residue, which was chromatographed over 30 g of silica gel, eluting with chloroform/methanol, 4:1 (to remove less polar byproducts), followed by chloroform/methanol/acetic acid, 20:5:1. Fractions containing the free base of **31** (R_f = 0.3) were combined and evaporated to yield 1.3 g (66%) of pure product. This was taken up in 15 mL of anhydrous methanol and treated at 0 °C with methanolic HCl to pH 2. The solution was filtered, and the filtrate was concentrated and diluted with a small amount of ether. The desired methoxy mycin hydrochloride **31** separated as 1.05 g (74%) of a red solid: mp 176–177 °C (methanol/ether); IR (KBr) 3520–3100, 1620, 1415, 995 cm^{-1}; UV (CH_3OH) 204 (ϵ 23 800), 251 (26 120), 285 (5710), 484 nm (6870); NMR ($CDCl_3$) δ 12.80 (br s, 2 H), 8.1–7.3 (br m, 7 H), 5.32 (br s, 1 H), 4.8–4.5 (m, 2 H), 4.22 (s, 1 H), 4.1–3.5 (m, 3 H), 3.65 (s, 3 H), 3.5 (m, 1 H), 2.4–1.8 (m, 4 H), 1.38 (s, 3 H), 1.35 (d, 3 H); mass spectrum, *m/e* 499 (M^+), 370, 352, 338, 334, 320, 304, 278 (base); $[\alpha]^{25}_D$ = +252.25° (*c* = 0.2244, methanol).

Anal. Calcd for $C_{26}H_{29}NO_9 \cdot HCl \cdot {}^1/_2H_2O$ (544.98): C, 57.30; H, 5.73; N, 2.57; Cl, 6.51. Found: C, 57.26; H, 5.84; N, 2.51; Cl, 6.67.

Acknowledgment. We wish to express our thanks to the personnel of the Physical Chemistry Department of Hoffmann-La Roche for their determination of spectroscopic and analytical data. The X-ray structure determination of the epoxide **21** was carried out by Dr. Jack Blount and his staff.

Registry No. **8**, 1709-63-3; **9**, 78-79-5; **10**, 128243-24-3; **11**, 69448-11-9; **12**, 90269-76-4; **13**, 128269-84-1; **14a**, 128243-25-4; **14b**, 128300-80-1; **15a**, 128243-26-5; **15b**, 128243-31-2; **16a**, 128243-27-6; **16b**, 128300-81-2; **17a**, 128243-28-7; **17b**, 128300-82-3; **18a**, 128243-29-8; **18b**, 128300-83-4; **19a**, 128243-39-0; **19b**, 128243-33-4; **20a**, 128243-30-1; **20b**, 128243-32-3; **21**, 128300-79-8; **25**, 128243-34-5; **26**, 128243-35-6; **27**, 128243-37-8; **28**, 128243-36-7; **30**, 128243-40-3; **31**, 128300-86-7; **31** (free base), 128243-38-9; **32**, 128300-84-5; **33**, 128300-85-6.

Notes

Carbanions Derived from 3-Methoxyazetidinones: Precursors for the Preparation of 3,3-Disubstituted Azetidinones

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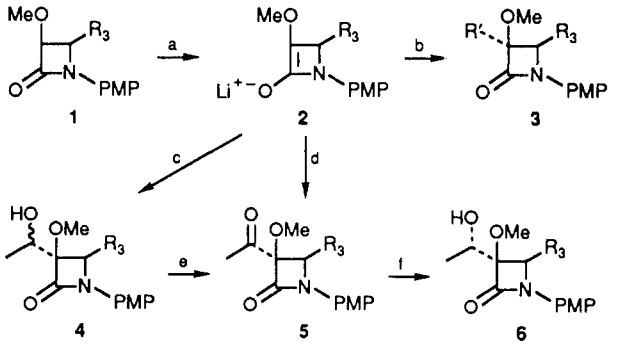
Carbapena(e)ms bearing a hydroxy or a methoxy group adjacent to the carbonyl group of the azetidinone moiety have received only limited attention.[1] As part of a program directed toward the synthesis of such compounds and other similar bicyclic azetidinones, the conversion of 3-methoxyazetidinones to the corresponding anions and subsequent reaction with various electrophiles was undertaken.

The conversion of azetidinones unsubstituted at C-3 to the corresponding anions is well known.[2] Even 1,3-dilithioazetidin-2-ones have been generated.[3] However the studies related to formation of C-3 carbanions from azetidonones bearing a substituent other than imino[4] are few.[5] Specifically, anions such as **2** do not appear to have been investigated.

Scheme I[a]



a, R_3 = *trans*-cinnamyl; **b**, R_3 = phenyl; **c**, R_3 = α-methycinnamyl; **d**, R_3 = 2-furyl for all compounds. PMP = *p*-methoxyphenyl.

[a] (a) 1.1 equiv of LDA, THF, −78 °C; (b) excess CH_3I or C_2H_5I, −78 °C → room temperature; (c) acetaldehyde; (d) PCC, NaOAc, 4-Å molecular sieves; (e) 1.1 equiv of L-Selectride, 2.2 equiv of TMEDA, THF, −78 °C.

The formation of the carbanions is easily carried out by exposure of the azetidinones (**1**), prepared by a 2 + 2 cycloaddition of methoxyketene and the appropriate imine, to a slight excess of LDA in THF at −78 °C. These carbanions are stable at this temperature and show high diastereoselectivity in their subsequent reaction with various electrophiles (Scheme I). Thus 3-methoxy-3-ethylazetidinone (**3a**, R′ = ethyl, R = *trans*-cinnamyl) and 3-methoxy-3-methylazetidinone (**3b**, R′ = methyl, R = phenyl) were obtained in 85 and 95% yields, respectively, as the sole alkylation products. For compound **3a** a 12% NOE between the methylene protons of the ethyl group at C-3 and the C-4 proton supported the assigned stereochemistry in which the incoming group at C-3 and the substituent at C-4 are trans. The same relative stereochemistry of these two substituents is found in the natu-

(1) (a) Yoshioka, T.; Watanbe, A.; Fukagawa, Y.; Ishikura, T. *Tetrahedron Lett.* **1986**, *27*, 4335. (b) Watanabe, A.; Fukagawa, Y.; Yoshioka, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2091.

(2) (a) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208. (b) Yoshioka, A.; Chida, W.; Miyashita, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1353. (c) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 2049. This list is simply representative.

(3) Durst, T.; Van Der Elzen, R.; Legault, R. *Can. J. Chem.* **1974**, *52*, 3206.

(4) (a) Firestone, R. A.; Schelechow, N.; Johnston, D. B. R.; Christensen, B. G. *Tetrahedron Lett.* **1972**, 375. (b) Rasmusson, G. H.; Reynolds, G. F.; Arth, G. E. *Tetrahedron Lett.* **1973**, 145. (c) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 2794.

(5) Ojima et al. have alkylated a 3-(protected)aminoazetidinone via the corresponding anion. Ojima, I.; Qiu, X.; Chen, H.-J. C. *Tetrahedron* **1988**, *44*, 5307.

0022-3263/90/1955-5525$02.50/0

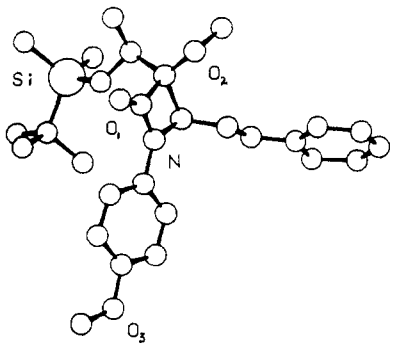


Figure 1. X-ray structure determination of TBDMS derivative of **6a**.

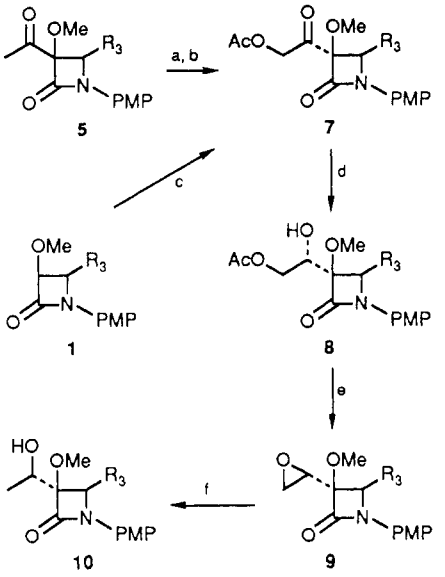
rally occurring antibiotic PS-5.[6] Current efforts to convert **3a** to a methoxy analogue of PS-5 are in advanced stages.

The reaction of the anions **2** with acetaldehyde was also highly diastereoselective with respect to ring substitution but gave a mixture of diastereoisomers **4** at the hydroxyethyl carbon. The presence of two diastereoisomers was readily seen in the NMR spectra of the mixture which gave two distinct signals in the 4.5–5.1 range (two doublet of doublets for **4a**, two singlets for all others). The isomer with the upfield shift for C-4 proton was designated as A, the other as B. The ratio of A to B varied from 1:1 to 2:1 in all cases examined. The yields of the mixtures of (hydroxyethyl)azetidinones were typically 80–90%. Oxidation of the mixture of diastereomeric (hydroxyethyl)azetidinones **4** with PCC furnished in each case a single acetyl compound **5** (ca. 80% yield), thereby confirming that the (hydroxyethyl)azetidinones differed only in the stereochemistry in the side chain. In each case the same acetyl compound was also obtained in similar overall yields to the two-step process described above, by addition of the anion to 10–15-fold excess of acetyl chloride.

It was not possible to increase the diastereoselectivity of the reaction of the anions **2** with acetaldehyde either by a change of countercation from lithium to magnesium, zinc or cerium, or by addition of trimethoxyborane or TMEDA. Furthermore we were unable to separate the isomers **4** or any of the derivatives. To allow access to either diastereoisomer the following approaches were devised.

The reduction of the acetyl compounds **5** was studied under a variety of conditions.[7] The best diastereoselectivity was observed on carrying out the reduction with L-Selectride (Aldrich) at −78 °C in THF in the presence of 2.2 equiv of TMEDA as an external chelating agent. Only diastereoisomer A (isolated yield, ca. 50–65%) could be detected in the 300-MHz proton spectrum of the product from reactions carried out under these conditions.[8] The stereochemistry of the hydroxyethyl compound **6a**, prepared as above, was determined by X-ray diffraction analysis of the corresponding TBDMS ether. An ORTEP diagram is included in Figure 1. The trans stereochemistry of the hydroxyethyl group at C-3 and the cinnamyl group at C-4 confirmed the above expectations. The relative stereochemistry of the hydroxyethyl group is 8*S**.[9] On the basis of similar behavior of the acetyl compounds on reduction with L-Selectride, it is highly likely that the stereochemistry of all other hydroxyethyl azetidinones **6b–d** is similar to that of **6a**.

Scheme II[a]



[a] (a) (i) 1.5 equiv of TBDMS-triflate, 2 equiv of 2,6-lutidine, CH_2Cl_2, reflux; (ii) 1.1 equiv of Br_2, CH_2Cl_2, 0 °C; (b) CsOAc, DMF, room temperature; (c) (i) LDA, THF, −78 °C; (ii) inverse addition to excess $AcOCH_2COCl$; (d) 1.1 equiv of L-Selectride, 2.2 equiv of TMEDA, THF, −78 °C; (e) (i) 1.1 equiv of NaH, DMF, 1.5 equiv of tosylimidazole, 0 °C; (ii) 1.5 equiv of NaOMe, THF–MeOH, (f) 1.5 equiv of L-Superhydride, THF, 5 → 7 °C.

Various attempts to invert the stereochemistry of the hydroxyethyl group in **6a** using external oxygen nucleophiles were futile due to the highly hindered environment of this group.[10] It was reasoned that the desired inversion could probably be accomplished with an internal nucleophile. The requisite compounds were prepared in two different ways.

The acetoxyacetyl compounds **7** could be obtained by inverse addition of the anions **2a** to a 10–15-fold excess of acetoxyacetyl chloride. Alternatively the acetyl compounds **5** could be converted to the acetoxyacetyl compound via a bromination–acetoxylation sequence. Since the reduction of the acetyl group in **7** was carried out under the same nonchelating conditions as **5** it was expected that it would yield the alcohols **8** having the same relative configuration as **6**. This assumption was verified by the sequence of reactions shown in Scheme II.

Conversion of **8** to the corresponding tosylates using NaH/tosylimidazole[11] followed by treatment with sodium methoxide in methanol afforded the epoxide.[12] Attempts

(6) (a) Okamura, K.; Hirata, S.; Koki, A.; Hori, K.; Shibamoto, N.; Okamura, Y.; Okabe, M.; Okamoto, R.; Kuono, K.; Fukagawa, Y.; Shimauchi, Y.; Ishikura, T. *J. Antibiot.* **1979**, *32*, 262. (b) Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, N.; Okamura, K.; Shimauchi, Y.; Ishikura, T. *J. Antibiot.* **1980**, *33*, 1128.

(7) The reduction under nonchelating conditions has been studied in some detail, and results will be submitted for publication separately. The results of reduction of **5a** and **5b** with other reducing agents will be included there.

(8) It was necessary to subject the mixture of products from L-Selectride reduction to column chromatography to remove starting material and some other unidentified impurities. However the observed high diastereoselectivity is *not* a consequence of any "accidental" purification, since as mentioned earlier, diastereomer A and B are inseparable in all the cases examined.

(9) Thienamycin numbering is used here. (a) Kahan, J. S.; Kahan, F. M.; Stapley, E. O.; Goegelman, R. J.; Hernandez, S. *Chem. Abstr.* **1976**, 85, 92190t. (b) Kahan, J. S.; Christensen, B. G.; Morison, R. B.; Ratcliffe, R. W.; Walton, L. J.; Ruswinkle, L. J.; Hoogsteen, K.; Kaczka, A.; Rhodes, R.; Hirshfield, J.; Arison, B. H.; Albers-Schonberg, G.; Kahan, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

(10) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Kulen, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 773. (c) Kellog, R. M.; Strijtveen, B.; Kruizinga, W. H. *J. Org. Chem.* **1981**, *46*, 4321.

(11) Fraser-Reid, B.; Hicks, D. R. *Synthesis* **1974**, 203.

(12) Similar epoxides (without the methoxy substituent at C-3) have been stereospecifically synthesized and opened up to provide 3-(hydroxyethyl)azetidinones: Bonini, C.; Fabio, R. D. *Tetrahedron Lett.* **1988**, 85.

to obtain these tosylates and epoxides in chromatographically pure form were unsuccessful. Reduction of the crude epoxides with Superhydride in THF furnished the diastereoisomer B, compounds **10**. Thus the acetyl compounds **5** served as precursors for both the diastereoisomers A and B. Using this sequence of reactions compounds **10a** and **10c** were prepared.

The overall yield for conversion of azetidinones **1** to the corresponding diastereoisomers A was 40–50%. The conversion of **1** to the diastereoisomers B was achieved in an overall yield of 10–15%. Conversion of compound **6a** to a variety of bicyclic azetidinones is being actively pursued.

The results outlined above are important in several regards. It has been shown that monocyclic 3-methoxyazetidinones with an additional substituent at C-3 can be obtained in a highly diastereoselective manner by conversion of 3-methoxyazetidinones **1** to the corresponding lithio derivatives and subsequent quenching with electrophiles. It should be emphasized that based on the additional studies, the results pertaining to anion formation, quenching, and the non-chelation controlled reduction have been found to be truly *general* in nature, being independent of the nature of the alkoxy group at C-3, the substituent at C-4, and at the azetidinone nitrogen atom. This has allowed access to a wide variety of 3,3-disubstituted azetidinones in a high state of diastereoisomeric purity. Results of those studies will be published separately.[13]

Experimental Section[14]

3a (R′ = Ethyl). To a vigorously stirred solution of 0.618 g (2 mmol) of azetidinone **1a** dissolved in about 125 mL of dry THF was added via canula 1.15 equiv of LDA in THF at −78 °C. This led to considerable darkening. After 15 min 0.5 mL of iodoethane was added. The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature over a period of about 3 h. The reaction mixture was quenched with 100 mL of 10% HCl and extracted with 3 × 50 mL of ethyl acetate. The combined organic layer was washed with saturated NaCl solution and was dried, etc. to furnish a yellow solid. TLC revealed the presence of the starting material and a new less polar compound. Column chromatography (3:1 hexane–ethyl acetate) furnished the product as a yellowish solid. Trituration with ether removed the color. Yield of 3a: 0.572 g (85%). Mp: 107–108 °C. IR: 1750 cm^{-1}. MS: 337 (M^+, 5.3), 238 (imine$^+$ + 1, 46), 237 (imine$^+$, 93.9), 236 (imine$^+$ − 1, 100). NMR: δ 7.4 (m, 7 H), 6.8 (m, 3 H), 6.4 (dd, 2 H, J = 8.3 Hz, J = 16.0 Hz), 4.4 (dd, 1 H, J = 0.7 Hz, J = 8.3 Hz), 3.7 (s, 3 H), 3.5 (s, 3 H), 2.1–2.0 (2 m, 2 H), 1.0 (apparent d, 3 H, J = 7.4 Hz). HRMS: calcd for $C_{21}H_{23}NO_3$ 337.1676, observed 337.1669.

3b (R′ = Methyl) (90% yield). Mp: 116–117 °C. IR: 1755 cm^{-1}. MS: 297 (M^+, 10), 211 (imine$^+$, 100), 196 (M^+ − 101, 31.3), 148 (M^+ − 149, 71). NMR: δ = 7.4 (m, 7 H), 7.1 (m, 2 H), 5.0 (s, 1 H), 3.6 (s, 3 H), 3.1 (s, 3 H), 1.7 (s, 3 H). HRMS: calcd for $C_{18}H_{19}NO_3$ 297.1365, observed 297.1363.

The anion of azetidinone **1a** was similarly prepared and reacted with acetaldehyde. A mixture of (hydroxyethyl)azetidinones **4a** was obtained in 80% yield following chromatography with 2:1 hexane–ethyl acetate. On the basis of appearance of two set of signals for the proton at the 4-position of the azetidinone ring (2 dd, first set 4.8 ppm, J = 0.6 Hz, J = 8.6 Hz second set 4.7 ppm, J = 0.8 Hz, J = 7.8 Hz); two methoy signals at 3.67 and 3.64 ppm and the appearance of a distorted triplet for the methyl group of the hydroxyethyl moiety (1.33 ppm) in the 300-MHz ^1H NMR spectrum of this foam, it was concluded that it was a mixture of two hydroxyethyl compounds. Other signals were not well resolved. The diastereoisomer with C-4 proton appearing at 4.7 ppm was designated as isomer A, that with the C-4 proton appearing at 4.8 ppm as isomer B. The ratio A:B was near 2:1. The mass spectrum of this mixture had peaks at 353 (M^+, 21.4), 309 (M^+ − 44, 25.6), 237 (imine$^+$, 99.7), 236 (imine$^+$ − 1, 99.7), 204 (M^+ − 149, 29.9), 149 ($C_8H_7NO_2^+$, 27.5), 84 (M^+ − 269, 100). IR peaks occured at 3300–3200 and 1755 cm^{-1}. Other (hydroxyethyl)azetidinones were similarly prepared in comparable yields.

Oxidation of 4a to 5a. To a solution of 1.06 g (3 mmol) of **4a** in 10 mL of dry CH_2Cl_2 was added 1 g of powdered fused sodium acetate and about 0.5 g of 4-Å molecular sieves. The reaction mixture was stirred vigorously while PCC (3 g, 13.9 mmol) was added in four equal portions over a period of about 10 min. Stirring was continued overnight after which another 2 g (ca. 1 mmol) of PCC was added and the reaction mixture was stirred for an additional 2 h. The reaction mixture was extracted with 3 × 50 mL ether. The combined organic layer was filtered thorugh Celite, and the product was chromatographed with 3:1 hexane–ethyl acetate to furnish 0.884 g (2.5 mmol, 84% yield) of acetyl compound. Mp: 81–82 °C (softening at 78–79 °C). IR: 1750, 1720 cm^{-1}. MS: 351 (M^+, 10.3), 308 (M^+ − 43, 7.4), 237 (imine$^+$, 3.9), 201 (M^+ − 149, 7), 43 ($C_2H_3O^+$, 100). NMR: δ 7.4–7.2 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 7.4 Hz, J = 16.0 Hz), 5.1 (dd, 1 H, J = 0.7 Hz, J = 7.4 Hz), 3.7 (s, 3 H), 3.5 (s, 3 H), 2.4 (s, 3 H). HRMS: calcd for $C_{21}H_{21}NO_4$ 351.1468, found 351.1428. The acetyl compound **5a** was also prepared in about 60% by the inverse addition of the anion **2a** to 10–15-fold excess of acetyl chloride at −78 °C. Other acetyl compounds were similarly prepared.

Selectride-TMEDA Reduction of 5a. A solution of 0.117 g (0.33 mmol) of the above acetyl compound and 10 mL of dry THF was cooled to −78 °C under nitrogen, and 0.12 mL (0.88 mmol) of dry TMEDA was added. To the clear solution was added 0.36 mL of a 1 M solution of L-Selectride in THF. After 1–2 h at −78 °C the reaction mixture was quenched with 10 mL of 10% HCl solution and saturated with NaCl and extracted with 3 × 30 mL of ethyl acetate. TLC of the crude product indicated the preence of the starting material and two other nonpolar compounds in addition to the (hydroxyethyl)azetidinone(s). Purification (2:1 hexane–ethyl acetate) led to isolation of 5 mg of a compound which had an R_f identical with that of the starting material and 55 mg (0.15 mmol, 45% yield) of the product **6a** as a white foam. NMR: δ 7.4–7.2 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 7.8 Hz, J = 16.0 Hz), 4.7 (dd, 1 H, J = 0.9, J = 8.0 Hz), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.67 (s, 3 H), 1.34–1.32 (d, 3 H, J = 6.5 Hz). This compound was judged to be diastereomerically pure isomer A. Other spectral properties were similar to those of **4a**. HRMS: calcd for $C_{21}H_{23}NO_4$ 353.1626, observed 353.1630.

The above procedure has been carried out on preparative scale with the difference that the Selectride solution was added from a pressure-equalizing dropping funnel over a period of several minutes. The isolated yield of **6a** was 60–70%.

6b (75% yield). Mp: 175–176 °C. IR: 3300, 1750 cm^{-1}. MS: 327 (M^+, 18.8), 282 (M^+ − 45, 4.3), 212 (imine$^+$ + 1, 47.0), 211 (imine$^+$, 100). NMR: δ 7.3–7.2 (m, 7 H), 6.8 (dd, 2 H, J = 2.3 Hz, J = 6.8 Hz), 5.1 (s, 1 H), 4.3 (m, 1 H), 3.7 (s, 3 H), 3.2 (s, 3 H), 2.2 (br s, 1 H), 1.3 (d, 3 H, J = 6.4 Hz). HRMS: calcd for $C_{19}H_{21}NO_4$ 327.1507, found 327.1476.

6c (50% yield). Semisolid. IR: 3300–3200, 1750 cm^{-1}. MS: 367 (M^+, 9.2), 252 (imine$^+$ + 1, 51.7), 250 (imine$^+$ − 1, 100). NMR: δ 7.4–7.2 (m, 7 H), 6.8 (dd, 2 H, J = 2.1 Hz, J = 6.8 Hz), 6.4 (br s, 1 H), 4.5 (s, 1 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 1.9 (d, 3 H, J = 1.6 Hz), 1.33 (d, 3 H, J = 6.5 Hz). Since 367 is a reference

(13) This work was financially supported by NSERC (Canada).

(14) **General.** Unless otherwise specified proton NMR spectra were recorded in $CDCl_3$ on a Varian XL300 or Gemini 200 spectrometer. For determination of diastereomeric purity of various (hydroxyethyl)azetidinones the 300-MHz spectrometer was used. The chemical shifts are reported in ppm (δ) downfield from tetramethylsilane which was used as an internal standard. Infrared spectra were recorded with a Perkin-Elmer 783 spectrophotometer by applying the solution of the compound (in dichloromethane or chloroform) as a thin film on an NaCl disk. Mass spectra were obtained with a VG Analytical 7070E mass spectrometer (EI-MS 70 eV; CI-MS 70 eV ionizing potential using diethyl ether as the reagent gas). Unless otherwise indicated the data corresponds to EI-MS spectra. Solvents for the extractions and chromatographic purifications were routinely distilled prior to use. Solvents used in various reactions were dried in usual manner. Tosylimidazole was prepared according to the literature procedure.[11] *n*-BuLi was titrated just prior to use.[15] Chromatography refers to flash chromatography[16] except that Merck 230–400-mesh silica was used and columns were filled to the height of about 25–35 cms. The elution was carried out by applying 10–15 psi of nitrogen pressure.

(15) Kofran, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(16) Kahn, M.; Still, W. C.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

peak, it was not possible to obtain HRMS for this compound.

6d (65% yield). Oil. IR: 3310, 1755 cm^{-1}. MS: 317 (M^+, 13), 273 (M^+ - 44, 4.6), 201 (imine$^+$, 100). NMR: δ 7.4-6.3 (series of m, 7 H), 5.1 (s, 1 H), 4.2 (q, 1 H, J = 5.2 Hz), 3.7 (s, 3 H), 3.4 (s, 3 H), 1.3 (d, 3 H, J = 5.2 Hz). HRMS: calcd for $C_{17}H_{19}NO_5$ 317.1393, found 317.1271.

The TBDMS derivative of **6a** was prepared in 89-95% yield by silylation[17] and purified (5:1 hexane-ethyl acetate). MP: 100-101 °C. IR: 1750 cm^{-1}. MS: 467 (M^+, 4.5), 436 (M^+ - 31, 2.8), 237 (imine$^+$, 94.4), 236 (imine$^+$ - 1, 100). NMR: δ 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.2 (dd, 1 H, J = 7.8 Hz, J = 16.0 Hz), 4.7 (dd, 1 H, J = 0.9 Hz, J = 7.8 Hz), 4.1 (q, 1 H, J = 6.3 Hz), 3.7 (s, 3 H), 3.6 (s, 3 H), 1.3 (d, 3 H, J = 6.3 Hz), 0.7 (s, 9 H), 0.06 (s, 6 H). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a CH_2Cl_2-hexane solution.[18]

Conversion of 5a to 7a. (i) A 0.353-g (1-mmol) sample of **5a** was dissolved in about 10 mL of dry CH_2Cl_2, and 0.23 mL (2 mmol) of 2,6-lutidine and 0.32 mL (1.5 mmol) of TBDMS-triflate were added. The clear homogeneous solution was heated under reflux for 3 h under N_2. The reaction mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The resulting yellow oil was chromatographed (5:1 hexane-ethyl acetate) to furnish the enol silyl ether in 95% yield as a yellow semisolid. IR: 1745 cm^{-1}. MS: 465 (M^+, 6.3), 434 (M^+ - 31, 3.2), 408 (M^+ - 57, 40.5), 237 (imine$^+$, 89), 236 (imine$^+$ - 1, 100). NMR: δ 7.3-7.1 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 8.2 Hz, J = 16.0 Hz), 4.6 (d, 1 H, J = 1.9 Hz), 4.3 (d, 1 H, J = 1.9 Hz), 4.0 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 0.8 (s, 9 H), 0.0 to -0.15.

(ii) Br_2 (0.33 g, 2.1 mmol) in 10 mL of dry CH_2CL_2 was added to a vigorously stirred solution of the above enol silyl ether (0.93 g, 2 mmol) in 25 mL of dry CH_2Cl_2 under N_2 at 0 °C. The colorless reaction mixture was brought to room temperature over a period of about 5 min, and the solvent was removed. The resulting yellow foam was dissolved in 10 mL of dry DMF, and 1.5 g (7.8 mmol) of powdered cesium acetate was added in one portion. The resulting heterogeneous reaction mixture was stirred at room temperature for 18 h. The reaction mixture was worked up by addition of 10 mL of water and extraction with 5 × 50 mL of ether. The combined organic fractions were dried and evaporated to furnish a yellow oil. Purification by column chromatography (5:1 hexane-ethyl acetate) furnished 0.523 g (1.3 mmol, 65% for two steps) of **7a** as a yellow oil. This product was identical in all regards with a sample prepared by reaction of the anion **2a** with acetoxyacetyl chloride by inverse addition. IR: 1750, 1740 cm^{-1}. MS: 409 (M^+, 5.3), 308 (M^+ - 101, 10), 236 (imine$^+$ - 1, 54), 43 ($C_2H_3CO^+$, 100). NMR: δ 7.4 (m, 7 H), 6.9 (m, 3 H), 6.3-6.2 (dd, 1 H, J = 8.2 Hz, J = 14.0 Hz), 5.2 (d, 1 H, J = 17.0 Hz), 5.1 (d, 1 H, J = 8.1 Hz), 4.8 (d, 1 H, J = 17.0 Hz), 3.7 (s, 3 H), 3.6 (s, 3 H), 2.1 (s, 3 H).

The Selectride reduction of **7a** gave **8a** in 50% yield as a yellow oil. IR: 3200, 1755, 1740 cm^{-1}. CI-MS: 412 (M^+ + 1, 1.8), 160 (M^+ - 252, 100). NMR: δ 7.4 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 2 H, J = 7.7 Hz, J = 16.1 Hz), 4.8 (dd, 2 H, J = 0.9 Hz, J = 7.8 Hz), 4.3 (m, 2 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 2.1 (s, 3 H). Tosylation in the usual manner[11] furnished a yellow mixture. Column chromatography and pooling of the fractions with NMR spectra consistent with the desired (s near 2.3 ppm) product provided the desired product in about 70% yield. However attempts to obtain this tosylate in chromatographically homogeneous form failed, and thus **8a** could not be completely characterized.

When subjected to 2.2 equiv of CH_3ONa in a THF-CH_3OH mixture at room temperature for 2 h, **8a** provided the epoxide **9a** as a yellow semisolid in about 80% crude yield. The latter was chromatographically nonhomogeneous and thus was not completely characterized.

The conversion **9a** to **10a** involved reaction with 1.5 equiv of Superhydride in THF at 5-7 °C for 48 h. The last step proceeded in about 50% yield after column chromatography (2:1 hexane-ethyl acetate). Semisolid. IR: 3300, 1750 cm^{-1}. NMR: δ 7.3-7.1 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 7.8 Hz, J = 16.0 Hz), 4.8 (dd, 1 H, J = 0.6, J = 7.8 Hz), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.64 (s, 3 H), 1.35-1.32 (d, 3 H, J = 6.4 Hz).

7c, a yellow oil, was prepared in 85% yield from **2c** by inverse addition to excess acetoxyacetyl chloride as above. IR: 1750, 1740 cm^{-1}. MS: 423 (M^+, 1.8), 322 (M^+ - 3.1), 250 (imine$^+$ - 1, 9.3), 84 (M^+ - 339, 100). NMR: δ 7.4 (m, 7 H), 6.8 (dd, 2 H, J = 2.2 Hz, J = 6.8 Hz), 6.6 (s, 1 H), 5.3 (d, 1 H, J = 7.9 Hz), 4.9 (s, 1 H), 4.8 (d, 1 H, J = 7.9 Hz), 3.7 (s, 3 H), 2.1 (s, 3 H), 1.9 (d, 3 H, J = 1.2 Hz). In converting this compound to the corresponding tosylate and the epoxide problems similar to the case of the simple cinnamyl compound were encountered. The opening of this epoxide to the secondary alcohol involved reaction with Superhydride in THF at 5-7 °C for 48 h. The reaction proceeded in about 50% yield.

10c, a semi-solid, had IR and mass spectra similar to that of the diastereoisomer A. NMR: δ 7.4-7.2 (m, 7 H), 6.8 (dd, 2 H, J = 2.0 Hz, J = 8.9 Hz), 6.4 (br s, 1 H), 4.6 (s, 1 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 1.9 (s, 3 H), 1.37 (d, 3 H, J = 6.4 Hz).

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(18) Details of data collection and structure solution are as follows. The diffraction intensities of a 0.03 × 0.30 × 0.30 mm crystal were collected at 295 K with graphite monochromatized Mo Kα radiation using $\theta/2\theta$ scan technique with profile analysis[19] to a $2\theta_{max}$ = 45° on an Euraf Nonius CAD-4 diffractometer. A total of 1815 unique reflections were measured of which only 794 were considered significant ($I_{net} > 2.5\sigma(I_{net})$). The normal Lorentz and polarization corrections were applied, but no absorption corrections made because of the small value of μ. Cell parameters were obtained by least-square treatment of the setting angles of 15 reflections with 26.0 < 2θ < 28.0°. The structure was solved by direct methods using the NRCVAX[20] system of programs and refined by full matrix least-squares to a final residuals of R_f and R_w of 0.095 and 0.102, respectively ($R_f = \Sigma(F_v - F_c)/\Sigma(F_v)$; $R_w = \Sigma w(F_v - F_c)^2/\Sigma(wF_v)^2$). The least-squares cycle was calculated with 33 atoms, 137 parameters, and 787 reflections. The relatively high residuals are probably due to the small size and poor quality of the crystals. The final difference map showed no peaks greater than 0.37 e Å^{-3}. Because of this only the Si atom was refined anisotropically and no attempt was made to locate the H atoms. The compound has a molecular weight of 462 and belongs to monoclinic group with P_{21}; a = 6.349 (3), b = 19.936 (8), and c = 10.6967 (20) Å; β = 99.39 (5)°; V = 1335.7 Å^{-3}; ρ_c = 1.148 mg m^{-3}; $Z = 2\Lambda$ = 0.70930 Å.

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Synthesis of Prostaglandins by Conjugate Addition and Alkylation of a Directed Enolate Ion. 4,5-Allenyl Prostaglandins[1]

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Over the previous two decades many elegant syntheses of prostaglandins, which in the more sophisticated forms, allow the stereospecific introduction of the various asymmetric carbons have been accomplished. However, among these approaches the cuprate addition/enolate alkylation of a suitable cyclopentenone[2] stands out because of brevity and convergence. The recent reports by Noyori[3] and Corey[4] and their colleagues have reduced to practice the conversion of 4-alkoxycyclopentenones to prostaglandin E_2 (PGE_2) by conjugate addition of an organocopper derivative of the lower side chain followed by alkylation of the resulting carbanion with methyl 7-halohept-2-enoate.[5]

(1) Contribution No. 772 from the Institute of Organic Chemistry.

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