The Synthesis of Novel Antitumor Antibiotics Structurally Related to the Anthracyclinones

Pat N. Confalone*,[1a] and Giacomo Pizzolato

Chemical Research Department, Natural Products Chemistry, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110-1199

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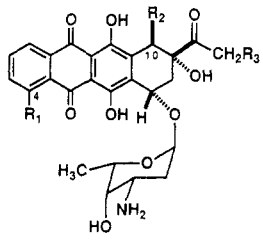
A practical synthesis of C(10)-functionalized derivatives of the anthracycline class of antitumor antibiotics is described. An efficient preparation of the tetracyclic epoxide **13** from the diquinone **8** and butadiene **9** yields a key intermediate for the stereospecific synthesis of the 7-deoxy aglycons **14a–20a**. The required cis-C(7)-hydroxy functionality is introduced stereospecifically to afford the aglycons **14b–20b**. Finally, a high-yield coupling reaction to the daunosamine derivative **25** serves to both resolve the racemic aglycons and afford the targeted optically active anthracyclines **30** and **31**.

Introduction

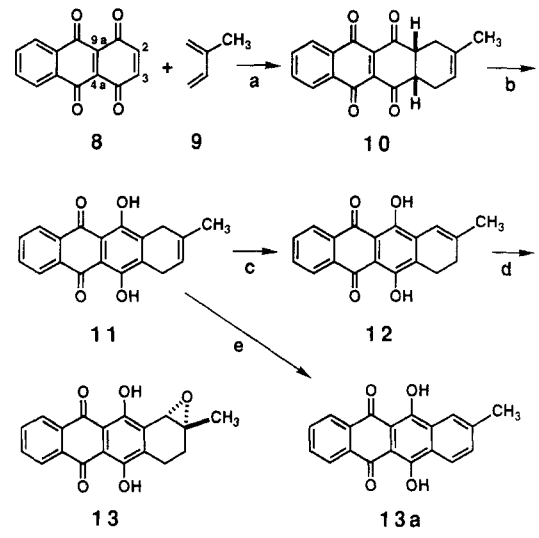
Daunorubicin (daunomycin) (**1**) and doxorubicin (adriamycin) (**2**) are two clinically efficacious anticancer compounds which exhibit activity against a wide spectrum of human tumors.[1b] The well-documented cumulative dose-dependent cardiotoxicity[2] of these agents has motivated several efforts[3] to synthesize analogous compounds devoid of this dose-limiting liability.



1 R_1 = OCH_3, R_2 = R_3 = H
2 R_1 = OCH_3, R_2 = H, R_3 = OH
3 R_1 = R_2 = R_3 = H
4 R_1 = R_2 = H, R_3 = OH
5 R_1 = R_2 = OCH_3, R_3 = OH

Reports[4] of an increase in antitumor activity for the C(4)-desmethoxy derivatives **3** and **4** vs the parent compounds **1** and **2**, respectively, coupled with the disclosure of important anticancer properties attributed to the C-(10)-substituted adriamycin **5**,[5] prompted us to target the general structure **6** for chemical synthesis and biological evaluation.

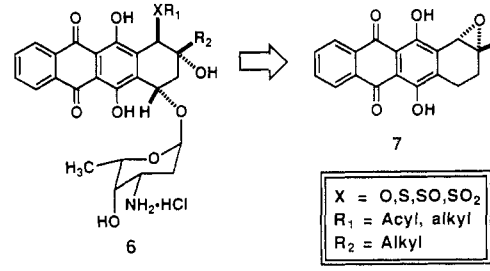
Scheme I[a]



[a] (a) Isoprene, toluene, 50 °C, 2.25 h; (b) NaOAc, AcOH, reflux, 2 min; (c) concentrated H_2SO_4, 0 °C, 2 min; (d) MCPBA, $NaHCO_3$, CH_2Cl_2, 25 °C, 3 h; (e) concentrated H_2SO_4, 0 °C, 15 min.

Results and Discussion

Retrosynthetic analysis indicated that the epoxides **7** are key intermediates. An efficient synthesis of a subset (R_2 = CH_3) of the class of compounds represented by **6** is presented in Scheme I.



X = O,S,SO,SO_2
R_1 = Acyl, alkyl
R_2 = Alkyl

The well-established[6] tendency of 2-substituted butadienes to add preferentially to the internal 4a-9a double bond of the diquinone **8**[7] has forced various measures

(1) (a) Present address: E. I. du Pont de Nemours & Co., Inc., Medical Products Department, Wilmington, DE 19880-0353. (b) For leading references, see: Fujioka, H.; Yamamoto, H.; Kondo, H.; Annoura, H.; Kita, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1509. See also: Carter, S. K. *J. Natl. Cancer Inst.* **1975**, *55*, 1265–74. Di Marco, A.; Arcamone, F.; Zunino, F. In *Antibiotics*; Corcoran, J. W., Hahn, F. E., Eds.; Springer Verlag: New York, 1975; Vol. III, pp 101–128. Arcamone, F. *Lloydia* **1977**, *40*, 45–66.

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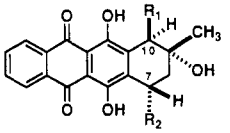
designed to overcome this chemoselectivity problem. For example, a synthesis of the tetracyclic compound **11** required "protection" of the 4a–9a olefin moiety of **8** as its corresponding epoxide.[8]

We have found a direct, preparatively useful synthesis of the tetracyclic olefin **11** which relies upon a judicious choice of reaction conditions to yield directly the Diels–Alder adduct **10**, the product of the desired reaction across the 2–3 double bond of **8**. This compound separates from the reaction mixture free of all byproduct impurities and is easily isolated by filtration. Conversion of the diketo tautomer **10** to the stable, red-orange dihydroxydihydronaphthacenedione **11** is achieved in quantitative yield upon brief exposure to sodium acetate in hot acetic acid. Dissolution of **11** in concentrated sulfuric acid for 2 min affords migration of the double bond into conjugation with the anthraquinone nucleus to yield the desired dark amber olefin **12**. Prolonged exposure of **11** to the reaction conditions must be avoided or the fully aromatized naphthacenedione **13a** is obtained, a result of the oxidizing power of sulfuric acid. Epoxidation of **12** yields the targeted red epoxide **13**, mp 214–215 °C.[9]

Conversion of the epoxide **13** to various mycins of general structure **6** ($R_2 = CH_3$) is accomplished in a stereospecific fashion. Ring opening of **13** with various nucleophiles under a variety of conditions, affords the desired 7-deoxy aglycons **14a–18a**. The stereochemistry of this

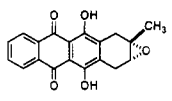


"a" Series: R_2 = H
"b" Series: R_2 = OH

14	R_1 = OAc
15	R_1 = SEt
16	R_1 = OCH_3
17	R_1 = SAc
18	R_1 = Cl
19	R_1 = SOEt
20	R_1 = SO_2Et

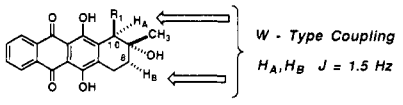
series was assigned by NMR decoupling experiments[10a] and is analogous to Kende's findings in a related case investigated in his synthesis of β-rhodomycinone.[10b] In our example, solvolysis of the epoxide **13** in 3% sodium acetate/acetic acid at 90 °C affords the acetate **14a**.[11] The thioether **15a** is readily generated from **13** by treatment with ethanethiol in methylene chloride at 25 °C in the presence of *p*-toluenesulfonic acid. The same acid catalyst yields the methoxy analogue **16a** when the epoxide **13** is

(7) Dimroth, O.; Hilcken, V. *Ber.* **1921**, *54*, 3050.
(8) Chandler, M.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1978**, 997–8.
(9) Epoxidation of the deconjugated olefin **11** yielded the isomeric epoxide **13b**, mp 268–269 °C. This result was very useful in studying the actual migration of the double bond in the conversion of **11** into **12** since their corresponding epoxides were readily separated by TLC (CH_2Cl_2/acetone, 95:5), unlike the olefins themselves which resisted all attempts at separation.



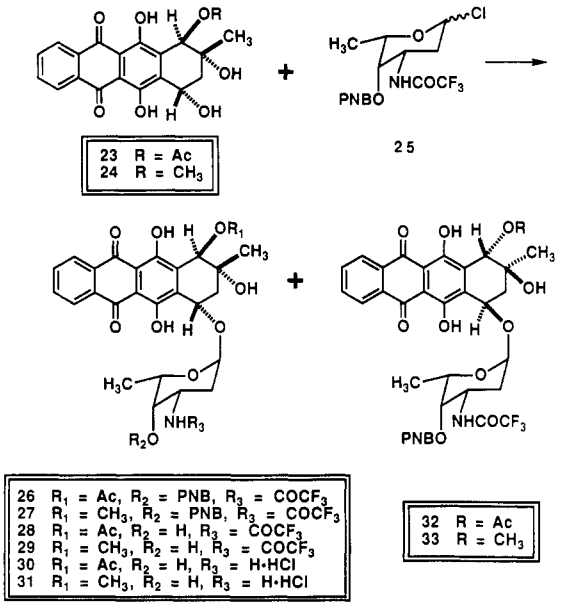
13b

(10) (a) Even with strong acid catalysis, the epoxide **13** predominantly undergoes trans-diaxial ring opening. The products were assigned the trans stereochemistry based upon NMR decoupling experiments which revealed a J = 1.50 Hz W-type long-range coupling attributable to a 1,3-diequatorial relationship between the benzylic hydrogen (H_A) attached to C(10) and the equatorial hydrogen (H_B) attached to C(8).



(b) Kende, A. S.; Tsay, Y.-G. *J. Chem. Soc., Chem. Commun.* **1977**, 140.
(11) In the absence of sodium acetate significant amounts of the cis isomer were obtained.

Scheme II



23	R = Ac
24	R = CH_3

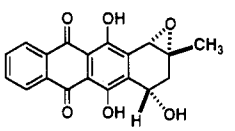
25

26	R_1 = Ac, R_2 = PNB, R_3 = $COCF_3$
27	R_1 = CH_3, R_2 = PNB, R_3 = $COCF_3$
28	R_1 = Ac, R_2 = H, R_3 = $COCF_3$
29	R_1 = CH_3, R_2 = H, R_3 = $COCF_3$
30	R_1 = Ac, R_2 = H, R_3 = H·HCl
31	R_1 = CH_3, R_2 = H, R_3 = H·HCl

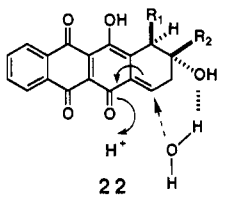
32	R = Ac
33	R = CH_3

briefly heated under reflux in methanol. The thioester **17a** is formed at 60 °C in toluene in the presence of sodium acetate and an excess of thioacetic acid. Interestingly, the preparation of the chloro derivative **18a** leads to the simultaneous production of its C(10)-epimer as well. This mixture of stereoisomers is obtained by treating **13** with 1 N HCl in tetrahydrofuran at room temperature. Separation of the epimers was not attempted since the target chloro aglycon **18b** is stereospecifically prepared by another route (see later).

Oxidation of these 7-deoxy aglycons (**a** series) to the aglycons themselves (**b** series) is easily accomplished by the methodology developed in our total synthesis of aklavinone.[12] Specifically, allylic bromination of the 7-deoxy aglycons **14a–17a** with NBS in aqueous carbon tetrachloride in the presence of AIBN yields the desired aglycons **14b–17b** via introduction of the required C(7)-hydroxy group in a stereospecific fashion. Interestingly, the mixture of chloro derivatives **18a** and its C(10)-epimer fails to react under these oxidative conditions. However, the desired chloro aglycon **18b** is prepared by an initial oxidation of the epoxide **13** itself to afford the novel epoxy aglycon **21**, whose structure was assigned by X-ray crystallography. This reaction also proved to be stereospecific, a result not easily predicted since the substrate **13** lacks both a bulky C(10) β-substituent as well as the C(9)-alcohol believed to aid in "directing" the hydrolysis of an intermediate enone such as **22**.[12]



21



22

The epoxy aglycon **21** readily undergoes a selective solvolysis of the oxirane moiety with 1 N HCl in tetrahydrofuran at 25 °C to afford the desired chloro analogue **18b** in excellent yield, uncontaminated by its C(10) α-epimer. Peroxidation of the sulfide **15a** with MCBPA yields the corresponding sulfoxide **19a** or the sulfone **20a** if either

(12) Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* **1981**, *103*, 4251.

1 or 2 equiv of peracid is employed. Although the 7-deoxy sulfoxide **19a** fails to undergo a smooth C(7) oxidation, the corresponding aglycon **19b** is readily prepared by peroxidation of the sulfido aglycon **15b** with 1 equiv of MCBPA. The sulfone **20a**, on the other hand, is readily converted to its aglycon **20b** under the standard conditions.[13]

The utility of these novel aglycons, unavailable from natural sources, for the synthesis of potential antitumor antibiotics structurally related to adriamycin is exemplified in Scheme II. In the examples shown, the aglycons **23** and **24** are coupled to the protected chlorodaunosamine **25**[14] using the method of Arcamone[15] to yield directly the protected mycins **26** and **27**. Since this coupling employs racemic aglycons and an optically active sugar, the resulting diastereomeric mycins **32** and **33** are also produced and are easily separated by chromatography. Fortunately, the coupling procedure provides only the desired α-anomers, thereby providing an easy "resolution" of the racemic aglycons. Mild basic hydrolysis with aqueous triethylamine readily cleaves the *O*-PNB ester of **26** and **27** to yield the *N*-trifluoroacetamido alcohols **28** and **29**, respectively. These substances are important targets for biological testing as well, since the corresponding *N*-trifluoroacetamido derivative of adriamycin is known to be less cardiotoxic. Alternatively, removal of both protecting groups from **26** and **27** can be achieved using more basic conditions (0.1 N NaOH, THF, 0 °C) and yields the free mycins **30** and **31**, respectively, isolated as their hydrochlorides.

Conclusion

In summary, we have developed a practical synthesis of several novel aglycons related to adriamycinone. These readily available compounds are coupled to daunosamine, a process which smoothly effects resolution of the racemic aglycons and affords the target mycin analogues. Stepwise deprotection yields the desired optically active adriamycin derivatives in excellent overall yields.

Experimental Section

Melting points are uncorrected. NMR spectra were determined at 60 or 100 MHz. Mass spectra were recorded at 70 eV using a direct insertion probe. Thin-layer chromatography was carried out by using Merck F-254 silica gel plates.

7,10-Dihydro-6,11-dihydroxy-8-methyl-5,12-naphthacenedione (11). A solution of 96.8 g (0.407 mol) of the diquinone 8[7] in 1 L of toluene was treated with 450 mL of isoprene (**9**). The mixture was heated at 50 °C for 2.25 h (mechanical stirring) and cooled. The adduct **10**, which separated exclusively, was filtered and washed well with ether to yield 44.6 g (36%) of pure diketone **10**. This was dissolved in 460 mL of acetic acid at reflux and treated with 27.4 g of sodium acetate (anhydrous). After ca. 2 min at reflux, the product **11** began to separate as a bright red precipitate. The reaction was removed from the oil bath, and when the temperature reached 90 °C, it was diluted with 450 mL of water and set aside to crystallize. The mixture was further diluted at 25 °C with 1 L of water, and the tetracyclic olefin **11** was filtered off, washed well with water followed by ether. After air drying, 42.0 g (34%) of the product **11** was obtained pure and was used as such in the next step. Recrystallization from chloroform afforded an analytical sample: mp 278–279 °C (lit.[8] mp 287–288 °C); IR (KBr) 1630, 1590, 1425, 1250 cm^{-1}; UV (CH_3OH) 226 (ϵ 16100), 258 (40800), 481 (11500), 514 nm (7900); NMR ($CDCl_3$ + DMSO) δ 13.48 (s, 1 H), 13.46 (s, 1 H), 8.33 (m, 2 H), 7.85 (m, 2 H), 5.6 (br s, 1 H), 3.5–3.2 (m, 4 H), 1.85 (br s, 3 H); mass spectrum *m/e* 306 (M^+, base), 291, 288, 277, 273.

Anal. Calcd for $C_{19}H_{14}NO_4$ (306.32): C, 74.50; H, 4.61. Found: C, 74.55; H, 4.61.

9,10-Dihydro-6,11-dihydroxy-8-methyl-5,12-naphthacenedione (12). In a 1-L, three-necked flask, 360 mL of concentrated sulfuric acid was cooled in an ice bath for 15 min and treated with 42.0 g (0.137 mol) of the olefin **11** (mechanical stirring) in one portion. The deep purple solution was stirred vigorously for 2 min and immediately poured into 4 L of ice–water. The bright red-amber conjugated olefin **12** was filtered off, washed well with 3 L of water, and finally, methanol. The product was pure enough for use in the next step and was obtained as 34.0 g (81%) of a dark red solid. For analysis, a sample was recrystallized from ethyl acetate to afford amber needles: mp 250–251 °C; IR (KBr) 1620, 1580, 1400, 1265 cm^{-1}; UV (CH_3OH) 209 (ϵ 33000), 273 (46900), 502 nm (17800); NMR ($CDCl_3$) δ 13.5 (s, 2 H), 8.37 (m, 2 H), 7.79 (m, 2 H), 6.76 (m, 1 H), 2.96 (t, 2 H, J = 8.0 Hz), 2.34 (br, 2 H), 2.04 (d, 3 H, J = 1.0 Hz); mass spectrum, *m/e* 306 (M^+, base), 304, 291, 288.

Anal. Calcd for $C_{19}H_{14}NO_4$ (306.32): C, 74.50; H, 4.61. Found: C, 74.53; H, 4.41.

1a,2,3,11b-Tetrahydro-4,11-dihydroxy-1a-methylnaphthaceno[1,2-*b*]oxirene-5,10-dione (13). To a suspension of 34.0 g (0.111 mol) of the conjugated olefin **12** in 375 mL of anhydrous methylene chloride at room temperature were added 50 g of sodium bicarbonate (anhydrous) and 22.5 g (0.111 mol) of metachloroperbonzoic acid (85%) in one portion. The mixture was stirred mechanically for 2 h, at which point an additional 2.0 g of the peroxidizing agent was added. The reaction was worked up after an additional hour by filtering the solids and washing once with water followed by methylene chloride. The solids were then partitioned between methylene chloride/water. The aqueous phase was further extracted with methylene chloride. The organic extracts were combined with the organic phase from the filtrate. The aqueous layer in the filtrate was also extracted an additional time. All organic phases were then washed twice with water, dried (Na_2SO_4), combined, and evaporated to yield 37.0 g (99%) of pure tetracyclic epoxide **13** as a red solid: mp 214–215 °C (ethyl acetate); IR (KBr) 1630, 1590, 1405, 1265 cm^{-1}; NMR ($CDCl_3$) δ 13.51 (s, 1 H), 13.35 (s, H), 8.36 (m, 2 H), 7.83 (m, 2 H), 4.35 (s, 1 H), 3.2–1.8 (m, 4 H), 1.61 (s, 3 H); mass spectrum, *m/e* 322 (M^+), 306, 304, 294 (base).

Anal. Calcd for $C_{19}H_{14}O_5$ (322.32): C, 70.80; H, 4.38. Found: C, 70.97; H, 4.19.

7β-(Acetyloxy)-7,8,9,10-tetrahydro-6,8α,11-trihydroxy-8-methyl-5,12-naphthacenedione (14a). A solution of 5.0 g (15.53 mmol) of the epoxide **13** in 190 mL of acetic acid in which 5.825 g (71.0 mmol) of sodium acetate had been dissolved was heated at 90 °C for 4 h under argon. The reaction was cooled to about 15 °C, and 3.2 g of the acetate **14a**, which had crystallized out, was filtered off and washed well with water, followed by methylene chloride. From the filtrate an additional 1.08 g of pure product was obtained by extraction. The total yield of **14a** was 4.28 g (73%) and was pure as such for the next step. For analysis, a sample was recrystallized from chloroform/pentane to give a red-orange solid: mp 254–255 °C; IR (KBr) 3465, 1730, 1630, 1580, 1410, 1370, 1240 cm^{-1}; UV (CH_3OH) 252 (ϵ 43000), 287 (9700), 482 (10850), 514 nm (7250); NMR ($CDCl_3$) δ 13.44 (s, 1 H), 13.38 (s, 1 H), 8.35 (m, 2 H), 7.80 (m, 2 H), 6.15 (s, 1 H), 3.00 (t, 2 H, J = 6.0 Hz), 2.08 (s, 3 H), 1.93 (m, 2 H), 1.5 (br s, 1 H), 1.41 (s, 3 H); mass spectrum, *m/e* 382 (M^+), 340, 322 (base), 304, 294.

Anal. Calcd for $C_{21}H_{18}O_7$ (382.37): C, 65.97; H, 4.75. Found: C, 65.88; H, 4.91.

7β-(Ethylthio)-7,8,9,10-tetrahydro-6,8α,11-trihydroxy-8-methyl-5,12-naphthacenedione (15a). To a suspension of 0.5 g (1.55 mmol) of the epoxide **13** in 5 mL of methylene chloride were added 5 mL of ethyl mercaptan and 0.05 g of *p*-toluenesulfonic acid hydrate. The mixture was stirred for 18 h at 25 °C, and the volatiles were then evaporated. The residue was partitioned between methylene chloride/10% sodium bicarbonate. The organic extracts afforded a crude residue of 0.6 g, which was chromatographed over 150 g of silica gel, eluting with CH_2Cl_2/acetone, 95:5. Fractions containing pure sulfido alcohol **15a** (R_f = 0.5) were combined and evaporated to yield 0.365 g (61%) of pure product as red needles: mp 196–197 °C (ethyl acetate/

(13) Alternatively, the sulfonyl aglycon **20b** was obtained in excellent yield by treating the sulfide **15b** with 2 equiv of MCPBA.

(14) Smith, T. H.; Fumiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653.

(15) Arcamone, F.; Bernardi, L.; Patelli, B.; Giardino, P.; Di Marco, A.; Casazza, A. A., Soranzo, C.; Pratesi, G. *Experientia* **1978**, *34*, 1255–7.

hexane); IR (KBr) 3510, 1620, 1580, 1400, 1250 cm^{-1}; UV (CH_3OH) 204 (ε 31570), 251 (37940), 486 (12480), 520 (9560), 660 nm (1920); NMR ($CDCl_3$) δ 13.76 (s, 1 H), 13.47 (s, 1 H), 8.35 (m, 2 H), 7.82 (m, 2 H), 4.02 (d, 1 H, J = 1.0 Hz), 3.1–2.8 (m, 4 H), 2.4–1.8 (m, 2 H), 1.66 (s, 3 H), 1.5 (br s, 1 H), 1.32 (t, 3 H, J = 7.0 Hz); mass spectrum, m/e 384 (M^+), 320, 304, 275 (base).

Anal. Calcd for $C_{21}H_{20}O_5S$ (384.45): C, 65.61; H, 5.24; S, 8.34. Found: C, 65.68; H, 5.28; S, 8.25.

7β-Methoxy-7,8,9,10-tetrahydro-6,8α,11-trihydroxy-8-methyl-5,12-naphthacenedione (16a). A suspension of 6.8 g (21.12 mmol) of the epoxide **13** in 1 L of absolute methanol was treated with 1.0 g of *p*-toluenesulfonic acid hydrate and heated under reflux for 0.75 h. The reaction was cooled to 25 °C; the product was filtered off and washed with methanol. The filtrate was evaporated, and the residue was triturated with ether. The insoluble solid was filtered off and combined with the first crop. The product was washed thoroughly with ether and dried to yield 6.0 g (60%) of pure methoxy alcohol **16a**: mp 237–238 °C (ethyl acetate); IR (KBr) 3470, 3390, 1630, 1580, 1410, 1250 cm^{-1}; UV (CH_3OH) 204 (ε 28010), 252 (44580), 288 (8510), 484 (11140), 517 (7630), 563 nm (760); NMR ($CDCl_3$) δ 13.69 (s, 1 H), 13.40 (s, 1 H), 8.34 (m, 2 H), 7.80 (m, 2 H), 4.33 (d, 1 H, J = 1.0 Hz), 3.67 (s, 3 H), 2.90 (m, 2 H), 2.0 (m, 2 H), 1.50 (s, 3 H), 1.3 (br s, 1 H); mass spectrum, m/e 354 (M^+), 346, 296 + 279 (base), 187.

Anal. Calcd for $C_{20}H_{18}O_6$ (354.36): C, 67.79; H, 5.12. Found: C, 67.90; H, 5.30.

7β-(Acetylthio)-7,8,9,10-tetrahydro-6,8α,11-trihydroxy-8-methyl-5,12-naphthacenedione (17a). To 25 mL of thioacetic acid pretreated with 0.75 g of sodium acetate (anhydrous) was added 5.0 g (15.53 mmol) of the epoxide **13** followed by 25 mL of dry toluene. The mixture was heated at 60 °C for 3 h, cooled, and poured into water. The mixture was filtered, and the solid poduct was washed thoroughly with ether and dried to afford 6.5 g of crude product. After recrystallization from chloroform, 3.64 g (59%) of pure thiol ester **17a**, mp 231–232 °C, was obtained: IR (KBr) 3450, 1685, 1625, 1595, 1410, 1150 cm^{-1}; UV (CH_3OH) 206 (ε 27450), 258 (48700), 292 (8600), 485 (11500), 518 (8200), 564 nm (1300); NMR ($CDCl_3$) δ 13.49 (s, 1 H), 13.41 (s, 1 H), 8.30 (m, 2 H), 7.78 (m, 2 H), 5.05 (br d, 1 H, J = 2.0 Hz), 3.1–2.8 (m, 2 H), 2.40 (s, 3 H), 1.8 (m, 2 H), 1.68 (br s, 1 H), 1.55 (s, 3 H); mass spectrum, m/e 398 (M^+), 380, 356, 348, 279 (base), 187.

Anal. Calcd for $C_{21}H_{18}O_6S$ (398.43): C, 63.31; H, 4.55; S, 8.05. Found: C, 63.25; H, 4.65; S, 7.85.

7β-Chloro-7,8,9,10-tetrahydro-6,8α,11-trihydroxy-8-methyl-5,12-naphthacenedione (18a). A suspension of 1.0 g (3.11 mmol) of the epoxide **13** in 50 mL of tetrahydrofuran was treated with 35 mL of 1 N HCl and stirred at 25 °C for 3 h. The reaction was partitioned between 1 N HCl and methylene chloride, and 1.2 g of crude product was obtained from the organic extracts. The residue was chromatographed over 300 g of silica gel, eluting with methylene chloride/acetone, 95:5. Fractions containing the chloro alcohol **18a** (R_f = 0.25) were combined and evaporated to yield 0.65 g (60%) of pure **18a** as a red-orange solid: mp 200–202 °C (ethyl acetate/hexane); IR (KBr) 3550, 1620, 1590, 1410, 1255 cm^{-1}; UV (CH_3OH) 205 (ε 24500), 252 (43100), 288 (8500), 482 (10700), 516 (6630); NMR ($CDCl_3$) δ 13.65 (s, 1 H), 13.38 (s, 1 H), 13.34 (s, 1 H), 8.34 (m, 2 H), 7.74 (m, 2 H), 5.34 (s, 1 H), 5.08 (s, 1 H), 3.2–2.5 (m, 2 H), 2.4–2.2 (m, 1 H), 1.8 (m, 1 H), 1.66 (s, 1.5 H), 1.5 (d, 1 H, J = 6.0 Hz), 1.31 (s, 1.5 H); mass spectrum, m/e 358, 340, 322, 300, 294, 279 (base).

Anal. Calcd for $C_{19}H_{15}ClO_4$ (358.78): C, 63.61; H, 4.21; Cl, 9.88. Found: C, 63.30; H, 4.15; Cl, 10.00.

7β-(Ethylsulfinyl)-7,8,9,10-tetrahydro-6,8α,11-trihydroxy-8-methyl-5,12-naphthacenedione (19a). A solution of 77 mg (0.2 mmol) of the sulfido alcohol **15a** in 5 mL of anhydrous methylene chloride was treated with 41 mg (0.2 mmol) of *m*-chloroperbenzoic acid. The reaction was allowed to proceed at 25 °C for 0.5 h and was then partitioned between 10% sodium bicarbonate/methylene chloride. The aqueous phase was extracted four times with methylene chloride. The organic phases were combined, dried (Na_2SO_4), and evaporated to yield 80 mg of residue. This was chromatographed on two thick-layer silica plates, eluting with methylene chloride/acetone, 95:5. The product was isolated at R_f = 0.21 as an amorphous red-orange solid: IR (KBr) 3340, 1630, 1400, 1250, 1015 cm^{-1}; UV (CH_3OH) 206 (ε 28970), 226 (19190), 258 (45400), 487 (10810), 520 (8380), 565 nm (2700); NMR ($CDCl_3$) δ 13.83 (s, 1 H), 13.35 (s, 1 H), 8.40 (m, 2 H), 7.85 (m, 2 H), 4.56 (d, 1 H, J = 3.0 Hz), 3.3–2.8 (m, 4 H), 2.5–1.8 (m, 2 H), 1.7 (br s, 1 H), 1.59 (s, 3 H), 1.4 (t, 3 H); mass spectrum, m/e 384, 382, 366, 323, 304 (base).

7β-(Ethylsulfonyl)-7,8,9,10-tetrahydro-6,8α,11-trihydroxy-8-methyl-5,12-naphthacenedione (20a). A suspension of 0.96 g (2.5 mmol) of the sulfido alcohol **15a** in 25 mL of anhydrous methylene chloride was treated with 1.015 g (5.0 mmol) of *m*-chloroperbenzoic acid and stirred at 25 °C for 1 h. The reaction mixture was partitioned between 10% sodium carbonate and methylene chloride. The residue from the organic extracts was chromatographed over 250 g of silica gel, eluting with methylene chloride/acetone, 95:5. Fractions containing the product were combined and evaporated to afford 0.65 g (63%) of pure sulfonyl alcohol **20a**: mp 219–220 °C dec (ethyl acetate/pentane); IR (KBr) 3460, 1625, 1585, 1303, 1120 cm^{-1}; UV (CH_3OH) 205 (ε 24410), 257 (37500), 290 (7070), 485 (8560), 517 (6150), 565 nm (1770); NMR ($CDCl_3$) δ 13.88 (s, 1 H), 13.32 (s, 1 H), 8.36 (m, 2 H), 7.85 (m, 2 H), 4.88 (d, 1 H, J = 3.0 Hz), 3.5–3 (m, 4 H), 2.9–2.0 (m, 2 H), 1.87 (s, 3 H), 1.6 (br s, 1 H), 1.41 (t, 3 H); mass spectrum, m/e 416 (M^+), 384, 366, 322, 297, 279.

Anal. Calcd for $C_{21}H_{20}O_7S$ (416.44): C, 60.57; H, 4.84; S, 7.70. Found: C, 60.61; H, 5.16; S, 7.65.

1a,2,3,11b-Tetrahydro-3,4,11-trihydroxy-1a-methylnaphthaceno[1,2-*b*]oxirene-5,10-dione (21). A suspension of 1.30 g (4.037 mmol) of the epoxide **13** in 1 L of carbon tetrachloride was heated to effect solution. This was treated with 3.0 mL of water, 1.20 g (6.74 mmol) of *N*-bromosuccinimide, and 0.2 g of 2,2′-azobis(2-methylpropionitrile), catalyst. The reaction was heated under reflux for 2 h, cooled, and partitioned between water and methylene chloride. The organic extracts afforded a residue, which was chromatographed over 300 g of silica gel, eluting with methylene chloride/acetone, 95:5. Fractions containing the epoxy aglycon **21** (R_f = 0.3) were combined and evaporated to afford 0.70 g (51%) of product as a red-orange solid: mp 216–217 °C (ethyl acetate); IR (KBr) 3515, 1620, 1580, 1250, 1000 cm^{-1}; UV (CH_3OH) 208 (ε 26750), 252 (39500), 258 (38600), 290 (7300), 489 (10000), 527–80 nm (1100); NMR ($CDCl_3$) δ 13.40 (s, 1 H), 13.32 (s, 1 H), 8.38 (m, 2 H), 7.85 (m, 2 H), 5.21 (m, 1 H), 4.54 (s, 1 H), 3.03 (d, 1 H, J = 12.0 Hz), 2.62 (m, 1 H), 1.98 (dd, 1 H, J = 16.0 and 6.0 Hz), 1.65 (s, 3 H); mass spectrum, m/e 338 (M^+), 320, 304, 280 (base).

Anal. Calcd for $C_{19}H_{14}O_6$ (338.32): C, 67.45; H, 4.17. Found: C, 67.32; H, 4.40.

General Procedure for the Stereospecific Introduction of the C(7)-Alcohol. The following procedure which describes the stereospecific conversion of the 10-acetoxy-7-deoxy aglycon **14a** into its corresponding aglycon **14b** is illustrative of the general method employed for the preparation of aglycons **15b–17b** and **20b**, whose physical properties are noted following the experimental details.

10β-Acetoxy-7,8,9,10-tetrahydro-6,7α,9α,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (14b). A suspension of 2.15 g (5.62 mmol) of the acetoxy alcohol **14a** in 2.25 L of carbon tetrachloride was stirred mechanically and heated under reflux for 0.5 h to effect dissolution. At 60 °C, 4.5 mL of water, 1.12 g (6.31 mmol) of N-bromosuccinimide, and 0.28 g of 2,2′-azobis(2-methylpropionitrile) were added sequentially. The reaction was heated under reflux for 0.75 h, at which point an additional 0.115 g of NBS was added, and the reaction allowed to proceed at that temperature for 0.25 h.

The mixture was cooled to 25 °C in an ice bath and diluted with 1.3 L of tetrahydrofuran and 1.4 L of 10% potassium carbonate. After 10 min, the mixture was partitioned between water (brought to pH 1 by 2 N HCl) and methylene chloride. The aqueous layer was extracted an additional time with methylene chloride. The organic extracts were combined, dried (Na_2SO_4), and evaporated. The residue was triturated with methylene chloride. The insoluble solid was filtered off, washed thoroughly with methylene chloride, and recrystallized from chloroform/methanol/hexane to afford 0.98 g (44%) of pure acetoxy aglycon **14b** as bright red needles: mp 255–256 °C; IR (KBr) 3460, 1733, 1625, 1585, 1240 cm^{-1}; UV (CH_3OH) 231 (ε 17800) 250 (28650), 285 (7220), 482 nm (7620); NMR (DMSO-d_6) δ 13.13 (s, 2 H), 8.15 (m, 2 H), 7.86 (m, 2 H), 6.07 (s, 1 H), 5.19 (s, 1 H), 5.08 (m, 2 H), 2.04 (s, 3 H), 2.01 (m, 2 H), 1.26 (s, 3 H); mass spectrum, m/e

398 (M^+), 380, 338, 320 (base), 280.

Anal. Calcd for $C_{21}H_{18}O_8$ (398.35): C, 56.38; H, 4.07. Found: C, 56.42; H, 3.92.

10β-(Ethylthio)-7,8,9,10-tetrahydro-6,7α,9α,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (15b). By the above procedure, **15a** was converted in 24% yield to the sulfido aglycon **15b**, obtained as an amorphous solid: IR (KBr) 3440, 1680, 1620, 1280 cm^{-1}; UV (CH_3OH) 204 (ε 19580), 252 (23400), 486 nm (7400); NMR ($CDCl_3$) δ 13.68 (s, 1 H), 13.60 (s, 1 H), 8.35 (m, 2 H), 7.85 (m, 2 H), 5.24 (br m, 1 H), 4.12 (d, 1 H, J = 3.0 Hz), 3.57 (s, 1 H), 3.47 (br d, 1 H, J = 6.0 Hz), 2.97 (q, 2 H, J = 8.0 Hz), 2.43 (m, 1 H), 2.13 (m, 1 H), 1.65 (s, 3 H), 1.32 (t, 3 h, J = 8.0 Hz); mass spectrum, m/e 400 (M^+), 382, 353, 348, 304 (base).

10β-Methoxy-7,8,9,10-tetrahydro-6,7α,9α,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (16b). Similarly, **16a** was converted in 51% yield to the methoxy aglycon **16b**, obtained as a red-orange solid: mp 215–217 °C (ethyl acetate); IR (KBr) 3560, 3430, 1695, 1628, 1100 cm^{-1}; UV (CH_3OH) 205 (ε 29660), 252 (41760), 287 (8940), 486 (10750), 518 (6990), 568 nm (1000); NMR ($CDCl_3$) δ 13.55 (s, 1 H), 13.50 (s, 1 H), 8.35 (m, 2 H), 7.85 (m, 2 H), 5.23 (br m, 1 H), 4.40 (d, 1 H, J = 1.0 Hz), 3.70 (s, 3 H), 3.5 (m, 2 H), 2.5–2.0 (m, 2 H), 1.51 (s, 3 H); mass spectrum, m/e 370 (M^+), 352, 338, 334, 278 (base).

Anal. Calcd for $C_{20}H_{18}O_7$ (370.36): C, 64.86; H, 4.90. Found: C, 64.39; H, 4.99.

10β-(Acetylthio)-7,8,9,10-tetrahydro-6,7α,9α,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (17b). Similarly, **17a** was converted in 56% yield to the thioester aglycon **17b**, obtained as a red-orange solid: mp 256–257 °C dec (ethyl acetate); IR (KBr) 3580, 3520, 1700, 1625, 1585, 1370, 1260 cm^{-1}; UV (CH_3OH) 206 (ε 30080), 253 (46320), 257 (45050), 269 (9390), 487 (11450), 519 (7560), 570 nm (270); NMR ($CDCl_3$) δ 13.58 (s, 1 H), 13.34 (s, 1 H), 8.32 (m, 2 H), 7.81 (m, 2 H), 5.23 (m, 1 H), 5.18 (d, 1 H, J = 2.0 Hz), 3.66 (d, 1 H, J = 6 Hz), 3.47 (s, 1 H), 2.39 (s, 3 H), 2.29 (m, 2 H), 1.50 (s, 3 H).

Anal. Calcd for $C_{21}H_{18}O_7S$ (414.43): C, 60.86; H, 4.38; S, 7.74. Found: C, 61.10; H, 4.19; S, 7.75.

10β-(Ethylsulfonyl)-7,8,9,10-tetrahydro-6,7α,9α,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (20b). Similarly, **20a** was converted in 42% yield to the sulfonyl aglycon **20b**, obtained as a red solid: mp 215–216 °C (ethyl acetate); IR (KBr) 3480, 1628, 1300, 1130, 990 cm^{-1}; UV (CH_3OH) 206 (ε 20100), 252 (28200), 257 (27900), 290 (33100), 486 (7300), 570 nm (860); NMR ($CDCl_3$) δ 13.67 (s, 1 H), 13.56 (s, 1 H), 8.36 (m, 2 H), 7.86 (m, 2 H), 5.39 (m, 1 H), 4.94 (d, 1 H, J = 3.0 Hz), 3.76 (s, 1 H), 3.61 (m, 1 H), 3.26 (m, 2 H), 3.03 (m, 1 H), 2.23 (m, 1 H), 1.83 (s, 3 H), 0.96 (s, 3 H); mass spectrum, m/e 432 (M^+), 396, 348, 321 (base), 304, 293.

Anal. Calcd for $C_{21}H_{20}O_8S$ (432.44): C, 58.33; H, 4.66; S, 7.41. Found: C, 57.73; H, 4.75; S, 7.15.

10β-Chloro-7,8,9,10-tetrahydro-6,7α,9α,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (18b). A solution of 1.0 g (2.96 mmol) of the epoxy aglycon **21** in 80 mL of tetrahydrofuran was treated with 50 mL of 1 N HCl and stirred at 25 °C for 1.5 h. The reaction was partitioned between water and methylene chloride. The organic phases yielded a residue which was chromatographed over 200 g of silica gel, eluting with methylene chloride/acetone, 95:5. Fractions containing the chloro aglycon **18b** were combined and evaporated to yield 0.7 g (63%) of product as a red-orange solid: mp 218–219 °C (ethyl acetate); IR (KBr) 3420, 1627, 1585, 1400, 1235 cm^{-1}; UV (CH_3OH) 206 (ε 20200), 252 (31600), 287 (7420), 486 (8390), 518 (4620), 572 nm (620); NMR ($CDCl_3$) δ 13.51 (s, 1 H), 13.45 (s, 1 H), 8.36 (m, 2 H), 7.85 (m, 2 H), 5.32 (m, 1 H), 5.17 (d, 1 H, J = 2.0 Hz), 3.85 (s, 1 H), 3.47 (m, 1 H), 2.7–2.0 (m, 2 H) 1.61 (s, 3 H); mass spectrum, m/e 376, 374 (M^+), 358, 356, 338, 320 (base), 304.

Anal. Calcd for $C_{19}H_{15}ClO_6$ (374.787): C, 60.89; H, 4.34; Cl, 9.45. Found: C, 61.05; H, 4.10; Cl, 9.36.

10β-(Ethylsulfinyl)-7,8,9,10-tetrahydro-6,7α,9α,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (19b). To a solution of 120 mg (0.3 mmol) of the sulfido aglycon **15b** in 8 mL of anhydrous methylene chloride was added 60 mg (0.3 mmol) of *m*-chloroperbenzoic acid (85%) in one portion. The reaction was stirred 0.5 h at room temperature and was then partitioned between 10% sodium bicarbonate and methylene chloride. The residue from the organic extracts was chromatographed on two thick-layer silica plates, eluting twice with CH_2Cl_2/acetone, 9:1. The product was isolated at R_f = 0.2 and yielded 64 mg (51%) of pure sulfoxy aglycon **19b** as a red solid: mp 184–186 °C (ethyl acetate); IR (KBr) 3450, 3300, 1623, 1050 cm^{-1}; UV (CH_3OH) 207 (ε 28100), 226 (21000), 258 (39900), 285 (9200), 489 (10800), 522 (7500), 575 nm (2400); NMR ($CDCl_3$) δ 13.63 (s, 1 H), 13.54 (s, 1 H), 8.34 (m, 2 H), 7.84 (m, 2 H), 5.32 (m, 1 H), 4.63 (d, 1 H, J = 2.5 Hz), 3.82 (s, 1 H), 3.56 (br s, 1 H), 3.12 (m, 2 H), 2.7–2.1 (m, 2 H), 1.55 (s, 3 H), 1.38 (t, 3 H); mass spectrum, m/e 380, 362, 336, 320, 304 (base).

Anal. Calcd for $C_{21}H_{20}O_7S$ (416.44): C, 60.57; H, 4.84; S, 7.70. Found: C, 60.45; H, 4.69; S, 7.47.

(7*S*,9*R*,10*R*)-7-[[3-(Trifluoroacetamido)-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-10-acetoxy-9-methyl-5,12-naphthacenedione (28). A solution of 0.80 g (1.75 mmol) of racemic acetoxy aglycon **14b**, vigorously stirred under argon in 50 mL of dry dimethylformamide, was treated sequentially at 25 °C with 16.0 g, of powdered molecular sieves, 2.153 g (5.23 mmol) of the chloro sugar **25**[14] dissolved in 20 mL of dry methylene chloride, and 1.346 g of silver triflate in 10 mL of dry DMF. After 1.5 h the sieves were filtered and washed with 20 mL of ethyl acetate. The filtrate was partitioned between brine and ethyl acetate. The organic extracts afforded a residue which was chromatographed over 100 g of silica gel, eluting with methylene chloride/acetone, 96:4. Fractions containing the desired coupling product **26** (R_f = 0.5) were combined and evaporated to yield 0.54 g (80%) of pure **26** used directly in the next (deprotection) step. The diastereomer **32** could be isolated at R_f = 0.25 upon further elution.

To a suspension of 0.54 g (0.7 mmol) of **26** in 5 mL of methanol was added at 0 °C a mixture of 6 mL of $Et_3N/H_2O/CH_3OH$ (1:1:2). The reaction was stirred at 25 °C for 10 min, cooled again to 0 °C, and diluted with 20 mL of ice–water. Aqueous acetic acid was added dropwise to the solution until the color changed from purple to orange. The mixture was extracted with 60 mL of ethyl acetate, which was then washed with 2 × 50-mL portions of water. The organic layer was dried (Na_2SO_4) and evaporated to give a red residue, which was chromatographed over 20 g of silica gel, eluting with methylene chloride/acetone, 9:1. Fractions containing the acetoxy mycin **28** (R_f = 0.15) were combined and evaporated to yield 0.351 g (80%, based on **26**) of the product **28** as an orange solid: mp 173–174 °C (ethyl acetate/hexane); IR (KBr) 3500, 1760, 1723, 1630, 1590, 1230, 1010, 990 cm^{-1}; UV (CH_3OH) 203 (ε 30200), 233 (21200), 251 (36500), 286 (9200), 325 (2350), 472 (9500), 484 (9710), 573 (350); NMR ($CDCl_3$) δ 13.46 (s, 1 H), 13.27 (s, 1 H), 8.32 (m, 2 H), 7.82 (m, 2 H), 6.69 (br d, 1 H, J = 10 Hz), 6.30 (s, 1 H), 5.49 (br d, 1 H, J = 4.0 Hz), 5.18 (t, 1 H, J = 3.0 Hz), 4.31 (m, 2 H), 3.78 (s, 1 H), 3.65 (br d, 1 H, J = 7.0 Hz), 2.4–1.8 (m, 5 H), 2.05 (s, 3 H), 1.35 (s, 3 H), 1.32 (d, 3 H, J = 5.0 Hz); mass spectrum, m/e 623 (M^+), 398, 380, 338, 320; $[\alpha]^{25}_D$ = +141.41° (c = 0.099, CH_3OH).

Anal. Calcd for $C_{29}H_{28}F_3NO_{11}$ (623.53): C, 55.86; H, 4.53; N, 2.25; F, 9.14. Found: C, 55.03; H, 4.41; N, 2.19; F, 9.18.

(7*S*,9*R*,10*R*)-7-[(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-10-methoxy-9-methyl-5,12-naphthacenedione Hydrochloride (31). A mechanically stirred solution of 4.0 g (10.81 mmol) of the racemic methoxy aglycone **16b** in 250 mL of anhydrous dimethylformamide, to which 80 g of powdered molecular sieves had been added, was treated under argon, simultaneously over 5 min, at 25 °C with 13.30 g (32.31 mmol) of the chloro sugar **25** (dissolved in 100 mL of anhydrous methylene chloride) and 6.73 g of silver triflate (dissolved in 50 mL of anhydrous dimethylformamide). After 2.0 h the sieves were filtered off, and the filtrate was partitioned between brine and ethyl acetate. The organic extracts afforded 21 g, which was chromatographed over 700 g of silica gel, eluting with methylene chloride/acetone, 95:5. Fractions containing the desired coupling product **27** (R_f = 0.5) were combined and evaporated to yield 2.9 g (73%) of the protected methoxy mycin **27** used directly in the next step. The diastereomer **33** was obtained at R_f = 0.30 upon further elution.

A solution of 2.9 g (3.96 mmol) of the protected methoxy mycin **27** in 300 mL of tetrahydrofuran was cooled to 0 °C and treated with 300 mL of 0.1 N sodium hydroxide. The reaction was stirred at 0 °C for 3 h and partitioned between 10% sodium bicarbonate and methylene chloride. The organic extracts yielded 1.6 g of

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.

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Notes

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

Tony Durst* and Madan Kumar Sharma

Ottawa-Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada

Eric J. Gabe* and F. L. Lee

Chemistry Division, National Research Council of Canada, Ottawa, Ontario K1A 0R6, Canada

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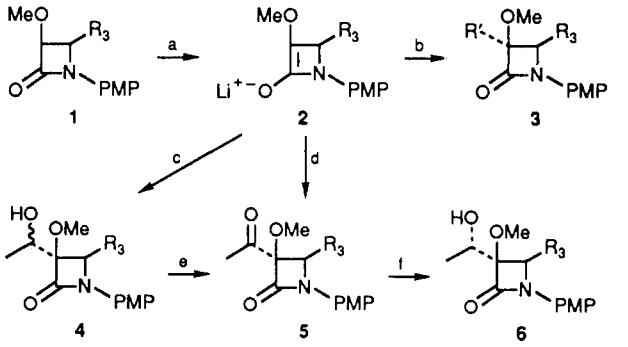
Carbapena(e)ms bearing a hydroxy or a methoxy group adjacent to the carbonyl group of the azetidinone moiety have received only limited attention.[1] As part of a program directed toward the synthesis of such compounds and other similar bicyclic azetidinones, the conversion of 3-methoxyazetidinones to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

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