by the addition of *n*-butyllithium (1.41 mL of a 1.42 M solution in hexane, 2.00 mmol) to a stirred solution of diisopropylamine (0.32 mL, 2.26 mmol, freshly distilled from calcium hydride) in anhydrous tetrahydrofuran (4.9 mL, distilled from sodium benzophenone ketyl) which was maintained at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 15 min and then at 0 °C for 15 min before it was cooled again to −78 °C. This solution was added at a rate of approximately 0.3 mL/min via a motor-driven syringe pump to a stirred solution of the ketone (1.00 mmol) and methylene bromide (0.28 mL, 4.00 mmol, freshly distilled from phosphorus pentoxide) in anhydrous tetrahydrofuran (2.0 mL) that was maintained at −78 °C under nitrogen. After the addition was complete, the resulting dark solution was stirred for 1 h at −78 °C, and then it was poured into a mixture of ice (10 g) and ether (20 mL). After the ice had melted, the resulting solution was stirred, and 10% aqueous hydrochloric acid was added slowly until the aqueous layer was slightly acidic (pH = 6). The layers were separated and the aqueous layer was extracted with ether (20 mL). The organic layer and the ether extract were combined, washed with brine (10 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded a black oil which was column chromatographed on silica gel. Elution with ether gave an orange oil which was Kugelrohr distilled to provide the corresponding dibromomethyl alcohol as a clear colorless oil.

*n*-Butyllithium (1.47 mL of a 1.5 M solution in hexane, 2.20 mmol) was cooled to −100 °C and then added at a rate of approximately 0.07 mL/min via a motor-driven syringe pump to a vigorously stirred (mechanical stirrer) solution of the dibromomethyl alcohol (1.00 mmol) in anhydrous tetrahydrofuran (4.4 mL) which was maintained at −100 °C under nitrogen. After the addition was complete, the resulting reaction mixture was stirred for 1 h at −100 °C, and then it was allowed to slowly warm to 0 °C. It was stirred at this temperature for 5 min, before it was treated with 1 M aqueous oxalic acid (2.20 mL). The resulting solution was stirred at 0 °C for 5 min, and then it was poured into a mixture of water (10 mL) and ether (10 mL). After this mixture was shaken vigorously, the layers were separated, and the aqueous layer was extracted with ether (10 mL). The organic layer and the ether extract were combined, washed with brine (10 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a yellow oil. The ratio of the conjugated and nonconjugated cyclopropyl ketones present was determined by quantitative $^{13}C$ NMR spectroscopy. Control experiments established that the reaction products were stable both to the quenching procedure and to the conditions of the workup procedure.

**Homologation of Bicyclo[3.1.0]hexan-2-one (13).** Treatment of **13** (184 mg, 1.91 mmol) with (dibromomethyl)lithium according to the general procedure gave 292 mg (56% yield) of a mixture of 2-*exo*-(dibromomethyl)bicyclo[3.1.0]hexan-2-*endo*-ol [**14**, $^{13}C$ NMR $\delta$ 85.3 (C-2), 56.6 ($CHBr_2$), 32.3 (C-3), 26.4 (C-4), 24.3 (C-1), 17.8 (C-5), 6.9 (C-6)] and 2-*endo*-(dibromomethyl)bicyclo-[3.1.0]hexan-2-*exo*-ol [**15**, $^{13}C$ NMR $\delta$ 85.5 (C-2), 55.2 ($CHBr_2$), 33.5 (C-3), 25.9 (C-4), 25.7 (C-1), 17.5 (C-5), 7.0 (C-6)] as a clear colorless oil after Kugelrohr distillation (60–70 °C, 0.05 mm). Analysis of this material by quantitative $^{13}C$ NMR spectroscopy showed that **14** and **15** were present in a ratio of 90:10, respectively.

Reaction of this mixture of **14** and **15** (250 mg, 0.91 mmol) with *n*-butyllithium according to the general procedure afforded a yellow oil. Analysis of this material by $^{13}C$ NMR spectroscopy showed that **16** and **17** were present in a ratio of 60:40. Kugelrohr distillation (50–65 °C, 0.9 mm) of this material provided 69 mg (68% yield) of this mixture of **16** and **17**.

**Homologation of Nortricyclanone (2).** Treatment of **2** (800 mg, 7.39 mmol) with (dibromomethyl)lithium according to the general procedure gave 1.541 g (74% yield) of 3-(dibromomethyl)nortricyclan-3-ol (**18**) as a clear colorless oil after Kugelrohr distillation (55–60 °C, 0.04 mm): $^{13}C$ NMR $\delta$ 87.6 (C-3), 53.7 ($CHBr_2$), 39.4 (C-4), 32.6 (t), 31.1 (t), 20.2 (C-2), 14.1 (d), 13.2 (d); $^1H$ NMR $\delta$ 5.90 (s, 1 H, $CHBr_2$), 3.20–2.80 (m, 1 H, OH), 2.40–0.80 (complex m, 8 H).

Reaction of **18** (212 mg, 0.75 mmol) with *n*-butyllithium according to the general procedure afforded a yellow oil. Analysis of this material by $^{13}C$ NMR spectroscopy showed that **3** and **4** were present in a ratio of 85:15. Kugelrohr distillation (75 °C, 0.25 mm) of this material provided 61 mg (67% yield) of this mixture of **3** and **4**.

**Homologation of Bicyclo[4.1.0]heptan-2-one (16).** Treatment of **16** (530 mg, 4.82 mmol) with (dibromomethyl)lithium according to the general procedure gave 805 mg (58% yield) of a mixture of 2-*exo*-(dibromomethyl)bicyclo[4.1.0]heptan-2-*endo*-ol [**19**, $^{13}C$ NMR $\delta$ 73.3 (C-2), 60.2 ($CHBr_2$), 31.1 (C-3), 22.2 (C-5), 19.8 (C-1), 18.6 (C-4), 11.3 (C-6), 11.2 (C-7)] and 2-*endo*-(dibromomethyl)bicyclo[4.1.0]heptan-2-*exo*-ol [**20**, $^{13}C$ NMR $\delta$ 72.8 (C-2), 60.6 ($CHBr_2$), 32.1 (C-3), 22.2 (C-5), 18.9 (C-1), 15.1 (C-4), 12.3 (C-6), 5.2 (C-7)] as a clear colorless oil after Kugelrohr distillation (70–80 °C, 1.5 mm). The $^1H$ NMR spectrum of the mixture contained singlets for the dibromomethyl substituents of **19** and **20** at $\delta$ 5.73 and 5.76, respectively. Integration of these resonances showed that **19** and **20** were present in a ratio of 60:40.

Reaction of this mixture of **19** and **20** (250 mg, 0.87 mmol) with *n*-butyllithium according to the general procedure afforded a yellow oil. Analysis of this material by $^{13}C$ NMR spectroscopy showed that **21** and **22** were present in a ratio of 45:55. Kugelrohr distillation (55–70 °C, 0.9 mm) of this material provided 91 mg (84% yield) of this mixture of **21** and **22**.

**Homologation of 8,9-Didehydroadamantan-2-one (5).** Treatment of a mechanically stirred solution of **5** (296 mg, 2.00 mmol) and methylene bromide (0.56 mL, 7.98 mmol) in anhydrous diethyl ether (4.0 mL, distilled from sodium benzophenone ketyl) that was maintained at −100 °C under nitrogen with lithium diisopropylamide according to the general procedure gave 726 mg of a brown oil. Column chromatography of this material on 60–200-mesh silica gel with methylene chloride as eluent provided 519 mg (81% yield) of 2-(dibromomethyl)-8,9-didehydroadamantan-2-ol (**23**) as a white solid: mp 97–97.5 °C; $^{13}C$ NMR $\delta$ 72.0 (C-2), 61.0 ($CHBr_2$), 53.7 (C-6), 36.0 (C-3), 31.1 (t), 30.5 (d), 30.3 (d), 29.6 (t), 29.4 (C-1), 27.8 (d), 27.1 (d); $^1H$ NMR $\delta$ 6.24 (s, 1 H, $CHBr_2$), 2.36 (s, 1 H, OH), 2.40–1.30 (complex m, 12 H).

Reaction of **23** (483 mg, 1.5 mmol) with *n*-butyllithium according to the general procedure afforded 290 mg of a yellow oil. Analysis of this material by $^{13}C$ NMR spectroscopy showed that only **6** was present. Column chromatography of this material on TLC-mesh silica gel with 1:1 methylene chloride and petroleum ether gave 163 mg (67% yield) of **6**.

**Acknowledgment.** This work was supported by a grant from the University of Delaware Research Foundation.

**Registry No.** **3**, 10039-11-9; **4**, 39163-38-7; **5**, 10497-56-0; **14**, 138899-07-7; **15**, 138899-08-8; **16**, 5771-58-4; **17**, 60582-64-1; **18**, 138923-69-0; **19**, 138899-09-9; **20**, 138899-10-2; **21**, 16335-43-6; **22**, 90243-81-5; **23**, 138899-11-3; bicyclo[3.1.0]hexan-2-one, 4160-49-0; (dibromomethyl)lithium, 37555-63-8.

## A Novel and Highly β-Selective Epoxidation of Δ⁵-Unsaturated Steroids with Permanganate Ion

M. S. Syamala, Jagattaran Das, Sundarababu Baskaran, and Srinivasan Chandrasekaran*

*Department of Organic Chemistry, Indian Institute of Science, Bangalore-560 012, India*

*Received August 29, 1991*

There has been considerable interest in recent years in the synthesis of 5β,6β-epoxides of Δ⁵-unsaturated steroids[1-3] particularly since this functionality is present in a number of biologically active steroids such as withaferin A,[4] withanolide B,[5] and jabarasalactone.[6] Due to the

(1) (a) Shiota, M.; Ogihara, T.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 40. (b) Hanson, J. R.; Truneh, A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2001.

(2) Muto, T.; Umehara, J.; Masumori, H.; Miura, T.; Kimura, M. *Chem. Pharm. Bull.* **1985**, *33*, 4749.

(3) Marchon, J. C.; Ramasseul, R. *Synthesis* **1989**, 389.

0022-3263/92/1957-1928$03.00/0 

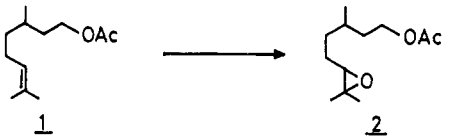
**Table I. $KMnO_4$–$CuSO_4$ Oxidation of $\Delta^5$-Unsaturated Steroids**

| substrate | t (h) | product[a] | β:α | yield (%)[b] |
|---|---|---|---|---|
| **3a** | 2 | **4a** | 93:7 | 92 |
| **3b** | 1 | **4b** | 92:8 | 90 |
| **3c** | 1 | **4c** | 92:8 | 91 |
| **3d** | 1 | **4d** | 100:0 | 94 |
| **3e** | 1 | **4e** | 100:0 | 92 |
| **5** | 1 | **6** | 94:6 | 90 |
| **7** | 1 | **8** | 92:8 | 95 |
| **9** | 1 | **10** | 100:0 | 70 |

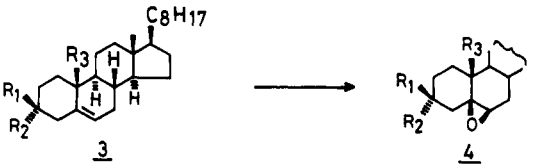
[a] The spectral data and melting points of all the compounds are in agreement with those reported in the literature (see Experimental Section). [b] Isolated yield.

presence of a C(10)-angular methyl group on the β-face of the steroid skeleton, epoxidation of the $\Delta^5$-alkene with peracid invariably yields the 5α,6α-epoxide as the major product.[7] Synthesis of β-epoxides of $\Delta^5$-unsaturated steroids has been accomplished via formation of halohydrins in two or three steps with moderate yields.[8] Earlier attempts to effect stereoselective β-epoxidation involved the introduction of a bulky 3α-halo substituent that would block the entry of the reagent from the α-face.[1] Miura[2] reported epoxidation of cholesteryl acetate by iodosobenzene in the presence of chromium, manganese, or iron tetraphenylporphyrin with a high degree of stereoselectivity (70–90%) but in very poor yields (15–25%). Under very high dilution, β-epoxidation of steroids has been achieved with chromyl acetate in moderate yields, but this procedure is complicated by the formation of side products.[9] A recent report on the successful β-epoxidation using ruthenium tetramesitylporphyrin (Groves–Quinn catalyst)[10] required a few days for the epoxidation to go to completion for most of the steroids studied.[3]

Recent work from our laboratories has shown that a mixture of $KMnO_4$–$CuSO_4 \cdot 5H_2O$ in dichloromethane in the presence of a catalytic amount of water and *tert*-butyl alcohol is effective in converting olefins to α-hydroxy ketones/α-diketones[11] and for the synthesis of γ- and δ-lactones from γ- and δ-hydroxyalkenes respectively.[12] It is believed that *tert*-butyl alcohol acts as a phase-transfer catalyst[13] and that water and *tert*-butyl alcohol form the third phase, i.e., omega phase,[14,15] over the surface of the inorganic solid in which the reaction takes place. Interestingly, oxidation of citronellol acetate (**1**) and cholesteryl acetate (**3a**) with this reagent system produces the corresponding epoxides **2** and **4a**, respectively, as the only products. It is well known that epoxides are not major products in the normal permanganate oxidations of olefins.[16] However, in line with omega phase catalysis, it is possible that more lipophilic substrates would lead to epoxides instead of α-hydroxy ketones/α-diketones.




**1** **2**




**3** **4**

a. $R_1$ = OAc ; $R_2$ = H ; $R_3$ = Me.

b. $R_1$ = OCOPh ; $R_2$ = H ; $R_3$ = Me.

c. $R_1$ = $OCOC_5H_{11}$ ; $R_2$ = H ; $R_3$ = Me.

d. $R_1$ = H ; $R_2$ = OCOPh ; $R_3$ = Me

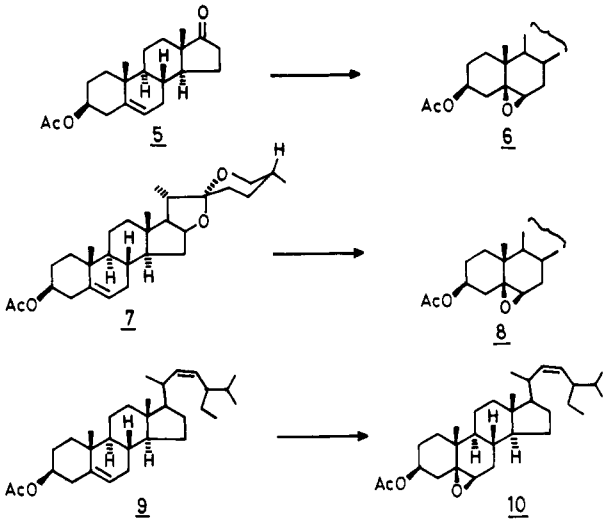
e. $R_1$ = OAc ; $R_2$ = H ; $R_3$ = $CH_2OAc$

A number of $\Delta^5$-unsaturated steroids were subjected to heterogeneous permanganate oxidation in the presence of a catalytic amount of water and *tert*-butyl alcohol in order to test the validity of this hypothesis. The results are summarized in Table I. Each of the steroids studied afforded the corresponding epoxide as the sole product in 90–95% yield within 1 h of reaction at room temperature (28 °C). There are a number of salient features of this methodology which are worth mentioning. In all the cases examined the 5β,6β-epoxides are formed with a high degree of stereoselectivity[17] (>92%), although the β-face is the sterically more hindered face of these molecules.[7] The nature of the 3β-ester does not affect either the rate of the reaction or the stereoselectivity of the product. Thus cholesteryl benzoate (**3b**) and cholesteryl caproate (**3c**) formed the 5β,6β-epoxides **4b**[3] and **4c**,[3] respectively, in 90% yield.

The stereochemistry of the substituent at the 3-position does not have any profound effect on the stereoselectivity. 3α-Cholesteryl benzoate (**3d**) also gave the β-epoxide **4d**[18] (94%). This stereoselective epoxidation is compatible with a number of functional groups in the steroid molecule. Thus, the keto-steroid **5** and diosgenin acetate (**7**) yielded the corresponding β-epoxides **6**[3] and **8**,[19] respectively (90–95%). This reaction is also regioselective in that the oxidation of stigmasterol acetate (**9**) led to the β-epoxide **10**[9] (70%) where the trisubstituted double bond has re-

(4) Glotter, E.; Kirson, I.; Lavie, D.; Abraham, A. *Bio-Organic Chemistry*; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. 2, p 57.
(5) Lavie, D.; Kirson, I.; Glotter, E. *Isr. J. Chem.* **1968**, *6*, 671.
(6) Tschesche, R.; Schwang, H.; Legler, G. *Tetrahedron* **1966**, *22*, 1121.
(7) Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: London, 1968; Chapter 3, p 70.
(8) Matthews, G. J.; Hassner, A. In *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J. A., Eds.; Van Nostrand: New York, 1972; Vol. 2, p 2.
(9) Galagovsky, L. R.; Burton, G.; Gros, E. G. *Z. Naturforsch.* **1989**, *44b*, 806.
(10) Groves, J. T.; Quinn, R. *J. Am. Chem. Soc.* **1985**, *107*, 5790.
(11) Baskaran, S.; Das, J.; Chandrasekaran, S. *J. Org. Chem.* **1989**, *54*, 5182.
(12) Baskaran, S.; Islam, I.; Vankar, P. S.; Chandrasekaran, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1670.
(13) The reactions also take place when a catalytic amount of normal phase transfer catalyst like benzyltriethylammonium bromide is added instead of *tert*-butyl alcohol.
(14) (a) Liotta, C. L.; Burgess, E. M.; Ray, C. C.; Black, E. D.; Fair, B. E. *ACS Symp. Ser.* **1987**, *326* (*Phase Transfer Catal.: New Chem. Catal. Appl.*), 15. (b) Liotta, C. L.; Burgess, E. M.; Ray, C. C.; Black, E. D.; Fair, B. E. *Prepr. Am. Chem. Soc. Div. Pet. Chem.* **1985**, *30*, 367.
(15) Similar catalytic activity has also been referred to as *Thin Layer Phase Transfer Catalysis*. Arrad, O.; Sasson, Y. *J. Am. Chem. Soc.* **1988**, *110*, 185.
(16) (a) Freeman, F. *Rev. React. Species Chem. React.* **1976**, *1*, 179. (b) Stewart, R. In *Oxidation in Organic Chemistry*; Wiberg, K. B., Ed.; Academic Press: New York, 1965; Part A. (c) Lee, D. G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*; Open Court: La Salle, 1980. (d) Rappe, A. K.; Goodard, W. A., III. *J. Am. Chem. Soc.* **1982**, *104*, 448. (e) Rappe, A. K.; Goodard, W. A., III. *J. Am. Chem. Soc.* **1982**, *104*, 3287.
(17) The assignment of the stereochemistry to the epoxides and the ratio of the isomers are readily inferred from their $^1H$ NMR spectra. The 6β-H resonance of steroidal 5α,6α-epoxides appears in the range δ 2.82–2.86 ($J$ = 3.3–4.1 Hz), while the 6α-H signal of the corresponding 5β,6β-epoxides is found in the range δ 3.05–3.10 ($J$ = 2.1–2.7 Hz): Cross, A. D. *J. Am. Chem. Soc.* **1962**, *84*, 3206.
(18) Mukawa, F. *Nippon Kagaku Zasshi* **1960**, *81*, 1348; *Chem. Abstr.* **1962**, *56*, 7389c.
(19) Miramontes, L.; Romero, M. A.; Farjat, F. A. 1959, U.S. Patent, 2878246; *Chem. Abstr.* **1959**, *53*, 16218b.

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 5β,6β-epoxides of Δ⁵-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

$^1$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.[20] Esterification of the 3-OH group in all cases was conducted by standard procedures.[21]

**Representative Procedure: 3β-Acetoxy-5β,6β-epoxy-5β-cholestane (4a).** A mixture of $KMnO_4$ (4 g) and $CuSO_4 \cdot 5H_2O$ (2 g) was ground to a fine powder in a mortar and pestle. Water (200 μL) was added, and the slightly wet mixture was transferred to the reaction flask. To a stirred suspension of this mixture in $CH_2Cl_2$ (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 $CH_2Cl_2$. After evaporating the solvent, the crude product was recrystallized from methanol to give the β-epoxide **4a** (0.820 g, 92%), mp 110–112 °C (lit.[22] mp 111–112 °C). $^1$H NMR ($CDCl_3$): δ 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.

**3β-(Benzoyloxy)-5β,6β-epoxy-5β-cholestane (4b):** yield 90%; mp 172–173 °C (lit.[23] mp 173–174 °C).

**3β-(Hexanoyloxy)-5β,6β-epoxy-5β-cholestane (4c):** yield 91%; mp 74 °C (lit.[3] mp 74 °C).

**3α-(Benzoyloxy)-5β,6β-epoxy-5β-cholestane (4d):** yield 94%; mp 131–132 °C (lit.[18] mp 132 °C).

**3β,19-Diacetoxy-5β,6β-epoxy-5β-cholestane (4e):** yield 92%; obtained as an oil (lit.[24]).

**3β-Acetoxy-5β,6β-epoxy-5β-androstan-17-one (6):** yield 90%, mp 188–189 °C (lit.[3] mp 189–190 °C).

**(25*R*)-3β-Acetoxy-5β,6β-epoxy-5β-spirostan (*O*-acetyldiosgenin 5β,6β-epoxide) (8):** yield 95%; mp 187–190 °C (lit.[19] mp 188–192 °C).

**3β-Acetoxy-5β,6β-epoxy-5β-stigmast-22-ene (10):** yield 70%; mp 140 °C (lit.[9] mp 139–140 °C).

**Acknowledgment.** We thank CSIR, New Delhi for financial support and Professor K. M. Madyastha and Professor H. Schwarz for generous supply of some of the steroids.

**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; $KMnO_4$, 7722-64-7.

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

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

Charles W. Murtiashaw,* Ralph Breitenbach, Steven W. Goldstein, Susan L. Pezzullo, George J. Quallich, and Reinhard Sarges

*Process R & D, Central Research Division, Pfizer, Inc., Eastern Point Road, Groton, Connecticut 06340*

*Received May 7, 1991*

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.[1] A recent report by Sarges and co-workers[2] 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 hydantion.

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).[2] 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[3] **3** as a model. Con-

(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.

0022-3263/92/1957-1930$03.00/0 