Notes

Synthesis of Conformationally Mobile Bicyclic Tetrahydro-1,2-oxazines by Isomerization of Isoxazolidinylmethyl Tosylates

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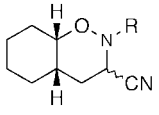
Received July 15, 1997

Introduction

Eschenmoser and his colleagues developed vinylnitrosonium cations (generated via silver ion-induced dehalogenation of α-chloroaldonitrones) as highly reactive enophiles that undergo [4 + 2]-cycloaddition with unactivated alkenes to provide, ultimately, 3-cyanoperhydro-1,2-oxazines as typified by structure **1**.[1] This paper



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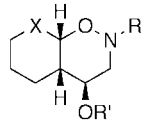

2 X = CH_2 or O

describes a new route to similar compounds, namely two bicyclic 4-oxygenated tetrahydro-1,2-oxazines (**2**), via isomerization of isoxazolidinylmethyl tosylates. These products are analogous to *cis*-decalins, are conformationally mobile, and exhibit broadened signals in their ^{1}H and ^{13}C NMR spectra at room temperature. Synthetic procedures will be discussed, as well as a detailed analysis of major conformers of the products using molecular modeling and NMR spectroscopy at −80 °C.

Results and Discussion

Synthesis. Cycloaddition of nitrone **3** to cyclohexene or 2,3-dihydropyran provided isoxazolidines **4a** and **4b**, respectively (Scheme 1).[2,3] Reduction with lithium aluminum hydride[4] gave alcohols **5a** and **5b**, which were converted to the isoxazolidinylmethyl tosylates **6a** and **6b**, respectively. Rearrangement of tosylate **6a** was effected by heating in acetone to give the crystalline tetrahydro-1,2-oxazine **8a** in high yield. The structure of **8a** was verified by X-ray crystallography.

In contrast, tosylate **6b** was heated in 2-butanone to provide an inseparable mixture of the reactant and its ring-enlarged isomer **8b**.[5] Prolonged heating did not effect complete isomerization, but rather led to decomposition, suggesting that a steady state between **8b** and **6b** had been achieved. The cis-ring fusion of these bicyclic tetrahydro-1,2-oxazines results from the concerted 1,3-dipolar addition of the nitrone.[6] The isomerization is reasonably thought of as proceeding via the aziridinium ion **7** (as was proposed[7] many years ago for a simpler analogue), with the tosylate ion preferentially opening the aziridinium ion with inversion of configuration, thus residing on the convex face of the ring system.

NMR Spectral Analysis. Bicyclic tetrahydro-1,2-oxazines **8a** and **8b** are conformationally mobile and exhibit broadened signals in their ^{1}H and ^{13}C NMR spectra at room temperature. At −80 °C in CD_2Cl_2 only two conformations are evident for each by ^{1}H NMR spectroscopy. If these compounds are analogous to *cis*-decalins, one may imagine an equilibrium between two conformations (Scheme 2) as a result of ring inversions.[8] Apparently the equilibrations are slow enough at room temperature on the NMR time scale to broaden the spectrum.

For the cyclohexene-derived product **8a**, the two conformers observed at −80 °C are in a ratio of 6 to 1 (determined by NMR integration). For the major conformer H(4) appears at δ 4.16 as a broadened ddd (J ∼ 2.4, 2.4, and 2.4 Hz), whereas for the minor conformer the analogous hydrogen appears at δ 4.60 as a ddd (J = 10.6, 10.5, and 5.3 Hz). These data suggest that the

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(1) (a) cf.: Kempe, U. M.; Das Gupta, T. K.; Blatt, K.; Gygax, P.; Felix, D.; and Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2187. (b) For a novel synthesis of indoles using variations of this procedure, see: Hattingh, W. C.; Holzapfel, C. W.; van Dyk, M. S. *Synth. Commun.* **1987**, *17*, 1491. (c) For a similar procedure using α,β-epoxyaldonitrones as precursors to vinylnitrosonium cations, see: Reidiker, M.; Graf, W. *Helv. Chim. Acta* **1979**, *62*, 2053. (c) For an intramolecular variant of the Riediker-Graf methodology, see: Denmark, S. E.; Cramer, C. J.; Dappen, M. S. *J. Org. Chem.* **1987**, *52*, 877.

(2) For preparation and cycloaddition of similar nitrones, cf.: (a) Inouye, Y.; Watanabe, Y.; Takahashi, S.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3763. (b) Hara, J.; Inouye, Y.; Kakisawa, H. *Bull Chem. Soc. Jpn.* **1981**, *54*, 3871. (c) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397.

(3) All compounds were prepared in racemic form, although only one enantiomer is depicted. The diasteromers shown in Scheme 1 represent the major isomers formed, those that were isolated and purified, and those for which characterization data are reported in the Experimental Section.

(4) Belzecki, C.; Panfil, I. *J. Org. Chem.* **1979**, *44*, 1212.

(5) For the preparation of a similar compound using the Eschenmoser procedure, see: Levinger, S.; Shatzmiller, S. *Tetrahedron* **1978**, *34*, 563.

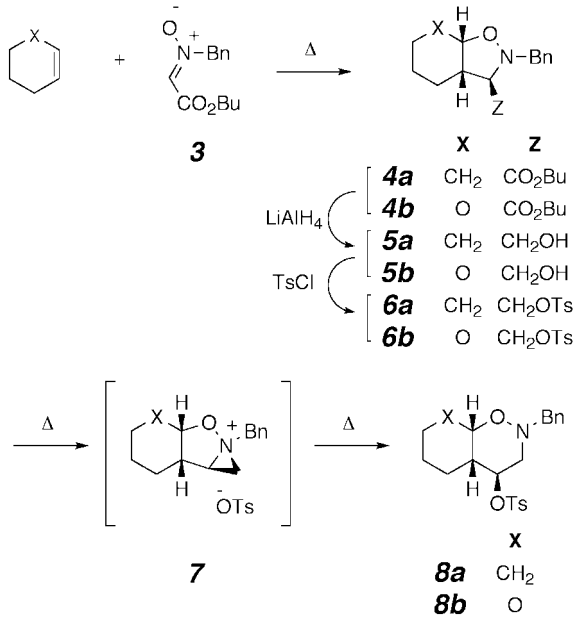
(6) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, pp 83−168.

(7) (a) Fuson, R. C.; Zirkle, C. L. *J. Am. Chem. Soc.* **1948**, *70*, 2760. See also: (b) Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1965**, *30*, 821. (c) Cossy, J.; Dumas, C.; Pardo, D. G. *Synlett* **1997**, 905.

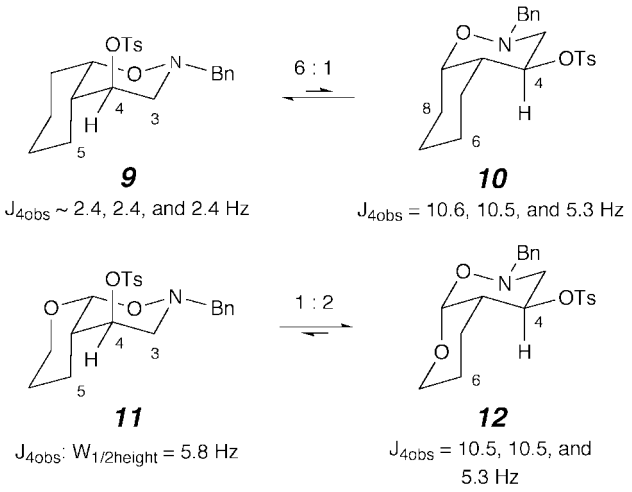
(8) Although nitrogen inversion can generate an additional *N*-axially substituted conformer for each of **9**−**12**, that process should have a lower kinetic barrier than chair−chair ring inversion. No *N*-axial conformers were observed to lie within the first 3 kcal/mol of the global minimum energy conformation calculated with MM2*. For a similar conformational analysis of a simpler analogue, see: Riddell, F. G.; Williams, D. A. R. *Tetrahedron* **1974**, *30*, 1097.

S0022-3263(97)01299-1 CCC: $15.00
Published on Web 05/29/1998

Scheme 1



Scheme 2

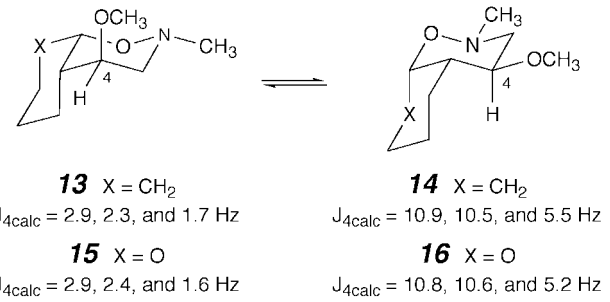


major conformer resembles structure **9**, while the minor conformer resembles structure **10**. It is pertinent to note that the X-ray structure most closely resembles conformer **9**.

For the dihydropyran-derived product **8b**, the two conformers observed at −80 °C (CD_2Cl_2) are in a ratio of 2 to 1 (determined by NMR integration). For the major conformer, H(4) appears at δ 4.58 as a ddd (J = 10.5, 10.5, and 5.3 Hz), whereas for the minor conformer, the analogous hydrogen appears at δ 4.27 as a broad singlet ($W_{1/2height}$ = 5.8 Hz). These data suggest that in contrast to the cyclohexene-derived analogue, the major pyran conformer resembles structure **12**, while the minor conformer resembles structure **11**.

Conformational Analysis. It is interesting to speculate on the reasons for the observed conformational preferences. In conformer **10** for the cyclohexene-derived compound, there are two 1,6-H/H interactions [between pairs H(4)/H(6ax) and H(4)/H(8ax)]. In conformer **9** only one such interaction exists [between the pair H(3ax)/H(5ax)]; the other is replaced by a 1,3-diaxial OTs/H interaction, which should cause less steric strain;[9] thus conformer **9** should be slightly more stable than **10**.

Scheme 3



For the dihydropyran-derived product, both conformations **11** and **12** possess one anomeric stabilization, thus this is not a decisive factor. Also, each has only a single 1,6-H/H interaction [H(3ax)/H(5ax) in **11** and H(4)/H(6ax) in **12**], so apparently the axial tosyloxy group makes conformer **11** less stable than conformer **12**.

Molecular Modeling. Molecular modeling studies were performed[10] with the structures **13**−**16**, which are truncated analogues of **9**−**12** chosen to remove most of the degrees of freedom associated with the appendages (Scheme 3). Even though the force field used[10] is not parametrized to treat properly the atoms involved in the C−O−N−C and O−C−O−N−C arrays, the calculated[11] vicinal NMR coupling constants for H(4) in **13**−**16** (see Scheme 3) matched exceptionally well with those observed for each of the conformers **9**−**12**.

Conclusions

A new synthesis for two bicyclic tetrahydro-1,2-oxazines (**8a** and **8b**) has been presented, as well as a clear demonstration of the conformational preferences of these compounds. This procedure is complementary to the Eschenmoser methodology[1] for the preparation of these heterocycles and provides a potential leaving group at a different ring position. Modeling results reported herein demonstrate their utility for conformational analysis and prediction of NMR coupling constants for ring systems such as **8a** and **8b**. Further transformations of these products are under investigation, as well as an extension of this synthesis methodology to the preparation of analogous compounds starting with nitrone **3** and cyclic alkenes having rings smaller and larger than six members.

Experimental Section

General Methods. Flash chromatography was carried out using Merck 60 230−400 mesh silica gel.[12] NMR spectra were run in $CDCl_3$ at room temperature at 300 MHz for ^{1}H and either 22.5 or 75.5 MHz for proton decoupled ^{13}C unless otherwise noted. J values are reported in hertz. Proton NMR assignments for compounds **8a** and **8b** were carried out with the aid of low-temperature COSY spectra. IR spectra were recorded neat

(9) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 695−697.

(10) The conformational search was performed using the Monte Carlo protocol, and the structures were minimized using the modified MM2* force field as implemented in Macromodel (version 6.0).

(11) In Macromodel, coupling constants are calculated using a modified Karplus algorithm: Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

unless otherwise noted. High-resolution mass spectra were obtained at the Nebraska Center for Mass Spectrometry at the University of Nebraska−Lincoln. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

[Oxido(phenylmethyl)imino]acetic Acid, Butyl Ester (3). This procedure was adapted from one in the literature.[2c] A mixture of *N*-benzylhydroxylamine[13] (1.00 g, 8.13 mmol), *n*-butyl glyoxylate[14] (1.00 g, 8.47 mmol), $CaCl_2$ (500 mg), and $NaHCO_3$ (1.6 g) in 20 mL of THF was stirred and refluxed under N_2 for 1 h. The reaction mixture was filtered over Celite. Evaporation of the solvent left nitrone **3** (2.15 g) as a yellow solid which was an *E*/*Z* isomer mixture (the *E*/*Z* ratio based upon ^{1}H NMR integration was often about 1.2:1, but it was variable and even changed over time in the NMR tube). Normally, nitrone **3** was not purified before the next step; however, an analytical sample was prepared by recrystallization from benzene/petroleum ether to give white crystals: mp 62−64 °C; IR ($CHCl_3$) 3021 (m), 1720 (m), 1215 (s), 780 (s), 730 (s), 670 (s) cm^{-1}; ^{1}H NMR δ 7.55−7.35 (m, 5H), 7.21 (s, 0.5H, =CH, isomer A), 7.07 (s, 0.5H, =CH, isomer B), 5.71 (s, 1H, CH_2Ar, isomer A), 4.99 (s, 1H, CH_2Ar, isomer B), 4.21 (t, J = 6.6, 1H, OCH_2, isomer A), 4.18 (t, J = 6.6, 1H, OCH_2, isomer B), 1.71−1.30 (m, 4H), 0.95 (t, J = 7.2, 1.5H, CH_3, isomer A), 0.92 (t, J = 7.2, 1.5H, CH_3, isomer B); ^{13}C NMR δ (*E*/*Z* isomer mix) 161.2, 160.3, 133.5, 131.9, 129.7, 129.4, 129.2, 128.9, 128.7, 128.4, 126.9, 125.2, 73.4, 66.4, 65.2, 64.8, 30.4, 18.9, 13.5. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.52; H, 7.44; N, 5.92.

(3α,3aα,7aα)-(±)-Octahydro-2-(phenylmethyl)-1,2-benzisoxazole-3-carboxylic Acid, Butyl Ester (4a). This procedure is similar to one by DeShong et al.[15] Nitrone **3** (256 mg, 1.089 mmol) in 7 mL of cyclohexene was stirred and refluxed under N_2 for 24 h. Evaporation of the solvent left the crude product in quantitative yield as a yellow, viscous oil. Purification by flash chromatography (1:1 ether/petroleum ether) yielded 0.318 g (92%) of ester **4a**. The product was inefficiently recrystallized from pentane to yield white crystals: mp 56.5−57.5 °C; IR 1750 (s) cm^{-1}; ^{1}H NMR δ 7.37 (m, 2H), 7.28 (m, 3H), 4.28 (d, J = 13.1, 1H), 4.17 (dd, J = 8.9, 4.1, 1H, H-7a), 4.14 (d, J = 13.1, 1H), 4.02 (ddd, J = 10.8, 6.5, 6.5, 1H), 3.98 (ddd, J = 10.8, 6.5, 6.5, 1H), 3.28 (d, J = 3.6, 1H, H-3), 2.56 (m, 1H, H-3a), 1.97−1.19 (m, 12H), 0.90 (t, J = 7.5, 3H); ^{13}C NMR δ 171.4, 136.1, 129.5, 128.1, 127.4, 75.2, 72.4, 64.7, 63.3, 45.4, 30.4, 27.6, 26.1, 23.4, 20.4, 18.9, 13.6; HRMS calcd for $C_{19}H_{27}NO_3$ (M^+) 317.1991, found 317.1992.

(3α,3aα,7aα)-(±)-Hexahydro-2-(phenylmethyl)-4*H*-pyrano[3,2-*d*]isoxazole-3-carboxylic Acid, Butyl Ester (4b). Ester **4b** was prepared by a procedure analogous to that employed for the preparation of compound **4a**; dihydropyran was substituted for cyclohexene. Purification by flash chromatography (2:1 ether/petroleum ether) yielded ester **4b** in 65% yield as a pale yellow oil: IR 1740 (s) cm^{-1}; ^{1}H NMR δ 7.42−7.38 (m, 2H), 7.34−7.22 (m, 3H), 5.08 (d, J = 3.3, 1H, H-7a), 4.44 (d, J = 12.5, 1H), 4.15 (d, J = 12.5, 1H), 4.02 (m, 1H), 4.01 (t, J = 6.8, 2H), 3.75 (d, J = 11.1, 1H, H-3), 3.44 (m, 1H), 2.89 (ddd, J = 11.1, 7.1, 3.3, 1H, H-3a), 1.95−1.25 (m, 8H), 0.91 (t, J = 7.2, 3H); ^{13}C NMR δ 170.6, 136.4, 129.2, 128.1, 127.4, 100.0, 66.9, 66.3, 65.0, 64.9, 47.0, 30.3, 21.3, 20.2, 18.8, 13.5; MS *m*/*z* 319 (M^+), 91 (base); HRMS calcd for $C_{18}H_{25}NO_4$ (M^+) 319.1783, found 319.1782.

(3α,3aα,7aα)-(±)-Octahydro-2-(phenylmethyl)-1,2-benzisoxazole-3-methanol (5a). This procedure was adapted from one by Belzecki and Panfil.[4] A mixture of ester **4a** (256 mg, 0.808 mmol) and $LiAlH_4$ (290 mg, 7.642 mmol) was stirred and refluxed in 10 mL of anhydrous diethyl ether under N_2 for 0.5 h. After sequential addition of H_2O (0.3 mL), 10% aqueous NaOH (0.3 mL), and H_2O (0.9 mL), the mixture was filtered over Celite and washed with ether. The filtrate was concentrated in vacuo to provide crude alcohol **5a** as a yellow oil (0.161 g). The product was purified by flash chromatography (diethyl ether) to yield 120 mg (60%) of the desired alcohol as a colorless oil. The analytical sample was prepared by crystallization from a large amount of petroleum ether to yield off-white crystals: mp 78−79.5 °C; IR 3450 (br) cm^{-1}; ^{1}H NMR δ 7.35 (m, 5H), 4.25 (d, J = 13.1, 1H), 4.06 (d, J = 13.1, 1H), 4.03 (dd, J = 9.0, 4.5, 1H, H-7a), 3.44 (dd, J = 11.3, 4.7, 1H), 3.37 (dd, J = 11.3, 4.4, 1H), 2.85 (dt, J = 4.4, 4.0, 1H, H-3), 2.58 (br s, 1H), 2.23 (m, 1H, H-3a), 1.94−1.10 (m, 8H); ^{13}C NMR δ 136.6, 129.2, 127.9, 127.0, 74.9, 72.2, 63.3, 63.0, 43.2, 27.7, 26.3, 23.4, 20.6. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.92; H, 8.85.

(3α,3aα,7aα)-(±)-Hexahydro-2-(phenylmethyl)-4*H*-pyrano[3,2-*d*]isoxazole-3-methanol (5b). Alcohol **5b** was prepared by a procedure analogous to that employed for the preparation of compound **5a**. The product was isolated by flash chromatography (diethyl ether) in 63% yield as a pale yellow solid. Inefficient recrystallization from 2:1 petroleum ether/benzene yielded white crystals (40%): mp 87−88 °C; IR 3460 (br) cm^{-1}; ^{1}H NMR δ 7.42−7.22 (m, 5H), 5.03 (d, J = 3.6, 1H, H-7a), 4.47 (d, J = 12.6, 1H), 4.11 (d, J = 12.6, 1H), 4.03 (dm, J = 12.0, 1H), 3.45 (m, 2H), 3.34 (dd, J = 11.4, 2.7, 1H), 3.20 (ddd, J = 10.8, 2.9, 2.7, 1H, H-3), 2.68 (m, 1H, H-3a), 2.00−1.40 (m, 4H); ^{13}C NMR δ 137.1, 129.1, 128.3, 127.4, 100.5, 65.9, 65.8, 64.9, 60.5, 43.6, 21.5, 20.4. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found C, 67.71; H, 7.76; N, 5.58.

(3α,3aα,7aα)-(±)-Octahydro-2-(phenylmethyl)-1,2-benzisoxazole-3-methanol, 4-Methylbenzenesulfonate (Ester) (6a). 4-(Dimethylamino)pyridine (0.450 g, 3.868 mmol), *p*-toluenesulfonyl chloride (1.406 g, 7.373 mmol), and Et_3N (1.0 mL, 6.519 mmol) were added to a stirring solution of alcohol **5a** (1.518 g, 6.144 mmol) in 11 mL of CH_2Cl_2. Stirring was continued under Ar at room temperature for 20 h, at which time diethyl ether (11 mL) was added. The white precipitate was removed by filtration and washed with ether. The combined filtrates were washed with 10% aqueous $CuSO_4$ (4×), 10% aqueous $NaHCO_3$ (2×), and saturated brine. After drying over Na_2SO_4 and concentration in vacuo, 2.153 g (87%) of the desired tosylate **6a** was isolated as a pale yellow solid. Compound **6a** was recrystallized inefficiently from ether/pentane to yield off-white crystals: mp 92−93 °C; IR 1370 (m), 1180 (m) cm^{-1}; ^{1}H NMR δ 7.69 (d, J = 8.5, 2H), 7.30 (d, J = 8.5, 2H), 7.28 (m, 5H), 4.18 (d, J = 13.2, 1H), 4.02 (d, J = 13.2, 1H), 3.94 (m, 1H, H-7a), 3.88 (dd, J = 9.6, 7.4, 1H), 3.68 (dd, J = 9.6, 5.9, 1H), 2.97 (m, 1H, H-3), 2.45 (s, 3H), 2.09 (m, 1H, H-3a), 1.93−1.20 (m, 8H); ^{13}C NMR δ 144.6, 136.4, 132.5, 129.7, 129.2, 128.1, 127.7, 127.2, 74.3, 70.8, 69.1, 63.3, 43.7, 28.1, 26.0, 23.8, 21.5, 20.5. Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78. Found: C, 65.84; H, 6.96.

(3α,3aα,7aα)−(±)-Hexahydro-2-(phenylmethyl)-4*H*-pyrano[3,2-*d*]isoxazole-3-methanol, 4-Methylbenzenesulfonate (Ester) (6b). Compound **6b** was prepared by a procedure analogous to that employed for the preparation of tosylate **6a**. The product was purified by recrystallization from methanol to yield off-white crystals (53%): mp 99−101 °C; IR 1380 (s), 1195 (s) cm^{-1}; ^{1}H NMR δ 7.73 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7, 2H), 7.42−7.20 (m, 5H), 4.97 (d, J = 3.5, 1H, H-7a), 4.33 (d, J = 12.9, 1H), 4.07 (d, J = 12.9, 1H), 4.02 (dd, J = 10.1, 5.1, 1H), 4.02 (m, 1H), 3.90 (dd, J = 10.1, 6.3, 1H), 3.42 (m, 2H, H-3, H-6), 2.45 (s, 3H), 2.36 (ddd, J = 10.5, 6.9, 3.5, 1H, H-3a), 1.70−1.40 (m, 4H); ^{13}C NMR δ 144.9, 137.1, 132.4, 129.8, 128.9, 128.1, 127.7, 127.2, 100.1, 71.5, 66.1, 64.9, 62.8, 46.2, 21.9, 21.5, 20.3; MS *m*/*e* 403 (M^+), 91 (base); HRMS calcd for $C_{21}H_{25}NO_5S$ (M^+) 403.1453, found 403.1454.

(4α,4aα,8aα)-(±)-Octahydro-2-(phenylmethyl)-2*H*-1,2-benzoxazin-4-ol, 4-Methylbenzenesulfonate (Ester) (8a). A solution of tosylate **6a** (202 mg, 0.504 mmol) in 15 mL of acetone was stirred and refluxed for 24 h. Removal of solvent left 200 mg (99%) of the desired product as a colorless oil that slowly solidified. The analytical sample was prepared by recrystallization from ether/pentane to provide white crystals: mp 88−89 °C. Two conformers (ratio 6:1) of product **8a** were observed in the ^{1}H NMR spectrum at −80 °C: IR 1170 (m), 1355 (s) cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2, −80 °C), major conformer, δ 7.66 (d, J = 8, 2H, ortho SO_2ArH), 7.31−7.23 (m, 7H, meta SO_2ArH and Ph), 4.19 (s, 1H, H-8a), 4.16 (br ddd, J ∼ 2.4, 2.4, 2.4, 1H, H-4), 3.81 (d, J = 14.5, 1H, benzylic H), 3.64 (d, 1H, benzylic H), 2.76 (d, J = 12.1, 1H, H-3), 2.56 (dd, J = 12.1, 1.3, 1H, H-3), 2.37 (s, 3H, CH_3), 1.67 (br d, J = 12.5, 1H), 1.58 (br d, J = 13, 2H), 1.40−1.03 (m, 6H, 4 CH_2); minor conformer, δ 7.81 (d, J =

(13) *N*-Benzylhydroxylamine was purchased from Aldrich as the hydrochloride or prepared from benzaldehyde oxime by a general procedure: House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

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8.3, 2H, ortho SO_2ArH), 7.37 (d, 2H, meta SO_2ArH), 7.31−7.23 (m, 5H, Ph), 4.60 (ddd, J = 10.6, 10.5, 5.3, 1H, H-4), 3.85 (d, J = 14.5, 1H, benzylic H), 3.69 (m, 1H, H-8a), 3.64 (d, 1H, benzylic H), 3.43 (dd, J = 10.7, 5.3, 1H, H-3), 2.68 (dd, J = 10.7, 10.5, 1H, H-3), 2.40 (s, 3H, CH_3), 1.94 (dm, J = 10.5, 1H, H-4a), 1.40−1.03 (m, 8H, 4 CH_2); ^{13}C NMR δ 144.2, 136.3, 133.9, 129.5, 128.4, 127.8, 127.2, 126.7, 78.5 (br), 72.8 (br), 62.1, 54.9 (br), 38.8, 28.8, 24.1, 21.2. Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78. Found: C, 65.74; H, 6.95.

(4α,4aα,8aα)-(±)-Hexahydro-2-(phenylmethyl)-2*H*,5*H*-pyrano[3,2-*e*]-1,2-oxazin-4-ol, 4-Methylbenzenesulfonate (Ester) (8b). Isoxazolidine **6b** (33 mg, 0.082 mmol) and 4 mg of anhydrous K_2CO_3 were stirred in refluxing 2-butanone (2 mL) for 44 h. The mixture was filtered and concentrated to provide 33 mg (100%) of a viscous, colorless oil which was revealed by ^{1}H NMR to be a 1:4.2 mixture (inseparable by TLC) of reactant **6b** and the desired product **8b**, respectively. Two conformers (ratio 2:1) of product **8b** were observed in the ^{1}H NMR spectrum at −80 °C. IR 1180 (s), 1370 (s) cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2, −80 °C) major conformer, δ 7.81 (d, J = 8.1 Hz, 2H, ortho SO_2ArH), 7.36 (d, 2H, meta SO_2ArH), 7.32−7.19 (m, 5H, Ph), 4.68 (d, J = 2.7, 1H, H-8a), 4.58 (ddd, J = 10.5, 10.5, 4.7, 1H, H-4), 3.80 (m, 1H, H-7), 3.44 (dd, J = 11.0, 4.7, 1H, H-3), 3.25 (dd, J = 11.7, 11.7, 1H, H-7), 2.71 (d, J = 11.0, 1H, H-3), 2.10 (s, 3H, CH_3), 1.85−0.60 (m, 5H, H-4a, H-5, and H-6); minor conformer, δ 7.70 (d, J = 8.0, 2H, ortho SO_2ArH), 7.32−7.19 (m, 7H, meta SO_2ArH and Ph), 5.14 (br s, 1H, H-8a), 4.27 (br s, 1H, H-4), 3.90 (m, 1H, H-7), 3.83 (d, J = 13.8, 1H, benzylic H), 3.71 (d, 1H, benzylic H), 3.30 (dd, J = 11.5, 11.5, 1H, H-7), 2.81 (d, J = 12.9, 1H, H-3), 2.73 (d, 1H, H-3), 2.10 (s, 3H, CH_3), 1.75 (m, 1H, H-4a), 1.85−0.60 (m, 4H, H-5 and H-6); ^{13}C NMR δ 144.7, 135.3, 133.4, 129.7, 129.1, 128.0, 127.7, 127.2, 97.4 (br), 76.2 (br), 65.6, 62.4, 54.8 (br), 38.7, 21.8, 21.5; MS m/z 403 (M^+), 91 (base); HRMS calcd for $C_{21}H_{25}NO_5S$ (M^+) 403.1453, found 403.1461.

Acknowledgment. Financial support of the research at Hendrix College by a grant from the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged. The National Science Foundation-Instrumentation Laboratory Improvement Program, Research Corp., and The Roy and Christine Sturgis Charitable and Educational Trust are thanked for generously funding the purchase of an NMR spectrometer at Hendrix College. Dr. Frederick E. Evans (National Center for Toxicological Research) is gratefully acknowledged for running some NMR spectra.

JO971299F