselgel 60 F$_{254}$ plates, 0.25 mm thickness. Elemental analyses were obtained from the Purdue Microanalytical Laboratory. The mass spectra were determined on a Finnigan 4000 spectrometer using an ionization potential of 70 eV. The chemical ionization mass spectra (CIMS)

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were obtained using 2-methylpropane as the reagent gas. High-resolution mass spectra were recorded on a Kratos MS50 spectrometer. Conformational energy minimizations were performed using the QUANTA/CHARMm programs (Polygen Corp.) on a Silicon Graphics 4D/120 computer.

13-Nitrooxyberberine (2). A solution of 10% aqueous nitric acid (300 mL) was added to a solution of oxyberberine (8.00 g, 22.8 mmol) in methylene chloride (200 mL). The two-phase mixture was stirred vigorously at room temperature for 3 h, after which time the starting material was no longer detectable by analytical thin-layer chromatography. The mixture was diluted with water (300 mL). The organic layer was extracted with methylene chloride (4 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried ($MgSO_4$) and evaporated. The material was chromatographed on a silica gel column (300 g, 60–200 mesh, 5 × 45 cm), eluting with 4% (v/v) acetone in methylene chloride. The major product, which eluted second, was crystallized from methylene chloride/methanol to give orange crystals of **2** (8.24 g, 91.3%): mp 226.5–227.5 °C; IR (KBr) 2910, 2820, 1650, 1605, 1585, 1500, 1485, 1465, 1360, 1300, 1280, 1260, 1210, 1160, 1075, 1020, 910 cm^{-1}; ^1H NMR (200 MHz) δ 7.39 (d, 1 H, J = 9.2 Hz), 7.26 (d, 1 H, J = 9.2 Hz), 7.00 (s, 1 H), 6.77 (s, 1 H), 6.03 (s, 2 H), 4.21 (t, 2 H, J = 5.9 Hz), 4.00 (s, 3 H), 3.97 (s, 3 H), 2.90 (t, 2 H, J = 5.9 Hz); ^{13}C NMR (50 MHz) δ 158.33, 152.59, 149.84, 149.51, 147.31, 133.46, 131.23, 130.77, 123.87, 119.15, 118.92, 118.20, 116.79, 108.10, 106.28, 101.79, 61.54, 56.49, 40.13, 29.05; EIMS m/e (relative intensity) 396 (M^+, 100); high-resolution EIMS calcd for $C_{20}H_{16}N_2O_7$ m/e 396.0958 (M^+), found 396.0947. Anal. Calcd for $C_{20}H_{16}N_2O_7$: C, 60.61; H, 4.07; N, 7.07. Found: C, 60.51, H. 3.99; N, 7.37.

12,13-Dinitrooxyberberine (3). The compound that eluted first during the column chromatography above was crystallized from methanol to give yellow crystals of **3** (76.5 mg 0.8%): mp 231–232 °C; IR (KBr) 3446, 1661, 1576, 1522, 1484, 1345, 1325, 1268, 1102, 1037, 868 cm^{-1}; ^1H NMR (200 MHz) δ 7.90 (s, 1 H), 6.79 (s, 1 H), 6.78 (s, 1 H), 6.04 (s, 2 H), 4.10 (t, 2 H, J = 6.1 Hz), 4.07 (s, 3 H), 4.04 (s, 3 H), 2.97 (t, 2 H, J = 6.1 Hz); ^{13}C NMR δ 157.21, 153.65, 151.78, 150.75, 147.34, 140.01, 137.46, 133.73, 127.49, 119.26, 118.81, 117.89, 115.05, 107.82, 106.82, 102.08, 62.01, 56.92, 41.18, 28.54; CIMS m/e (relative intensity) 442 (MH^+, 100); high-resolution EIMS calcd for $C_{20}H_{15}N_3O_9$ (M^+) m/e 441.0808, found 441.0807. Anal. Calcd for $C_{20}H_{15}N_3O_9$: C, 54.43; H, 3.43; N, 9.52. Found: C, 54.38; H, 3.41; N, 9.53.

4,6,7,12b,13,14-Hexahydro-2,3-dimethoxy-1,3-dioxolo[6,7]-isoquino[1,2-*c*][1,4]benzodiazepine (12a-Homoazatetrahydroberberine, 4). 13-Nitrooxyberberine (**2**, 1.00 g, 2.53 mmol) was added to a stirred suspension of lithium aluminum hydride (0.50 g, 13.2 mmol) in dry THF maintained at 0 °C under argon. The reaction mixture was heated and maintained at reflux for 3 h, after which time the starting material was no longer detectable by TLC. The mixture was cooled to 0 °C, followed by the dropwise addition of water (0.5 mL), 15% aqueous NaOH (0.5 mL), and water (2 mL). After the mixture was stirred at room temperature for 30 min, the solids were filtered off and washed with hot ethyl acetate. The combined filtrates were dried ($MgSO_4$), evaporated, and adsorbed onto silica gel. The material was chromatographed on a silica gel column (50 g, 60–200 mesh, 2 × 40 cm), eluting with hexane (85)–ethyl acetate (14.5)–diethylamine (0.5). The compound which eluted first was crystallized from methanol, giving colorless crystals of **4** (133.5 mg, 14.9%): mp 197–199 °C; FTIR ($CHCl_3$) 3018, 2905, 2837, 1482, 1255, 1215, 1079, 1041, 754, 669 cm^{-1}; ^1H NMR (500 MHz) δ 6.66 (d, 1 H, J = 8.5 Hz), 6.56 (s, 1 H), 6.51 (s, 1 H), 6.50 (d, 1 H, J = 8.5 Hz), 5.86 (dd, 2 H, J_1 = 6.3 Hz, J_2 = 1.44 Hz), 4.61 (d, 1 H, J = 14.41 Hz), 4.10 (dd, 1 H, J_1 = 9.05 Hz, J_2 = 4.10 Hz), 3.93 (d, 1 H, J = 14.4 Hz), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.11 (dd, 1 H, J_1 = 13.5 Hz, J_2 = 4.1 Hz), 3.10 (dd, 1 H, J_1 = 13.4 Hz, J_2 = 9.1 Hz), 2.91 (dt, 1 H, J_1 = 16.2 Hz, J_2 = 8.8 Hz), 2.73 (dd, 2 H, J_1 = 8.8 Hz, J_2 = 3.3 Hz), 2.57 (dt, 1 H, J_1 = 16.2 Hz, J_2 = 3.3 Hz), 1.60 (br s, 1 H, exchangeable with D_2O); ^{13}C NMR (125 MHz) δ 148.18, 147.67, 146.08, 145.36, 144.04, 129.64, 128.19, 124.22, 113.38, 111.28, 108.43, 106.82, 100.57, 64.17, 61.05, 56.05, 50.77, 50.08, 42.23, 29.40; CIMS m/e (relative intensity) 355 (MH^+, 100). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.73; H, 6.34; N, 7.98.

***cis*-13-Aminotetrahydroberberine (5).** The compound that eluted second during the column chromatography above was crystallized directly from the chromatography solvent to give pale yellow crystals of **5** (160.8 mg, 17.9%): mp 206–209 °C; FTIR ($CHCl_3$) 3027, 3009, 2942, 2911, 2838, 2815, 2755, 1504, 1495, 1785, 1459, 1390, 1355, 1281, 1248, 1224, 1100, 1076, 1042, 858, 810, 784, 772, 766 cm^{-1}; ^1H NMR δ 7.12 (d, 1 H, J = 8.5 Hz), 6.87 (d, 1 H, J = 8.5 Hz), 6.71 (s, 1 H), 6.61 (s, 1 H), 5.93 (s, 2 H), 4.18 (d, 1 H, J = 15.8 Hz), 4.05 (d, J = 2.3 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.63 (br s, 1 H), 3.49 (d, 1 H, J = 15.8 Hz), 3.13 (m, 2 H), 2.64 (m, 2 H), 1.45 (br s, 2 H, exchangeable with D_2O); CIMS m/e (relative intensity) 355 (MH^+, 100), 338 ($MH^+ - NH_3$, 64). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.76; H, 6.51; N, 7.73.

4,6,7,12b,13,14-Hexahydro-2,3-dimethoxy-1,3-dioxolo[6,7]-isoquino[1,2-*c*][1,4]benzodiazepine-*4,4,13,13,12b*-d_5 (12*a*-Homoazatetrahydroberberine-*8,8,14,14,15*-d_5, 6). 13-Nitrooxyberberine (**2**, 400.3 mg, 1.011 mmol) was reacted with lithium aluminum deuteride (0.50 g, 13.2 mmol). The reaction conditions and workup were analogous to the reaction of **2** with lithium aluminum hydride. The compound which eluted first was crystallized from methanol to give colorless crystals of **6** (19 mg, 5.3%): mp 194–197 °C; FTIR (KBr) 2992, 2943, 2908, 2830, 2772, 2706, 1481, 1450, 1241, 1224, 1194, 1169, 1056, 1040, 994, 941, 913, 888, 871, 833, 803 cm^{-1}; ^1H NMR (500 MHz) δ 6.69 (d, 1 H, J = 8.4 Hz), 6.58 (s, 1 H), 6.54 (s, 1 H), 6.52 (d, 1 H, J = 8.4 Hz), 5.89 (dd, 2 H, J_1 = 6.0 Hz, J_2 = 1.4 Hz), 3.84 (s, 3 H), 3.83 (s, 3 H), 2.95 (dt, 1 H, J_1 = 16.1 Hz, J_2 = 9.4 Hz), 2.75 (dd, 2 H, J_1 = 9.4 Hz, J_2 = 3.1 Hz), 2.59 (dt, 1 H, J_1 = 16.1 Hz, J_2 = 3.1 Hz); CIMS 360 (MH^+, 100).

***cis*-13-Aminotetrahydroberberine-*8,8,13,14*-d_4 (7).** The compound which eluted second was crystallized from methanol to give white crystals of **7** (17 mg, 4.8%): mp 208 °C; IR (KBr) 3449, 3349, 3035, 3000, 2923, 2830, 2804, 2715, 1604, 1580, 1562, 1490, 1424, 1386, 1336, 1280, 1260, 1242, 1182, 1158, 1113, 1093, 1063, 1040, 1018, 954, 931, 882, 862, 839, 810, 789 cm^{-1}; NMR (200 MHz) δ 7.12 (d, 1 H, J = 8.5 Hz), 6.87 (d, 1 H, J = 8.5 Hz), 6.70 (s, 1 H), 6.61 (s, 1 H), 5.93 (s, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.13 (m, 2 H), 2.64 (m, 2 H), 1.45 (br s, 2 H), CIMS m/e (relative intensity) 359 (MH^+, 100), 342 ($MH - NH_3^+$, 55).

X-ray Analysis of 3. Crystal Data. Compound **3**: $C_{20}H_{15}N_3O_9$, f_w = 441.36; monoclinic; a = 8.249 (2), b = 14.263 (2), c = 16.193 (2) Å, β = 97.46 (1)°, V = 1889.1 (9) $Å^3$, Z = 4, ρ_{calcd} = 1.552 g/cm^3, F_{000} = 912.0, μ = 1.17 cm^{-1}, space group $P2_1$ from systematic absences.

Data Collection. A yellow needle of compound **3** having approximate dimensions of 0.63 × 0.13 × 0.11 mm was mounted on a glass fiber in a random orientation. The data collection was performed with Mo Kα radiation (λ = 0.710 73 Å) on an Enraf-Nonius CAD4 computer controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator.[16] Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range of $12 < 2\theta < 17°$, measured by the computer controlled diagonal slit method of centering. The data were collected at a temperature of 20 ± 1° using the $\omega - 2\theta$ scan technique. The scan rate varied from 2 to 20°/min (in ω). Data were collected to a maximum 2θ of 45.0°. A total of 2620 unique reflections were collected. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 1.2 cm^{-1} for Mo Kα radiation. No absorption correction was necessary.

Structure Analysis. The structure was solved by direct methods using SHELX. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located and added to the structure factor calculations but their positions were not refined. Only 2043 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 456 variable parameters and converged with unweighted and weighted agreement factors of 0.040 and 0.046, respectively.[17] The highest peak in the final difference Fourier had a height of 0.24 e/$Å^3$ with an estimated error based on δF of 0.04.[18] Plots of $E_w(|F_o| - |F_c|)^2$ versus F_o, reflection order in data collection, sin θ/λ, and various

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classes of indices showed no unusual trends. All calculations were performed on a VAX computer using SDP/VAX.[19]

X-ray Analysis of 4. Crystal Data. Compound 4: $C_{20}H_{22}N_2O_4$, $M_r = 354.41$; monoclinic; $a = 11.853$ (3), $b = 10.235$ (1), and $c = 15.144$ (4) Å, $\beta = 108.34$ (1)°, $V = 1743$ (1) $Å^3$, $Z = 4$, $\rho_{calcd} = 1.350$ g/cm^3, $F_{000} = 752.0$, $\mu = 0.88$ cm^{-1}, space group $P2_1/c$ from systematic absences.

Data Collection. A pale yellow chunk of compound 4 having approximate dimensions of 0.31 × 0.19 × 0.10 mm was mounted on a glass fiber in a random orientation. The data collection was performed with Mo Kα radiation ($\lambda = 0.71073$ Å) on an Enraf-Nonius CAD4 computer controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator.[16] Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range of $9 < 2\theta < 17°$, measured by the computer controlled diagonal slit method of centering. The data were collected at a temperature of 20 ± 1° using the $\omega - 2\theta$ scan technique. The scan rate varied from 1 to 20°/min (in ω). Data were collected to a maximum 2θ of 45.0°. A total of 2434 unique reflections were collected. Lorentz and polarization corrections were applied to the data. The linear absorption coefficients is 0.9 cm^{-1} for Mo Kα radiation. No absorption correction was necessary.

Structure Analysis. The structure was solved by direct methods using MULTAN. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located and added to the structure factor calculations but their positions were not refined. Because of the small size of the crystal, only 966 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 175 variable parameters and converged with unweighted and weighted agreement factors of 0.051 and 0.056 respectively.[17] The highest peak in the final difference Fourier had a height of 0.18 e/Å^3 with an estimated error based on δF of 0.05.[18] Plots of $E_w(F_o - F_c)^2$ versus Fo, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. All calculations were performed on a VAX computer using SDP/VAX.[19]

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Supplementary Material Available: X-ray data for 3 and 4 (25 pages). Ordering information is given on any current masthead page.

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Total Synthesis of L,L-Isodityrosine and Isodityrosine-Derived Agents: K-13, OF4949-III, and OF4949-IV

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Full details of the development of reaction conditions for implementation of an activated Ullmann condensation reaction that may be conducted without amino acid racemization and that have proven suitable for incorporation of the selectively protected catechol of functionalized L–Dopa derivatives are described. The application of this procedure in the total synthesis of L,L–isodityrosine (**15**), K-13 (**1**), and OF4949-III/OF4949-IV (**4**/**5**) is detailed. Full details of a study of the macrocyclization reaction required for formation of the 17–membered tripeptides incorporating a diaryl ether linked meta– and paracyclophane structural subunit are provided and illustrate that the cyclization in route to K–13/OF4949-I – OF4949-IV is optimally conducted on substrates bearing a carbamate derivative of the C-15/C-9 amine and a C-4 free phenol with C^{11}–N^{10}/C^{10}–N^{11} amide bond closure.

Introduction

K-13 (**1**), an isodityrosine-derived cyclic tripeptide isolated from *Micromonospora halophytica* ssp. *exilisia K-13* and identified by spectroscopic and chemical degradative studies,[2] has been shown to be a potent, noncompetitive inhibitor of angiotensin I converting enzyme ($I_{50} = 0.17$ μg/mL, $K_i = 0.35$ μM) and weak inhibitor of aminopeptidase B.[3] Consequently K-13[4-6] represents the newest addition to a class of isodityrosine-derived[7,8] cyclic peptides now including OF4949-I – OF4949-IV (**2**–**5**),[9-13] potent inhibitors of aminopeptidase B with confirmed immunopotentiating and antitumor properties isolated from *Penicillium rugulosum*, piperazinomycin (**6**),[14-17] and the bi-

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