Regiochemical Control by Nonbonded Interactions in an Intramolecular Nitrone Cycloaddition

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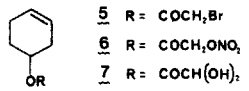
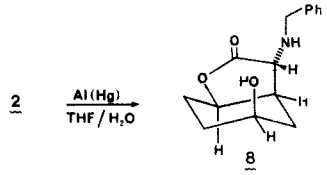
In the course of our work on total syntheses of the antitumor antibiotics actinobolin and bactobolin,[1] we contemplated preparing the key bridged lactone **3** via an intramolecular nitrone–olefin cycloaddition (Scheme I).[2] Recent studies by Inouye[3] and DeShong[4] suggested that starting nitrone **1** would be an equilibrating mixture of *E* and *Z* isomers. However, Dreiding models clearly showed that the more stable *E* isomer cannot achieve the alignment required for intramolecular cycloaddition. The *Z* isomer, on the other hand, can in principle cyclize to either the desired isoxazolidine **2** or the isomeric compound **4**. Models indicated that the transition state leading from **1Z** to **4** has a severe nonbonded interaction between the carbonyl oxygen and a quasi-axial allylic hydrogen at C-5, and therefore, we anticipated that **2** should be the favored cycloadduct. As described below, these predictions have been completely borne out.

Readily available 3-cyclohexen-1-ol[5] was converted in good overall yield to the glyoxylate hydrate **7** via bromo-



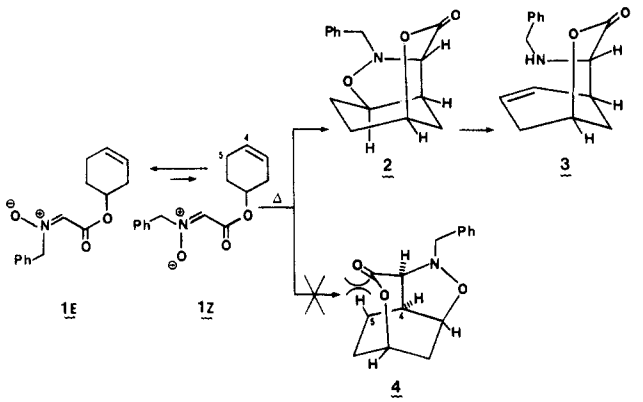
acetate **5** and nitrate ester **6** by using the Emmons–Kornblum procedure.[6] Treatment of **7** with *N*-benzylhydroxylamine afforded nitrones **1** as a 2:1 mixture of *E*:*Z* isomers (96% yield)[3] which could be separated by preparative TLC. However, both pure isomers rapidly equilibrated in solution to give the original 2:1 *E*:*Z* mixture, thus supporting our expectation that nitrone stereochemical interconversion would be a facile process.

Upon heating in chlorobenzene, nitrones **1** cyclized as we predicted to give *only* the desired regioisomeric isoxazolidine **2** (56%). When the N–O bond of adduct **2** was reduced with aluminum amalgam, a rearranged γ-lactone **8** was obtained, rather than the expected δ-lactone. The structure of **8** was established by X-ray crystallographic analysis of the corresponding hydrobromide salt, thus confirming the structure and stereochemistry assigned to adduct **2**.



It should be noted that the conversion of **1Z** to **2** rather than to **4** cannot be easily rationalized on stereoelectronic grounds. The work described here exemplifies how subtle nonbonded interactions can completely control the regiochemical outcome of a 1,3-dipolar cycloaddition, and such effects should be carefully considered in reactions of this type.[2,7,8]

Scheme I



Experimental Section

Preparation of Bromo Ester 5. A solution of 7.1 g (0.072 mol) of 3-cyclohexen-1-ol[5] and 10 mL of pyridine in 125 mL of methylene chloride was cooled to 0 °C in an ice bath. To this solution was added 15.0 g (0.075 mol) of bromoacetyl bromide over a period of 5 min. The mixture was stirred for an additional 10 min, was poured into 125 mL of ice–water, and was extracted with methylene chloride. The organic extract was washed with dilute HCl and water, dried over Na_2SO_4, and evaporated in vacuo. The residue was distilled [bp 69–71 °C (0.06 torr)] to provide 14.9 g (95%) of colorless bromide **5**: IR (film) 2950, 1735, 1285, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.9–2.4 (6 H, m), 3.8 (2 H, s), 5.1 (1 H, m), 5.6 (2 H, m); mass spectrum (CI, CH_4), *m/z* 221, 220 [$M^+ + H$], 219. Anal. Calcd for $C_8H_{11}O_2Br$: C, 43.86; H, 5.06. Found: C, 43.47; H, 5.02.

Preparation of Nitrate Ester 6. To a solution of 14.25 g (0.065 mol) of the bromo ester **5** in 100 mL of reagent grade acetone was added 10.78 (0.072 mol) of sodium iodide, and the mixture was stirred at room temperature for 5 h. The resulting precipitate was filtered and the solid was washed with dichloromethane. Concentration of the filtrate in vacuo afforded a yellow residue which was dissolved in dichloromethane. The solution was washed with 10% $NaHSO_3$ and water, dried over Na_2SO_4, and concentrated in vacuo to yield 17.3 g (100%) of the iodide as a light yellow liquid which was used without further purification: IR (film) 2950, 1735, 1280, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.8–2.4 (6 H, m), 3.7 (2 H, m), 5.1 (1 H, m), 5.6 (2 H, m); mass spectrum, *m/z* (relative intensity) 266 (1), 186 (1), 169 (22), 140 (1), 80 (100).

To a magnetically stirred solution of 4.00 g (0.015 mol) of iodo ester in 60 mL of acetonitrile was added 3.33 g (0.019 mol) of silver nitrate. The mixture was stirred in the dark for 12 h at room temperature. The resulting salts were collected and carefully washed with ether. The combined organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo to afford 2.75 g (98%) of **6** as a colorless liquid which was used without purification: IR (film) 2850, 1750, 1650, 1290, 1210, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.8–2.3 (6 H, m), 4.8 (2 H, s), 5.1 (1 H, m), 5.6 (2 H, m); mass spectrum (CI, CH_4), *m/z* 202 [$M^+ + H$], 201, 200, 155. Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51. Found: C, 47.52; H, 5.47.

Preparation of Glyoxylate 7. To a solution of 3.20 g (0.016 mol) of the nitrate ester **6** in 50 mL of Me_2SO was added 1.30 g (0.016 mol) of sodium acetate. After being stirred vigorously at room temperature for 20 min, the mixture was poured into 125 mL of ice-cold brine and was extracted with ether. The organic

(1) Garigipati, R. S.; Tschaen, D. M. and Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790.
(2) For an excellent review of intramolecular nitrogen cycloadditions, see: Padwa, A., Ed.; *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984; Vol. 2, p 277.
(3) Inouye, Y.; Watanabe, Y.; Takahashi, S.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3763.
(4) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397.
(5) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398.
(6) Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865. Emmons, W. D.; Freeman, J. P. *J. Am. Chem. Soc.* **1955**, *77*, 4415.
(7) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497.
(8) Taken from the Ph.D. Thesis of D. M. Tschaen, The Pennsylvania State University, 1984.

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extracts were washed with saturated sodium bicarbonate and water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography, eluting with ethyl acetate–hexane (1:2) to afford 1.78 g of the hydrated aldehyde which was distilled in a Kugelrohr apparatus [bp 90–95 °C (0.05 torr)] to yield 1.46 g (70%) of **7**: IR (film) (hydrate) 3400, 2950, 1740, 1440, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.8–2.5 (6 H, m), 5.2 (1 H, m), 5.6 (2 H, m), 9.4 (1 H, s); mass spectrum, *m/z* (relative intensity) 154 (1), 125 (1), 81 (100), 80 (88), 79 (36), 77 (11).

Synthesis of Nitrones 1Z and 1E. A mixture of 2.79 g (0.02 mol) of *N*-benzylhydroxylamine and 0.200 g of calcium chloride in 75 mL of ether was cooled to 0 °C.[3] To this mixture was added 3.50 g (0.02 mol) of freshly distilled glyoxylate **7** in 30 mL of ether. After being stirred at 0 °C for 2 h, the mixture was filtered through Na_2SO_4 and concentrated in vacuo to provide a clear oil. This oil was dissolved in 100 mL of benzene and water was azeotroped off for 4 h. Removal of the solvent in vacuo yielded 5.65 g (96%) of a white waxy solid which was a 2:1 mixture of *E* and *Z* nitrone isomers, respectively: IR (film) 2950, 1710, 1550, 1200, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.7 (1 H, m), 1.8 (1 H, m), 2.1 (3 H, m), 2.4 (1 H, m), 4.9 (2 H, s, minor isomer), 5.1 (1 H, m), 5.6 (1 H, m), 5.65 (1 H, m), 5.7 (2 H, s, major isomer), 7.09 (1 H, s, minor isomer), 7.20 (1 H, s, major isomer), 7.35 (2 H, m), 7.43 (2 H, m), 7.53 (1 H, m); mass spectrum, *m/z* (relative intensity) 259 (1), 242 (2), 215 (1), 180 (3), 162 (10), 91 (100), 80 (95); exact mass calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1205.

(±)-(3α,3aβ,5α,7aβ)-Hexahydro-1-(phenylmethyl)-3,5-ethano-7*H*-pyrano[3,4-*c*]isoxazol-7-one (2). A magnetically stirred solution of 0.960 g (3.7 mmol) of the nitrone mixture **1** in 400 mL of dry chlorobenzene was heated at reflux for 16 h. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate–hexane (1:1), to yield 0.115 g of starting nitrone mixture **1** along with 0.534 g (56% based on recovered nitrone) of the adduct **2**: IR (film) 2950, 1735, 1495, 1390, 1230, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.6–2.1 (6 H, m), 3.11 (1 H, m), 3.89 (1 H, d, J = 8.2 Hz), 4.05 (1 H, d, J = 13.7 Hz), 4.18 (1 H, d, J = 13.7 Hz), 4.60 (1 H, m), 4.81 (1 H, m), 7.3–7.5 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 23.6, 25.5, 36.4, 60.1, 66.2, 73.6, 74.6, 127.4, 128.3, 128.8, 136.5, 168.7; mass spectrum, *m/z* (relative intensity) 259 (5), 215 (7), 160 (30), 91 (100); exact mass calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1221.

Cleavage of Isoxazolidine 2. A solution of 0.190 g (0.7 mmol) of isoxazolidine **2** in 35 mL of aqueous THF (THF:H_2O/10:1) was cooled to 0 °C. Small strips of aluminum foil (0.380 g) were sequentially exposed for 15–30 s to 1 M NaOH, distilled water, 0.5% aqueous mercuric chloride, distilled water, and THF and then added to the solution of **2**. After being stirred at 0 °C for 14 h, the mixture was filtered through Celite and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate and washed with 20 mL of water. The organic extract was dried over Na_2SO_4 and evaporated in vacuo. Purification of the residue by column chromatography on 30 g of silica gel, eluting with ethyl acetate, afforded 0.150 g (78%) of γ-lactone **8** as a white crystalline product. A sample which was crystallized from benzene–hexane had mp 83 °C: IR (film) 3300, 2950, 1775, 1650, 1450, 1190, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.6–2.3 (7 H, m), 3.59 (1 H, d, J = 5.8 Hz), 3.80 (1 H, m), 3.90 (1 H, d, J = 13.1 Hz), 3.99 (1 H, d, J = 13.1 Hz), 4.65 (1 H, m), 7.30–7.37 (5 H, m); mass spectrum, *m/z* (relative intensity) 261 (1), 217 (3), 170 (4), 160 (2), 146 (15), 106 (59), 91 (100); exact mass calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1380.

Hydrogen bromide gas was bubbled through a solution of 0.035 g (0.13 mmol) of the amino alcohol **8** in 8 mL of ether for 2 min. The mixture was stirred at room temperature for an additional 5 min during which time a white precipitate formed. Removal of the solvent in vacuo afforded 0.046 g (100%) of the white crystalline hydrobromide which was recrystallized from acetone–hexane: mp 142–143 °C; IR (KBr) 3400, 3150, 2950, 1780, 1570, 1440, 1180, 1000 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 200 MHz) δ 1.5–1.8 (6 H, m), 2.8 (1 H, m), 3.3 (3 H, bs), 3.8 (1 H, m), 4.4 (3 H, m), 4.8 (1 H, m), 7.4–77.5 (5 H, m); mass spectrum, *m/z* (relative intensity) 261 (1), 217 (4), 170 (5), 146 (21), 106 (88), 91 (100), 82 (12).

X-ray Crystal Structure Determination of the HBr Salt of 8. Unit cell dimensions determined from 25 reflections at moderate 2θ angles indicated a monoclinic cell of dimensions: a = 9.298 (2) Å; b = 15.613 (3) Å; c = 11.095 (5) Å; B = 96.83 (4)°, and v = 1599 (1) Å^3. The observed volume was consistent with that expected for Z = 4, using a calculated density of 1.496 g cm^{-3}. Observed systematic absence of $h\phi l$ for $l = 2n + 1$ and $\phi k\phi$ for $k = 2n + 1$ gave the space group $P2_1/c$. Applications of the zero-moment tests of Howells, Phillips, and Rogers indicated a centric cell.[9]

Data was collected using molybdenum K_α radiation [λ 0.71073 Å]. A total of 2236 reflections were collected to a 2θ of 44.32°; scan width: (0.60 + 0.347 tan θ); scan range: (1.0–5.0° min^{-1}); of these 1764 were unique nonzero reflections. Three standard reflections collected every hour were used to rescale the data to account for changes in orientation, temperature, etc., during data collection (drift correction 0.956–1.048). φ scans indicated absorption was not severe (N = 27.42 cm^{-1}) and no absorption corrections were applied. A total of 1396 observed reflections with intensities $I \gtrsim 2\sigma$ were used for refinement of 256 variables. These data were corrected for Lorentz and polarization factors and used in the refinement of the structure.

Inclusion of the hydrogens at fixed isotropic factors (B = 5.0 Å^2) and refinement of positional parameters along the full matrix anisotropic refinement of the non-hydrogen atoms using unit weights converged to R_1 = 0.037 and R_2 = 0.040 with an esd = 1.744 with a maximum shift of δ 0.17. A final difference electron density map showed no residual electron density greater than 0.15 e Å^{-3}. Final positional and thermal parameters are available as supplementary material.

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Registry No. **1E**, 102285-01-8; **1Z**, 102284-98-0; **2**, 102284-99-1; **5**, 102285-02-9; **6**, 102285-03-0; **7**, 102285-04-1; **8**, 102285-05-2; **8**·HBr, 102285-00-7; 3-cyclohexen-1-ol, 822-66-2; bromoacetyl bromide, 598-21-0; 3-cyclohexenyl iodoacetate, 102306-08-1; *N*-benzylhydroxylamine, 622-30-0.

Supplementary Material Available: Tables of X-ray crystallographic data on the HBr salt of **8** (5 pages). Ordering information is given on any current masthead page.

(9) Howells, E. R.; Phillips, D. C.; Rogers, D. *Acta Crystallogr.* **1950**, *3*, 210.

A Facile Intramolecular Michael Addition Reaction[1]

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The *p*-methoxybenzyl and 3,4-dimethoxybenzyl groups are useful protecting groups for alcohols because they can be removed simply, under neutral conditions at room temperature, by oxidation with a mild oxidizing reagent, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[2] It was the method of choice for the protection of the 4-hydroxyl group in (4-hydroxy-2,2,6,6-tetramethylcyclohexylidene)acetic acid ((±)-**1**). The treatment of (±)-**1** with 2.2 equiv each of sodium hydride and 3,4-dimethoxybenzyl chloride at ambient temperature overnight resulted in the formation of 3,4-dimethoxybenzyl [4-((3,4-dimethoxylbenzyl)oxy)-

(1) The support of this work by a grant from the National Science Foundation is gratefully acknowledged.

(2) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 885.

0022-3263/86/1951-2605$01.50/0