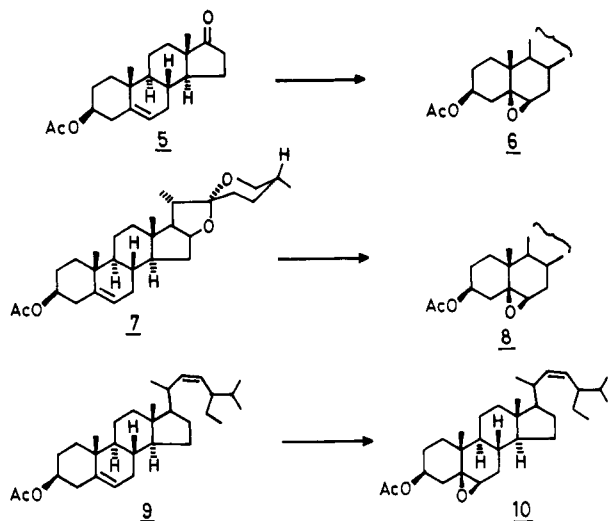


acted in preference to the disubstituted double bond in the side chain.



This present methodology, therefore, appears to be novel and has greater synthetic utility than the procedures available thus far, since the easily available permanganate ion has been utilized to obtain some not so easily accessible 5 $\beta$ ,6 $\beta$ -epoxides of  $\Delta^5$ -unsaturated steroids in high yields under very mild reaction conditions. The study of the mechanism of this reaction and the origin of its high stereoselectivity are presently under investigation.

### Experimental Section

<sup>1</sup>H NMR spectra were recorded at 90 MHz. TLC was performed on 0.25-mm E. Merck precoated silica gel plates (60F-254). Silica gel (230-400 mesh) supplied by Merck was used for flash chromatography. Melting points reported are uncorrected.

All the steroids used in this study except 3d were commercially available samples from Sigma, Schering AG, and Aldrich Chemical Co. Epicholesterol was prepared according to the reported procedure.<sup>20</sup> Esterification of the 3-OH group in all cases was conducted by standard procedures.<sup>21</sup>

**Representative Procedure: 3 $\beta$ -Acetoxy-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -cholestane (4a).** A mixture of KMnO<sub>4</sub> (4 g) and CuSO<sub>4</sub>·5H<sub>2</sub>O (2 g) was ground to a fine powder in a mortar and pestle. Water (200  $\mu$ L) was added, and the slightly wet mixture was transferred to the reaction flask. To a stirred suspension of this mixture in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added cholesteryl acetate (3a) (0.857 g, 2 mmol) followed by *tert*-butyl alcohol (1 mL). Within a few minutes the reaction mixture became warm and started refluxing for a while and then cooled down. After stirring for 2 h, the completion of the reaction being ascertained by TLC, the reaction mixture was filtered through a pad of Celite and washed thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. After evaporating the solvent, the crude product was recrystallized from methanol to give the  $\beta$ -epoxide 4a (0.820 g, 92%), mp 110-112 °C (lit.<sup>22</sup> mp 111-112 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.64 (s, 3 H), 0.87 (d, 6 H), 0.88 (d, 3 H, *J* = 6.4 Hz), 1.0 (s, 3 H), 2.02 (s, 3 H), 3.07 (d, 1 H, *J* = 2.2 Hz), 4.80 (m, 1 H). The reaction can easily be carried out on a 10-mmol (4.29-g) scale.

**3 $\beta$ -(Benzoyloxy)-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -cholestane (4b):** yield 90%; mp 172-173 °C (lit.<sup>23</sup> mp 173-174 °C).

**3 $\beta$ -(Hexanoyloxy)-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -cholestane (4c):** yield 91%; mp 74 °C (lit.<sup>3</sup> mp 74 °C).

**3 $\alpha$ -(Benzoyloxy)-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -cholestane (4d):** yield 94%; mp 131-132 °C (lit.<sup>13</sup> mp 132 °C).

**3 $\beta$ ,19-Diacetoxy-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -cholestane (4e):** yield 92%; obtained as an oil (lit.<sup>24</sup>).

**3 $\beta$ -Acetoxy-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -androstan-17-one (6):** yield 90%, mp 188-189 °C (lit.<sup>3</sup> mp 189-190 °C).

**(25*R*)-3 $\beta$ -Acetoxy-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -spirostan (*O*-acetyldiosgenin 5 $\beta$ ,6 $\beta$ -epoxide) (8):** yield 95%; mp 187-190 °C (lit.<sup>19</sup> mp 188-192 °C).

**3 $\beta$ -Acetoxy-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -stigmaster-22-ene (10):** yield 70%; mp 140 °C (lit.<sup>9</sup> mp 139-140 °C).

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**Registry No.** 3a, 604-35-3; 3b, 604-32-0; 3c, 1062-96-0; 3d, 42921-42-6; 3e, 21072-68-4; 4a, 1256-31-1; 4b, 6557-19-3; 4c, 123846-50-4; 4d, 107419-88-5; 4e, 34013-78-0; 5, 853-23-6; 6, 6585-68-8; 7, 1061-54-7; 8, 66965-01-3; 9, 4651-48-3; 10, 4092-62-0; KMnO<sub>4</sub>, 7722-64-7.

(24) Morand, P.; Kaufman, M. *Can. J. Chem.* 1971, 49, 3185.

### 2,3-Pyridine Annulation. The Enantioselective Synthesis of an Aldose Reductase Inhibitor

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Since their discovery in 1975, the spiro hydantoin aldose reductase inhibitors have been the focus of interest as possible pharmaceutical agents for the prevention and treatment of diabetic complications.<sup>1</sup> A recent report by Sarges and co-workers<sup>2</sup> discussed a new series of hydantoins derived from the 8-aza-4-chromanones, with the most potent example having 6-chloro-2-methyl substitution. When the corresponding racemic hydantoin was resolved, the (+)-enantiomer (2'*R*,4'*S*)-2 was shown to be the most active of the pair. As part of an overall effort to investigate the medicinal properties of 2, our laboratory sought an efficient method for the synthesis of this novel spiro hydantoin.

As originally reported, the synthetic approach to 2 relied on conversion of racemic azachromanone *rac*-1 to racemic hydantoin *rac*-2 followed by traditional resolution (Scheme I).<sup>2</sup> However, the authors also showed that an enantiomerically pure azachromanone could be converted directly into 2 without loss of optical purity. With the aim of avoiding a wasteful resolution, a program to develop an efficient synthesis of the optically active azachromanone was begun. The retrosynthetic strategy for the synthesis is shown in Scheme II, where, by disconnecting bonds *a* and *b*, the molecule is reduced to a functionalized pyridine and an optically pure 3-hydroxybutyrate synthon. It was anticipated that bond *a* would be formed through a 3-metallopyridine, while the formation of bond *b* was envisioned as the alkoxide displacement of a halogen from the 2-position of a suitable pyridine.

Initial investigations into this idea were conducted using the known 2-chloro-3-lithiopyridine<sup>3</sup> 3 as a model. Con-

(20) Houminer, Y. *J. Org. Chem.* 1975, 40, 1361.

(21) (a) Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* 1969, 8, 981. (b) Mueller, J.; Herz, J. E. *Steroids* 1979, 34, 793.

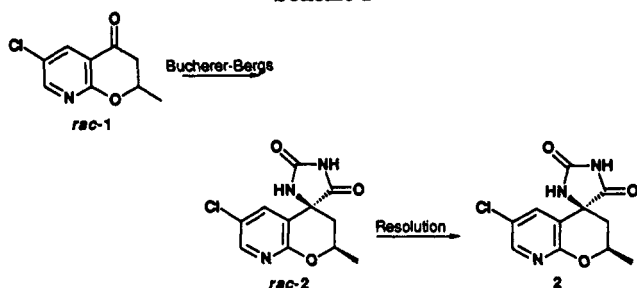
(22) Chakravorty, P. N.; Levin, R. *J. Am. Chem. Soc.* 1942, 64, 2317.

(23) Baxter, R. A.; Spring, F. S. *J. Chem. Soc.* 1943, 613.

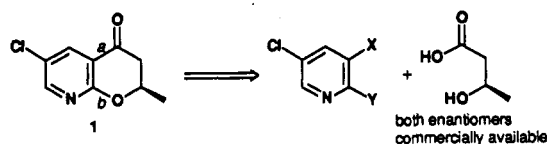
(1) Sarges, R.; Peterson, M. *J. Metabolism* 1986, 35 (Suppl. 1), 104.  
(2) Sarges, R.; Goldstein, S. W.; Welch, W. M.; Swindell, A. C.; Siegel, T. W.; Beyer, T. A. *J. Med. Chem.* 1990, 33, 1859.

(3) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* 1980, 21, 4137.

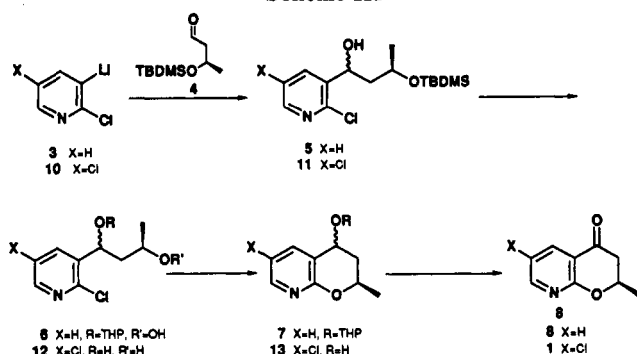
Scheme I



Scheme II



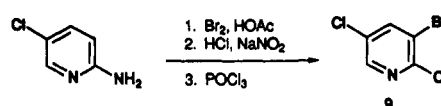
Scheme III



struction of the pyranone ring began by trapping of 3 with the known aldehyde 4 in THF at  $-78\text{ }^{\circ}\text{C}$  (54% yield).<sup>4</sup> The resulting secondary alcohols (1:1 diastereomeric mixture) were then converted to optically active azachromanone 8 by (1) protection of the hydroxyl as its tetrahydropyranyl (THP) ether (dihydropyran, pyridinium *p*-toluenesulfonate, 87%), (2) removal of the *tert*-butyldimethylsilyl (TBDMS) group by treatment with  $\text{Bu}_4\text{NF}$  (TBAF) in THF at room temperature (79% yield), (3) intramolecular cyclization ( $\text{NaH}$  in THF at reflux, 60% yield) to the mixture of protected chromanols 7, and (4) THP deprotection with pyridinium *p*-toluenesulfonate and oxidation by pyridinium chlorochromate (PCC) (Scheme III).<sup>5</sup>

Having demonstrated the feasibility of the desired 2,3-pyridine annulation on the 5-deschloro model, our attention turned to the real system. However, in contrast to the model study which employed direct metalation,<sup>6</sup> lithium-halogen exchange was utilized to provide the 2,5-di-

Scheme IV



chloro-3-lithiopyridine necessary for construction of the target molecule 1. 3-Bromo-2,5-dichloropyridine 9 was required for this purpose and was synthesized by a bromination-diazotization sequence using 2-amino-5-chloropyridine as starting material (Scheme IV).

When 9 was subjected to standard transmetalation conditions using isopropyl ether (IPE) as solvent,<sup>7</sup> 2,5-dichloro-3-lithiopyridine 10 was obtained. Trapping of this intermediate at  $-78\text{ }^{\circ}\text{C}$  with aldehyde 4 afforded the expected secondary alcohols 11 in 72% yield (1:1 mixture of diastereomers). Deprotection with TBAF (62%) followed by cyclization with potassium *tert*-butoxide in 2-methyl-2-propanol at reflux provided the diastereomeric bicyclic azachromanols 13 in 78% yield.

Interestingly, the diastereomeric alcohols 12 exhibited markedly different rates in the cyclization reaction. The 4*S*,2*R* alcohol was completely cyclized in 15 min by potassium *tert*-butoxide in refluxing 2-methyl-2-propanol while the 4*R*,2*R* isomer required 3.5 h for the same level of conversion.<sup>8</sup> This rate effect may be due to the ability of the faster reacting 4*S*,2*R* isomer to adopt a pseudochair transition state in which the methyl group and the benzylic oxygen are both equatorial. The results are also consistent with a computational analysis. Transition states computed using semiempirical (AM1)<sup>9</sup> MO calculations predict unfavorable interactions between the benzylic oxygen and the 6-chloro substituent in the 4*R*,2*R* isomer.

PCC oxidation ( $\text{CH}_2\text{Cl}_2$ , 78% yield) completed the synthesis of the optically active azachromanone 1. Conversion of 1 to 2 was accomplished by using the modified Bucherer-Bergs conditions reported previously by Sarges et al.<sup>2</sup> (33% unoptimized yield).

A novel method for the 2,3-annulation of pyridines has been demonstrated in two systems. Application of the method to 9 provided a useful enantioselective synthesis of a precursor to the potent aldose reductase inhibitor 2. This route allows access to other 2,3-disubstituted pyridines.

## Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Unless otherwise stated, NMR spectra were recorded on a Bruker WM-250 and referenced to residual proto-solvent peaks. IR spectra were obtained as  $\text{CHCl}_3$  solutions unless otherwise noted. Low-resolution mass spectra were run on a Finnegan 4510 GC/MS single quadrupole and high-resolution mass spectra were run on a VG-70/250S. Microanalyses were performed by the Analytical Department of Pfizer Central Research. Unless otherwise stated,

(4) Hungerbuehler, E.; Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* 1981, 64, 1467.

(5) Several attempts to streamline the cyclization process were unsuccessful. Neither the diol nor the keto alcohol showed a willingness to cyclize. A conceptually related approach to 2,3-pyranopyridines has been published: Bargar, T. M.; Dulworth, J. K.; Kenny, M. T.; Massad, R.; Daniel, J. K.; Wilson, T. *J. Med. Chem.* 1986, 29, 1590.

(6) The application of the direct deprotonation approach to commercially available 2,5-dichloropyridine was briefly investigated. Unfortunately, when 2,5-dichloropyridine was exposed to 1 equiv of LDA followed by trapping with trimethylsilyl chloride, a single compound was isolated in high yield but subsequently identified as the undesired 2,5-dichloro-4-(trimethylsilyl)pyridine. Direct lithiation of halopyridines has been found<sup>3</sup> to be a selective and predictable reaction for pyridines which contain only one halogen. 2-Chloropyridine lithiates in the 3-position, while 3-chloropyridine is known to lithiate specifically in the 4-position. However, with both 2- and 3-chloro groups present in the same molecule, it was not clear which directing effect would dominate.

(7) The use of either this solvent or diethyl ether is critical to the success of the reaction. If, instead, THF is used, one obtains a nonregioselective trapping by the aldehyde, resulting in a mixture of both the 3- and 4-pyridyl derivatives. A similar scrambling of a lithiated pyridine has been reported. See: Mallet, M.; Queguiner, G. *Tetrahedron* 1979, 35, 1625. Lithiated benzenes have also exhibited this sort of behavior: Bridges, A. J.; Patt, W. C.; Stickney, T. M. *J. Org. Chem.* 1990, 55, 773.

(8) The two diastereomers were separated by column chromatography. The less polar and more slowly reacting diastereomer, when cyclized, provided a single chromanol. An NOE NMR experiment on this chromanol indicated a *trans* relationship between the hydroxyl and the methyl group. Based on this reasoning the stereochemistry was assigned as 4*R*,2*R*. See the experimental section for details of the separation and NOE experiment.

(9) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* 1985, 107, 3902. AM1 calculations were performed using the MOPAC program, Version 6.0, on a Cray Y-MP2E.

all reagents and solvents were obtained commercially and used without purification. Silica gel (70–230 mesh) was obtained from Baker and TLC plates (Kieselgel 60 F<sub>254</sub>) from EM Science. Isopropyl ether (IPE) was dried over 4A molecular sieves.

**3,4-Dihydro-4-hydroxy-2(R)-methyl-2H-pyrano[2,3-b]pyridine (8).** A solution of 7 (120 mg, 0.48 mmol) and PPTS (24 mg, 0.1 mmol) in 8 mL of MeOH was stirred at rt for 5 days. The resulting solution was concentrated on the rotary evaporator to an oil (0.120 g) which was chromatographed on silica gel (1:1 Et<sub>2</sub>O/hexanes) yielding the expected chromanol (diastereomeric mixture, 30 mg, 38%). A mixture of chromanol (30 mg, 0.182 mmol), PCC (156 mg, 0.726 mmol), Celite (314 mg), and CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) was stirred at rt for 4 h. The resulting suspension was filtered through Celite and concentrated to a brown solid. Column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) provided the desired chromanone (10 mg, 34%, 13% for the two steps) as a white solid, mp 122–124 °C: [ $\alpha$ ]<sub>D</sub> = +54.3° (c = 0.35, MeOH); *R*<sub>f</sub> 0.63 (Et<sub>2</sub>O); IR (KBr) 3365, 2920, 1700, 1588, 1460, 959, 733, 580 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.55 (d, 3 H, *J* = 7 Hz), 2.70 (m, 2 H), 4.60 (m, 1 H), 7.01 (dd, 1 H, *J* = 5 and 8 Hz), 8.17 (dd, 1 H, *J* = 2 and 8 Hz), 8.40 (dd, 1 H, *J* = 2 and 5 Hz); HRMS calcd for C<sub>9</sub>H<sub>9</sub>NO 163.0633, found 163.0635.

**3-Bromo-5-chloropyridin-2-one.** A solution of 2-amino-3-bromo-5-chloropyridine (100 g, 0.482 mol) in water (815 mL) and concentrated HCl (130 mL) was stirred at 0 °C as a solution of sodium nitrite (33.26 g, 0.482 mol) in water (272 mL) was added. The resulting suspension was allowed to warm to rt and stirred for 18 h. The solids were filtered, washed with CCl<sub>4</sub> (2 × 50 mL), and dried in a vacuum oven (40 °C) to yield 75.1 g (75%) of yellow solid, mp 170–173 °C: IR (Nujol) 3111, 3041, 2947, 2919, 1696, 1585, 1462, 1377, 1234, 839, 726, 539, 523 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.72 (d, 1 H, *J* = 2.2 Hz), 8.08 (d, 1 H, *J* = 2.2 Hz), 12.41 (br s, 1 H); HRMS calcd for C<sub>5</sub>H<sub>3</sub>BrClO 206.9086, found 206.9093.

**3-Bromo-2,5-dichloropyridine (9).** A solution of 3-bromo-5-chloropyridin-2-one (84.3 g, 0.404 mol) in DMF (100 mL) was stirred at rt as POCl<sub>3</sub> (56.5 mL, 0.61 mol) was added via dropping funnel over 3 h. The resulting black solution was then heated to 70 °C and allowed to stir for 3 days. Upon cooling to rt, the solution was poured into 1 L of ice/water and filtered. The solid was dried in a vacuum oven to provide 81.8 g (89%) of 9 as an off-white solid, mp 39–41 °C: IR 2989, 1547, 1400, 1366, 1027, 894, cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.0 (d, 1 H, *J* = 2.2 Hz), 8.35 (d, 1 H, *J* = 2.2 Hz); HRMS calcd for C<sub>5</sub>H<sub>2</sub>BrCl<sub>2</sub> 224.8748, found 224.8749.

**3-[3(R)-(tert-Butyldimethylsiloxy)-1-hydroxybutyl]-2,5-dichloropyridine (11).** A cooled (-70 °C) solution of *n*-BuLi (129.3 mL of 1.18 M hexanes solution, 0.153 mol) in isopropyl ether (IPE) was stirred as a solution of 3-bromo-2,5-dichloropyridine (36.45 g, 0.161 mol) in IPE (225 mL) was added over 30 min. The resulting white suspension was treated with a solution of 3(R)-(tert-butyldimethylsiloxy)butyraldehyde (34.1 g, 0.169 mol) in IPE (106 mL) and allowed to stir for an additional 30 min at -70 °C followed by warming to rt. After the addition of 480 mL of water, the biphasic mixture was separated and the organic layer was extracted with IPE (2 × 200 mL). The combined organic layers were washed once with water, heated with G-60 DARCO, filtered through Celite, and concentrated on the rotary evaporator. The resulting hazy yellow liquid was heated at 80 °C under high vacuum overnight to yield the desired product (mixture of diastereomers) as an amber oil (40.5 g, 72%): *R*<sub>f</sub> 0.36 (25% Et<sub>2</sub>O in hexanes); IR 3440, 2952, 2854, 1549, 1414, 1378, 1256, 1118, 1062, 836, 775 cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>)  $\delta$  0.1 (s, 6 H), 0.82 (s, 9 H), 1.18 (m, 3 H), 1.72 (m, 2 H), 4.16 (m, 1 H), 4.42 (m, 1 H), 5.10 (m, 1 H), 7.92 (d, 1 H, *J* = 2.6 Hz), 8.13 (d, 1 H, *J* = 2.6 Hz).

**2,5-Dichloro-3-[1,3(R)-dihydroxy-1-butyl]pyridine (12).** A cooled (5 °C) THF (161.5 mL) solution of 10 (40.38 g, 0.115 mol) was treated with 115.3 mL of a 0.1 M solution of tetrabutylammonium fluoride in THF. Following warming to room temperature and stirring for 2.5 h, the clear dark solution was concentrated in vacuo. After the resulting oil was dissolved in water and extracted with Et<sub>2</sub>O (2 × 150 mL), the combined organic extracts were washed once with water, concentrated to an oil, and chromatographed on silica gel (10% Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>) to provide the product as a semisolid (16.8 g, 62%, mixture of diastereomers):

*R*<sub>f</sub> 0.35 and 0.22 (25% Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>); IR (CHCl<sub>3</sub>) 3426, 2965, 1551, 1416, 1378, 1256, 1228, 1118, 903, 739, 521 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.30 (m, 6 H), 1.53 (m, 2 H), 1.96 (m, 2 H), 2.42 (m, 1 H), 2.73 (m, 1 H), 4.10 (m, 1 H), 4.28 (m, 1 H), 4.30 (s, 1 H), 4.63 (d, 1 H, *J* = 4.5 Hz), 5.18 (m, 1 H), 5.31 (m, 1 H), 8.02 (d, 1 H, *J* = 2.6 Hz), 8.24 (m, 1 H); HRMS calcd for C<sub>9</sub>H<sub>12</sub>Cl<sub>2</sub>NO<sub>2</sub> 236.0243, found 236.0243. The diastereomers could be separated by column chromatography, 230–400-mesh silica gel, 9:1 CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O.

**6-Chloro-3,4-dihydro-4-hydroxy-2(R)-methyl-2H-pyrano[2,3-b]pyridine (13).** A mixture of 11 (16.4 g, 0.069 mol) and *t*-BuOH (115 mL) was stirred at rt as 23.39 g (0.208 mol) of potassium *tert*-butoxide was added. After heating at reflux for 3 h, the reaction was concentrated, diluted with water (150 mL) and extracted with IPE (3 × 150 mL). The combined extracts were washed with water, dried over MgSO<sub>4</sub>, and concentrated to a clear oil which was chromatographed on silica gel (CH<sub>2</sub>Cl<sub>2</sub> as eluent) to yield 10.8 g (78%) of the desired product as a mixture of diastereomers: *R*<sub>f</sub> 0.39 (25% Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>); IR (CHCl<sub>3</sub>) 3261, 2974, 1592, 1572, 1448, 1402, 1276 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.47 (d, 3 H, *J* = 6.3 Hz), 1.49 (d, 3 H, *J* = 6.3 Hz), 1.78 (m, 2 H), 2.08 (m, 2 H), 3.02 (d, 1 H, *J* = 4.5 Hz), 3.15 (d, 1 H, *J* = 7.7 Hz), 4.39 (m, 1 H), 4.58 (m, 1 H), 4.80 (m, 1 H), 4.93 (m, 1 H), 7.64 (d, 1 H, *J* = 2.6 Hz), 7.83 (d, 1 H, *J* = 2.6 Hz), 8.00 (d, 1 H, *J* = 2.6 Hz), 8.08 (d, 1 H, *J* = 2.6 Hz); HRMS calcd for C<sub>9</sub>H<sub>11</sub>ClNO<sub>2</sub> 199.0398, found 199.0404. NOE NMR experiment: The diastereomerically pure chromanols were obtained by cyclization of the chromatographically obtained pure diols from the mixture of 11. The NOE experiment involved irradiation and observation of the benzylic proton and the proton on the carbon bearing the methyl group. In the case of the chromanol derived from the slower reacting less polar diol, the two protons did not cross-polarize one another, whereas in the other diastereomer the two protons did cross-polarize one another.

**6-Chloro-3,4-dihydro-2(R)-methyl-4-oxo-2H-pyrano[2,3-b]pyridine (1).** A suspension of 13 (10.56 g, 0.0529 mol), Celite (14.25 g), and PCC (28.51 g, 0.132 mol) in CH<sub>2</sub>Cl<sub>2</sub> (106 mL) was stirred for 2 h at rt. The resulting reaction mixture was filtered through a pad of silica gel (100 g) and concentrated on the rotary evaporator. The crude white solid was recrystallized from IPE to yield 8.15 g (78%) of the pure azachromanone >92% ee,<sup>10</sup> mp 85–87 °C: [ $\alpha$ ]<sub>D</sub> = +73.8° (c = 1.0, MeOH), *R*<sub>f</sub> 0.28 (50% Et<sub>2</sub>O in hexanes); IR 3029, 1708, 1587, 1444, 1307, 1218, 1184, 1021, 950, 860, 779, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.55 (d, 3 H, *J* = 7.0 Hz), 2.67 (m, 2 H), 4.67 (m, 1 H), 8.08 (d, 1 H, *J* = 2.6 Hz), 8.32 (d, 1 H, *J* = 2.6 Hz); mass spec 197 (M<sup>+</sup>). Anal. Calcd for C<sub>9</sub>H<sub>8</sub>ClNO<sub>2</sub>: C, 54.70; H, 4.08. Found: C, 54.74; H, 4.13.

**(2R,4'S)-6'-Chloro-2',3'-dihydro-2'-methylspiro[imidazolidine-4,4'(4'H)-pyrano[2,3-b]pyridine]-2,5-dione (2).** (Caution: This reaction should only be conducted in an efficient fume hood behind a safety shield.) A mixture of 1.49 g (0.00755 mol) of 1, 0.98 g (0.0151 mol) of KCN, 5.1 g (0.0531 mol) of ammonium carbonate, and 0.943 g (0.00889) of sodium bisulfite was finely crushed with mortar and pestle and added to 15 mL of formamide. The reaction was conducted and worked up according to the corresponding racemic reaction in ref 2. The resulting solids (813 mg; 40%) were collected by filtration and air dried. Recrystallization from CHCl<sub>3</sub>-MeOH-petroleum ether gave 677 mg (33.5%) of 1 as a white solid, mp >250 °C. HPLC analysis of this material on Cyclobond I (acetylated cyclodextrin, Astec) using 2.5% MeOH, 0.2% Et<sub>3</sub>N, and 0.2% HOAc in H<sub>2</sub>O as eluent showed only one peak for (+)-2, with no enantiomer or diastereomer detectable: [ $\alpha$ ]<sub>D</sub> = +217° (c = 1, MeOH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  1.35 (d, 3 H), 1.8 (t, 1 H), 2.35 (d, 1 H), 4.9 (m, 1 H), 7.75 (d, 1 H), 8.15 (d, 1 H), 8.35 (s, 1 H), 11.1 (bs, 1 H). Anal. Calcd for C<sub>11</sub>H<sub>10</sub>ClN<sub>3</sub>O<sub>3</sub>: C, 49.36; H, 3.76; N, 15.70. Found: C, 49.21; H, 3.63; N, 15.47.

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(10) Enantiomeric excess was determined by an NMR experiment using (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. For a description of this technique see: Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* 1977, 42, 384.

technical assistance, Dr. E. B. Whipple for NOE NMR experiments, and Dr. J. F. Blake for computational analysis.

**Registry No.** 1, 138126-72-4; 2, 126642-39-5; 7 (isomer 1), 138785-49-6; 7 (isomer 2), 138875-10-2; 8, 138785-50-9; 8 (reduced alcohol, isomer 1), 138785-56-5; 8 (reduced alcohol, isomer 2), 138875-09-9; 9, 138006-41-4; 10, 138785-51-0; 11 (isomer 1), 138785-52-1; 11 (isomer 2), 138785-54-3; 12 (isomer 1), 138785-53-2; 12 (isomer 2), 138785-55-4; 13 (isomer 1), 138875-07-7; 13 (isomer 2), 138875-08-8; 3-bromo-5-chloropyridin-2-one, 137628-16-1; 2-amino-3-bromo-5-chloropyridine, 26163-03-1.

**Supplementary Material Available:** NMR data for compounds 9, 11, 12, 13, and 3-bromo-5-chloropyridin-2-one (6 pages). Ordering information given on any current masthead page.

### Selectivity in [2 + 3] and [4 + 3] Annulations. Cope Rearrangement of (Silyloxy)divinylcyclopropane Systems Leading to Functionalized Bicyclo[3.2.*n*]alkenyl Derivatives

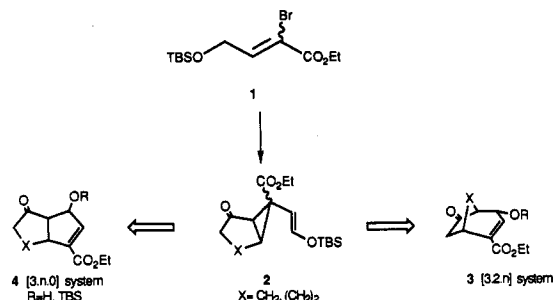
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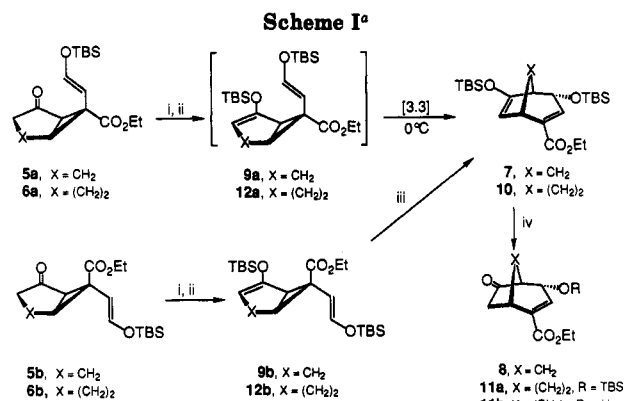
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Recently, we reported a mild, low-temperature procedure for the vinylcyclopropane-cyclopentene rearrangement (i.e. 2 → 4, Figure 1) that occurs at -78 °C in those systems where the vinyl moiety is terminated with a silyl enol ether.<sup>1</sup> With the availability of such mild conditions, the utility of the [2 + 3] cyclopentene annulation, previously possible only through thermolytic rearrangements,<sup>2-5</sup> can now be expressed in the synthesis of systems containing sensitive functionalities. The cyclopropanation of enones using ester dienolate anions rather than carbenoid species has been reported in 1986 for the nor-silyloxy derivatives of 1<sup>4</sup> and extended to the (silyloxy)bromocrotonate 1 in 1990.<sup>1</sup> A report was also published on the potential selectivity between the cyclopentene mode of the rearrangement (2 → 4) and the divinylcyclopropane-cycloheptadiene (Cope) rearrangement (2 → 3).<sup>3</sup> In this paper we report on the selectivity of silyl enol ether-terminated vinylcyclopropanes of type 2 to undergo either a cyclopentene rearrangement or, upon conversion to their enol ethers or enolate anions, the divinylcyclopropane-cycloheptadiene rearrangement.

The lithium dienolate of 1 was generated at -100 °C as previously reported<sup>1</sup> and allowed to add to cyclopentenone or cyclohexenone, providing cyclopropanes 5a,b and 6a,b, respectively. The stereochemistry of enol ethers was shown to be *E* in all cases (as evidenced by the value of coupling constants, *J* = 11.9–12.1 Hz). The cyclopropanes were obtained as mixtures of exo and endo isomers (denoting



**Figure 1.** Cyclopentene vs cycloheptadiene (Cope) rearrangement.



<sup>a</sup> (i) LDA, THF, -78 °C; (ii) TBSCl, HMPA, -78 °C → 0 °C (or rt); (iii) 150 °C, C<sub>6</sub>H<sub>6</sub>, sealed tube; (iv) 1 M HCl, THF, rt.

the position of vinyl group) in the ratio of 57/43 for 5 and 50/50 for 6.



From other studies it is now known that the lithium dienolate anions derived from esters of  $\alpha$ -bromocrotonates are mixtures of *E/Z* species (with respect to the enolate anion double bond).<sup>6</sup> This indicates a nonstereospecific addition to the enone, in contrast to the well-known stereospecificity observed for the Michael addition of ester enolates to enones.<sup>7</sup>

Treatment of the endo isomer 5a<sup>2,8</sup> with LDA at -78 °C resulted in the formation of the lithium enolate anion, which underwent the Cope rearrangement<sup>9,10</sup> at room temperature to give a chromatographically inseparable

(6) (a) Barbieri, G. Ph.D. Dissertation, Virginia Tech, 1990. (b) Hudlicky, T.; Barbieri, G., manuscript in preparation. (c) Hudlicky, T.; Fleming, A.; Lovelace, T. C. *Tetrahedron* 1989, 45, 3021.

(7) Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; Vol. 19, 227. *J. Org. Chem.* 1990, 55, 157.

(8) The yields of 5 and 6 could be improved significantly by careful control of the temperature and the addition rate of the enone solution in THF to the solution of lithium dienolate derived from 1.

(9) For reviews of the Cope rearrangement, see: (a) Mil'vitskaya, E. M.; Tarakanova, A. V.; Plate, A. F. *Russ. Chem. Rev.* 1976, 45, 469. (b) Rhoads, S. J.; Raulins, N. R. *Org. React.* 1975, 22, 1. (c) Piers, E. In *Comprehensive Organic Chemistry*; Pergamon: Oxford, 1991, in press. (d) Hudlicky, T.; Rulin, F.; Reed, J. W.; Gadamasetti, R. G. *Org. React.* 1992, 41, 1. For reviews on vinylcyclopropane-cyclopentene rearrangement, see: (e) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* 1989, 33, 247. (f) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 899.

(10) (a) Piers, E.; Jung, G. L. *Can. J. Chem.* 1987, 65, 1668. (b) Piers, E.; Jung, G. L.; Ruediger, E. H. *Can. J. Chem.* 1987, 65, 670.