Registry No. **1a**, 98-86-2; **1b**, 450-95-3; **1c**, 652-29-9; **1d**, 577-59-3; **2a**, 124382-13-4; **2b**, 124382-14-5; **2c**, 124382-15-6; **2d**, 124382-16-7; **3a**, 119-61-9; **3b**, 1144-74-7; **3c**, 853-39-4; **4a**, 114467-84-4; **4b**, 114467-81-1; **4c**, 53106-74-4; **5**, 365-00-4; **6**, 124382-17-8; **7**, 124382-18-9; **8**, 124382-19-0; **9a**, 83-33-0; **9b**, 700-76-5; **9c**, 1579-14-2; **9d**, 529-34-0; **9e**, 826-73-3; **10a**, 124382-20-3; **10b**, 124382-21-4; **10c**, 124382-23-6; **10d**, 124382-24-7; **10e**, 124382-25-8; **11b**, 124382-22-5; **11c**, 124382-26-9; XeF_2, 13709-36-9.

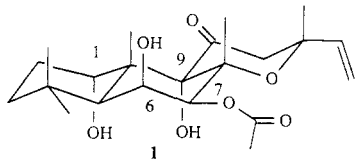
Regiocontrolled Reactions of 7-Desacetylforskolin. 2. Synthesis of 6- and 7-Carbamate Derivatives[1,2]

Gerard J. O'Malley,* Bettina Spahl, Robert J. Cherill, and Raymond W. Kosley, Jr.

Hoechst-Roussel Pharmaceuticals, Inc., Somerville, New Jersey 08876

Received July 24, 1989

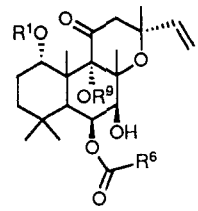
Forskolin (1), a labdane diterpene isolated from the Indian plant *Coleus forskohlii*,[3,4] exhibits unique biological activities attributed to the direct stimulation of adenylate cyclase.[5] The ability of forskolin to enhance c-AMP availability represents a novel therapeutic approach to the treatment of congestive heart failure. Although forskolin displays cardiotonic activity, poor aqueous solubility and insufficient metabolic stability are limitations for clinical applications. As part of a program directed toward the preparation of forskolin-based cardiotonics with improved stability and aqueous solubility, we report regiospecific manipulations which permit the selective preparation of a variety of carbamates and functionalized carbamates at either the 6- or 7-hydroxy positions of forskolin.



1

Recently, we reported[2] selective procedures for acylation at the 1- or 7-positions of the forskolin nucleus. The 1,9-dimethylformamide acetal moiety was introduced for protection of the 1- and 9-hydroxy groups of this system. For the present work, the 1,9-(dimethylformamide acetal) **2** of 7-desacetylforskolin (7-DAF) also served as an ideal starting material (Scheme I). In general, it is known that equatorial alcohols are less hindered than axial alcohols with respect to acylation,[6] and indeed the equatorial 7-hydroxy group of the labdane nucleus was reported[2] to be substantially less hindered and therefore more reactive than the axial 6-hydroxy group. Reaction of **2** with 1,1'-carbonyldiimidazole (CDI) in methylene chloride afforded the acylimidazole intermediate **3**, which upon reaction with pyrrolidine provided 7-desacetyl-7-(1-pyrrolidinocarbonyl)forskolin 1,9-(dimethylformamide acetal) (**4**) in 91% yield with complete regiospecificity. Hydrolysis of **4** in aqueous methanol at 60 °C removed the 1,9-(dimethylformamide acetal) protecting group to give the 7-(1-pyrrolidino) carbamate **5**. This method of carbamate formation offers advantages over the use of isocyanates or carbamoyl chlorides in that the conditions are milder and a wider variety of carbamates may be prepared from **3** using various primary or secondary amines.

Table I



compd	R^1, R^9	R^6	method[a]	yield,[b] %
6a	$N(CH_3)_2$		A B	82 87 (74)[c]
6b	$N(CH_3)_2$	$NHCH_2CH_2OH$	B	80 (68)[c]
6c	$N(CH_3)_2$	$NHNH_2$	A	75
6d	$N(CH_3)_2$	$NH(CH_2)_3N(CH_3)_2$	A	77
8a	H, H		C	50
8b	H, H	$NHCH_2CH_2OH$	C	62

[a] Method A: one-pot reaction from **2**. Method B: reaction from isolated 6,7-carbonate **7**. Method C: $MeOH/H_2O$, 60 °C. [b] Yields are for isolated material of analytical purity. [c] Yields in parentheses are for two steps from **2**.

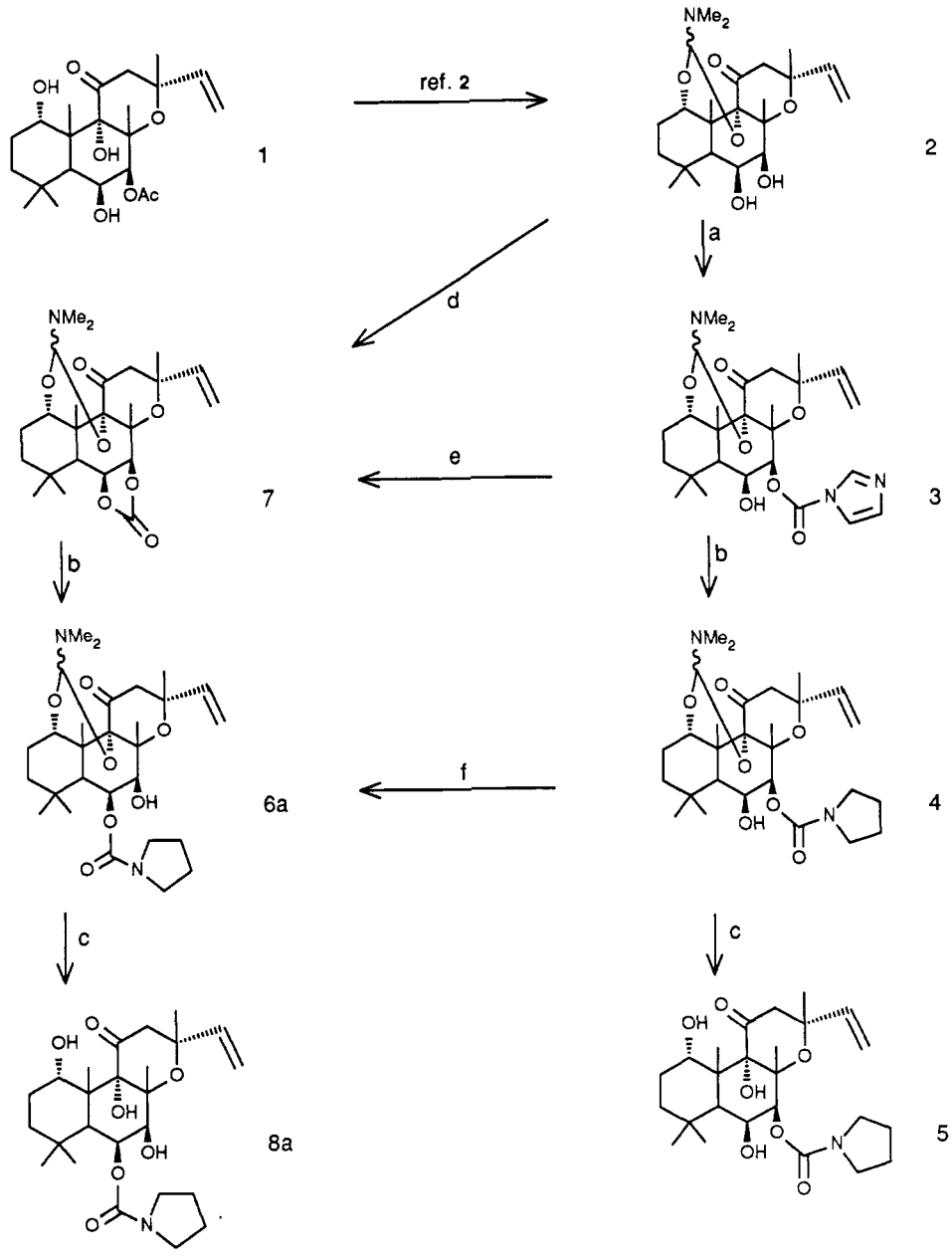
The reported O to O acylmigration of forskolin esters from the 7- to the 6-position in the presence of alumina[7] or under basic conditions,[2] prompted investigation of the possible rearrangement of the corresponding 7-carbamate derivatives. When a solution of **4** in *tert*-butyl alcohol/THF was treated with an excess of potassium *tert*-butoxide, a rearrangement occurred at 0 °C to provide the 6-(1-pyrrolidino) compound **6a** in 73% yield. Structural assignments of the two isomers were based on the ^1H NMR chemical shifts of the C-6 and C-7 protons.[8]

A direct regiospecific route to the 6-carbamate derivatives **6** and **8** from the 6,7-cyclic carbonate derivative **7** was also developed. The reaction of simple aliphatic and carbohydrate cyclic carbonates with amines has been reported; however, mixtures of carbamates are generally obtained.[9,10] Treatment of acylimidazole intermediate **3** with a hindered nonnucleophilic base such as triethylamine afforded the 6,7-carbonate **7** in 85% yield. Subsequent reaction of **7** with pyrrolidine provided 7-desacetyl-6-(1-pyrrolidinocarbonyl)forskolin 1,9-(dimethylformamide acetal) (**6a**) in 87% yield (method B). In practice, higher yields are achieved by performing the reaction sequence in one step from **2** via the in situ formation of the 6,7-carbonate **7** and treatment with amines to give the protected carbamates **6** (method A). The dimethylformamide protecting group may be removed under the same mild

(1) Dedicated to Prof. Dr. rer. nat. Wolfgang Hilger, Chairman of Hoechst A.G., in honor of his 60th birthday.
(2) For paper 1, see: Kosley, R. W., Jr.; Cherill, R. J. *J. Org. Chem.* **1989**, *54*, 2972.
(3) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; deSouza, N. J.; Fehlhaber, H.-W. *Tetrahedron Lett.* **1977**, 1669.
(4) For the chemistry of forskolin, see: Venkataraman, H.; Cha, J. K. *J. Org. Chem.* **1989**, *54*, 2505 and references cited therein.
(5) Seamon, K. B.; Daly, J. W. *Adv. Cyc. Nucl. Res.* **1986**, *20*, 1.
(6) Eliel, E. L.; Lukach, C. A. *J. Am. Chem. Soc.* **1957**, *79*, 5986.
(7) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; De Souza, N. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 767.
(8) Assignment of the C6 vs C7 protons can be made by the homonuclear off-resonance decoupling of the C5 proton. For **4**, irradiation of the C5 proton at 2.28 ppm caused the broad multiplet at 4.57 ppm (C6) to sharpen to a doublet of doublets. When the C5 proton of **6** (2.40 ppm) is decoupled, the triplet at 5.78 ppm became a sharp doublet.
(9) Baizer, M. M.; Clark, J. R.; Swidinsky, J. *J. Org. Chem.* **1957**, 22, 1595.
(10) Stout, E. I.; Doane, W. M.; Shasha, B. S.; Russell, C. R.; Rist, C. E. *Tetrahedron Lett.* **1967**, 4481.

0022-3263/90/1955-1102$02.50/0

Scheme I[a]



[a] (a) 1,1'-Carbonyldiimidazole, CH_2Cl_2, room temperature, 16 h; (b) pyrrolidine, room temperature, 16 h; (c) MeOH–H_2O (3:1), 60 °C, 48 h; (d) 1,1'-carbonyldiimidazole, Et_3N, CH_2Cl_2, room temperature, 16 h; (e) triethylamine, room temperature, 16 h; (f) KOtBu, tBuOH, THF, 0 °C, 4 h.

hydrolysis conditions employed for the conversion of **4** to **5**. Several examples of the 6-carbamate derivatives (**6a–d** and **8a,b**) prepared utilizing this new methodology are shown in Table I.

In summary, by inclusion or exclusion of triethylamine one can effect selective preparation of the 6- or 7-carbamate derivatives of 7-DAF. The 6,7-cyclic carbonate **7** is opened by nitrogen nucleophiles in a completely regiospecific manner to efficiently provide the 6-carbamates versus the more indirect method of rearrangement of the 7-carbamates. The regiospecific nature of these transformations may find applicability in forskolin research in particular and in the synthesis of hindered α-hydroxy carbamates in general.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP3-200 spectrophotometer in $CHCl_3$. Nuclear magnetic resonance spectra were recorded on a Varian XL-200 instrument, and chemical shifts are recorded in ppm relative to tetramethylsilane in $CDCl_3$. Coupling constants (J) are given in hertz. When the geminal coupling of the protons attached to the terminal carbon (C-15) of the vinyl group was not fully resolved, approximate values for the coupling constants are provided. Mass spectra were obtained with a Finnigan 4023, electron impact (EI) at 70 eV or chemical ionization (CI) using methane. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL, or Oneida Research Services, Inc., Whitesboro, NY. Thin-layer chromatography was run on silica plates 60F-254 (E. Merck), and flash chromatography was performed using silica gel 60 (230–400 mesh, E. Merck).

7-Desacetyl-7-(1-pyrrolidinocarbonyl)forskolin 1,9-(Dimethylformamide acetal) (4). A solution of 7-desacetylforskolin 1,9-dimethylformamide acetal[2] (**2**) (5.0 g, 11.8 mmol) in methylene chloride (100 ml) was treated with 1,1'-carbonyldiimidazole (2.3 g, 14.2 mmol), and the mixture was stirred at room temperature for 16 h. Pyrrolidine (4.2 g, 59 mmol) was added, and after 24

h the reaction mixture was washed with 0.01 N HCl until the washings became neutral. The dried (Na_2SO_4) organic phase was concentrated to an oil, which was chromatographed (hexane/ethyl acetate, 1:1) to give **4** as an amorphous solid (5.6 g, 91%): ^{1}H NMR δ 5.86 (dd, 1 H, J = 17, 10.6 Hz, C*H*=CH_2), 5.30 (dd, 1 H, J = 17, 1.5 Hz, CH=C*H*$_2$), 5.20 (d, 1 H, J = 3.9 Hz, H-7), 4.94 (dd, 1 H, J = 10.6, 1.5 Hz, CH=C*H*$_2$), 4.75 (s, 1 H, C*H*NMe_2), 4.57 (m, 1 H, H-6), 4.11 (m, 1 H, H-1), 3.43 (m, 4, H, pyrrolidine NCH_2), 2.86 (d, 1 H, J = 16.1 Hz, H-12), 2.42 (s, 6 H, NMe_2), 2.39 (d, 1 H, J = 16.1 Hz), 1.91 (m, 4 H), 1.72 (s, 3 H), 1.50 (s, 3 H), 1.36 (s, 3 H), 1.27 (s, 3 H), 1.03 (s, 3 H), (s, 3 H), 1.50 (s, 3 H), 1.36 (s, 3 H), 1.27 (s, 3 H), 1.03 (s, 3 H); IR 1705 cm^{-1}; MS (CI) 521 (31.2, M + H), 476 (100). Anal. Calcd for $C_{28}H_{44}N_2O_7$: C, 64.58; H, 8.53; N, 5.38. Found: C, 64.47; H, 8.44; N, 5.18.

7-Desacetyl-7-(1-pyrrolidinocarbonyl)forskolin (5). Compound **4** (1.0 g, 1.9 mmol) was dissolved in methanol (21 mL) and water (7 mL) and heated in an oil bath to 60 °C for 72 h. The mixture was allowed to cool to room temperature, and methylene chloride (100 mL) and water (50 mL) were added. The organic phase was separated, dried (Na_2SO_4), and concentrated to an oil, which was chromatographed (hexane/ethyl acetate, 1:1) to give **5** (0.7 g, 89%): mp 230–233 °C; ^{1}H NMR δ 5.98 (dd, 1 H, J = 17.2, 10.6 Hz, C*H*=CH_2), 5.33 (dd, 1 H, J = 17.2, 1 Hz, CH=C*H*$_2$), 5.24 (d, 1 H, J = 4.2 Hz, H-7), 4.99 (dd, 1 H, J = 10.6, 1 Hz, CH=C*H*$_2$), 4.56 (m, 1 H, H-1), 3.4–3.5 (m, 4 H, pyrrolidine CONC*H*$_2$), 3.18 (d, 1 H, J = 17.3 Hz, H-12), 2.50 (d, 1 H, J = 17.3 Hz, H-12), 1.74 (s, 3 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.26 (s, 3 H), 1.05 (s, 3 H); IR 1705 cm^{-1}; MS (CI) 466 (15.5, M + H), 447 (100). Anal. Calcd for $C_{25}H_{39}NO_7$: C, 64.48; H, 8.46; N, 3.01. Found: C, 64.44; H, 8.48; N, 3.15.

7-Desacetyl-6-(1-pyrrolidinocarbonyl)forskolin 1,9-(Dimethylformamide acetal) (6a). Method A. To a stirred solution of **2** (3.0 g, 7.1 mmol) in methylene chloride (60 mL) were added 1,1′-carbonyldiimidazole (1.38 g, 8.5 mmol) and triethylamine (1.65 g, 16.4 mmol). After stirring for 24 h at room temperature, pyrrolidine (2.5 g, 35.2 mmol) was added, and the mixture was stirred for an additional 24 h. The reaction mixture was diluted with methylene chloride (50 mL) and extracted repeatedly with 0.01 N HCl until the washings were neutral. The organic phase was dried (Na_2SO_4) and concentrated to an oil, which was chromatographed (hexane/acetone, 2:1) to give **6a** as a colorless amorphous solid (3.06 g): ^{1}H NMR δ 6.02 (dd, 1 H, J = 17.4, 10.6 Hz, C*H*=CH_2), 5.78 (t, 1 H, J = 4.1 Hz), 5.22 (dd, 1 H, J = 17.4, 1.2 Hz, C=C*H*$_2$), 4.99 (dd, 1 H, J = 10.6, 1.2 Hz, C=C*H*$_2$), 4.77 (s, 1 H, C*H*NMe_2), 4.22 (d, 1 H, J = 2.2 Hz, H-7), 4.15 (m, 1 H, H-1), 3.44 (m, 4 H, pyrrolidine NC*H*$_2$), 2.90 (d, 1 H, J = 16.3, H-12), 2.46 (d, 1 H, J = 16.3 Hz, H-12), 2.43 (s, 6 H, N(C*H*$_3$)$_2$), 2.40 (d, 1 H, J = 2.8 Hz, H-5), 1.7–1.9 (m, 4 H), 1.64 (s, 3 H), 1.49 (s, 3 H), 1.44 (s, 3 H), 1.09 (s, 3 H), 1.04 (s, 3 H); IR 1690, 1715 cm^{-1}; MS (CI), 521 (40.4, M + H), 476 (83.8), 315 (100). Anal. Calcd for $C_{28}H_{44}N_2O_7$: C, 64.58; H, 8.53; N, 5.38. Found: C, 64.22; H, 8.35; N, 5.34.

Method B. To a stirred solution of the 6,7-carbonate **7** (1.5 g, 3.3 mmol) in methylene chloride (30 mL) was added pyrrolidine (1.2 g, 16.5 mmol), and the mixture was stirred for 48 h at room temperature. The reaction mixture was diluted with methylene chloride (25 mL) and extracted repeatedly with 0.01 N HCl until the washings were neutral. The dried (Na_2SO_4) organic phase was concentrated to an oil, which was chromatographed (hexane/acetone, 2:1) to give **6a** as an amorphous solid (1.5 g), with identical chromatographic (hexane/acetone (2:1), R_f = 0.33) and spectral properties as the material obtained in method A.

Rearrangement of 4 to the 6-(1-Pyrrolidino) Carbamate (6a). To a stirred solution of **4** (1.5 g, 2.88 mmol) in *tert*-butyl alcohol (50 mL) and THF (10 mL) at 0 °C was added potassium *tert*-butoxide (4.7 g, 41.9 mmol). The mixture was stirred for 0.5 h at 0 °C and 4 h at ambient temperature. The reaction was quenched with ice and extracted with methylene chloride (2 × 100 mL), and the extracts were washed with water (3 × 50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, and the resulting oil was chromatographed (hexane/ethyl acetate, 1:1) to give **6a** as a colorless solid (1.1 g), which had chromatographic and spectral properties identical with those of the material obtained by method A.

7-Desacetylforskolin-6,7-carbonate 1,9-(Dimethylformamide acetal) (7). To a stirred solution of **2** (20.0 g, 47.3 mmol) in methylene chloride (300 mL) was added 1,1-′carbonyldiimidazole (9.66 g, 59.6 mmol), followed by triethylamine (6.1 g, 60.4 mmol). After being stirred at room temperature for 48 h, the mixture was washed with 10% HCl (2 × 50 mL) and water (50 mL), and the dried (Na_2SO_4) organic phase was concentrated in vacuo to an oil. The oil was chromatographed (hexane/acetone, 2:1), and the recovered material was crystallized from hexane/ethyl acetate to provide **7** (18.2 g, 85%): mp 138 °C; ^{1}H NMR δ 5.96 (dd, 1 H, J = 17.2, 10.6 Hz, C*H*=CH_2), 5.25 (d, 1 H, J = 17 Hz, CH=C*H*$_2$), 5.13 (m, 1 H, H-6), 5.03 (d, 1 H, J = 11 Hz, CH=C*H*$_2$), 4.85 (d, 1 H, J = 6.8 Hz, H-7), 4.77 (s, 1 H C*H*NMe_2), 4.24 (m, 1 H, H-1), 2.93 (d, 1 H, J = 15.7 Hz, H-12), 2.67 (d, 1 H, J = 3.8 Hz, H-5), 2.48 (d, 1 H, J = 15.7 Hz, H-12), 2.42 (s, 6 H, N(CH_3)$_2$), 1.54 (s, 3 H), 1.45 (s, 3 H), 1.40 (s, 3 H), 1.21 (s, 3 H), 1.11 (s, 3 H); IR 1805, 1720 cm^{-1}; MS (CI) 450 (4.6, M + H) 405 (33.8). Anal. Calcd for $C_{24}H_{35}NO_7$: C, 64.11; H, 7.86; N, 3.12. Found: C, 64.07; H, 7.80; N, 3.02.

7-Desacetyl-6-(1-pyrrolidinocarbonyl)forskolin (8a). This compound was prepared from **6a**, under conditions identical with those for the synthesis of **5**, to afford **8a**, mp 135–140 °C (crystallized from hexane/ethyl acetate): ^{1}H NMR δ 6.12 (dd, 1 H, J = 17, 10.6 Hz), 5.78 (t, 1 H, H-6), 5.25 (d, 1 H, J = 17 Hz, CH=C*H*$_2$), 5.01 (d, 1 H, J = 10.6 Hz, C=C*H*$_2$), 4.65 (m, 1 H, H-1), 4.24 (d, 1 H, J = 2.2 Hz, H-7), 2.23 (d, 1 H, J = 1.7 Hz, H-5), 1.64 (s, 3 H), 1.42 (s, 6 H), 1.09 (s, 3 H), 1.05 (s, 3 H); IR 1695, 1720 cm^{-1}; MS (CI) 466 (30.2, M + H). Anal. Calcd for $C_{25}H_{39}NO_7$: C, 64.48; H, 8.46; N, 3.01. Found: C, 64.35; H, 8.49; N, 2.90.

7-Desacetyl-6-(((2-hydroxyethyl)amino)carbonyl)forskolin 1,9-(Dimethylformamide acetal) (6b). This compound was prepared from **7** using method B, described above, with ethanolamine as the nucleophile to afford **6b**: mp 116–120 °C (crystallized from hexane/ethyl acetate); ^{1}H NMR δ 6.00 (dd, 1 H, J = 17, 11 Hz, C*H*=CH_2), 5.71 (m, 1 H, H-6), 5.23 (d, 1 H, J = 17 Hz, CH=C*H*$_2$), 4.99 (d, 1 H, J = 11 Hz, CH=C*H*$_2$), 4.76 (s, 1 H, C*H*NMe_2), 4.15 (m, 2 H, H-7, H-1), 3.6–3.8 (m, 2 H, NHC*H*$_2$C*H*$_2$), 3.2–3.4 (m, 2 H, C*H*$_2$C*H*$_2$OH), 2.42 (s, 6 H, N(C*H*$_3$)$_2$), 2.36 (d, 1 H, J = 1.7 Hz, H-5), 1.61 (s, 3 H), 1.44 (s, 6 H), 1.08 (s, 3 H), 1.04 (s, 3 H); IR 1720 cm^{-1}; MS (CI) 511 (M + H). Anal. Calcd for $C_{26}H_{42}N_2O_8$: C, 61.14; H, 8.31; N, 5.38. Found: C, 60.91; H, 8.27; N, 5.33.

7-Desacetyl-6-(hydrazinocarbonyl)forskolin 1,9-(Dimethylformamide acetal) (6c). This compound was prepared from **2** using method A, described above, with hydrazine as the nucleophile to afford **6c**: mp 143–150 °C (crystallized from hexane/ether); ^{1}H NMR δ 6.00 (dd, 1 H, J = 17, 11 Hz, C*H*=CH_2), 5.75 (t, 1 H, J = 3.6 Hz, H-6), 5.23 (d, 1 H, J = 17 Hz, CH=C*H*$_2$), 5.00 (d, 1 H, J = 11 Hz, CH=C*H*$_2$), 4.76 (s, 1 H, C*H*NMe_2), 4.19 (d, 1 H, J = 4.1 Hz, H-7), 4.14 (m, 1 H, H-1), 2.89 (d, 1 H, J = 16.4 Hz, H-12), 2.42 (s, 6 H, N(C*H*$_3$)$_2$), 1.58 (s, 3 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.08 (s, 3 H), 1.02 (s, 3 H); IR 1720 cm^{-1}; MS (CI) 482 (M + H, 59.1), 437 (100). Anal. Calcd for $C_{24}H_{39}N_3O_7$: C, 59.84; H, 8.18; N, 8.72. Found: C, 59.02; H, 8.09; N, 8.55.

7-Desacetyl-6-((*N*-(3-(dimethylamino)propyl)amino)carbonyl)forskolin 1,9-(Dimethylformamide acetal) (6d). This compound was prepared from **2** using method A described above, with 3-(dimethylamino)propylamine as the base to afford **6d** as an amorphous solid: mp 130–132 °C; ^{1}H NMR δ 6.01 (dd, 1 H, J = 17.2 Hz, J = 10 Hz, C*H*=CH_2), 5.65 (br t, 1 H, H-6), 5.22 (d, 1 H, J = 17.2 Hz, C=C*H*$_2$), 4.98 (d, 1 H, J = 10 Hz, C=C*H*$_2$), 4.76 (s, 1 H, C*H*NMe_2), 4.18 (d, 1 H, J = 4.3 Hz, H-7), 4.14 (m, 1 H, H-1), 3.15 (m, 2 H, CONHC*H*$_2$), 2.89 (d, 1 H, J = 16.4 Hz, H-12), 2.47 (d, 1 H, J = 10.4 Hz, H-12), 2.42 (s, 6 H, N(C*H*$_3$)$_2$), 1.61 (s, 3 H), 1.44 (s, 6 H), 1.07 (s, 3 H), 1.05 (s, 3 H); IR 1720 cm^{-1}; MS (EI) 551 (M, 51.5), 507 (40.5), 147 (100). Anal. Calcd for $C_{29}H_{49}N_3O_7$: C, 63.12; H, 8.97; N, 7.62. Found: C, 63.21; H, 9.04; N, 7.54.

7-Desacetyl-6-(((2-hydroxyethyl)amino)carbonyl)forskolin (8b). This compound was prepared from **6b**, under conditions identical for the synthesis of **5**, to afford **8b** as an amorphous solid: ^{1}H NMR δ 6.12 (dd, 1 H, J = 17 Hz, J = 11 Hz, C*H*=CH_2), 5.75 (m, 1 H, H-6), 5.22 (d, 1 H, J = 17 Hz, CH=C*H*$_2$), 5.02 (d, 1 H, J = 11 Hz, CH=C*H*$_2$), 4.65 (m, 1 H), 4.28 (d, 1 H, H-7), 3.74 (m, 2 H, NC*H*$_2$C*H*$_2$OH), 3.38 (m, 2 H, NC*H*$_2$C*H*$_2$OH), 1.61 (s, 3 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H); MS (CI), 456 (M + H). Anal. Calcd for $C_{23}H_{37}NO_8$: C, 60.63; H, 8.20; N, 3.08. Found: C, 60.44; N, 8.08; N, 2.94.

Acknowledgment. We would like to express our appreciation to Drs. Helen H. Ong and Richard C. Allen for many helpful suggestions and to Dana Hallberg and Anastasia Linville for providing the spectral data.

Registry No. 2, 105535-42-0; 3, 124021-54-1; 4, 118046-28-9; 5, 118026-87-2; 6a, 118104-56-6; 6b, 118075-70-0; 6c, 124021-55-2; 6d, 118046-40-5; 7, 105535-74-8; 8a, 118104-54-4; 8b, 118075-66-4.

A Versatile Intermediate for the Synthesis of Pyranoquinone Antibiotics

George A. Kraus* and Jianmin Shi

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Don Reynolds

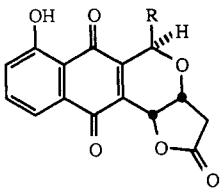
Veterinary Medical Research Institute, Iowa State Univeristy, Ames, Iowa 50011

Received June 26, 1989

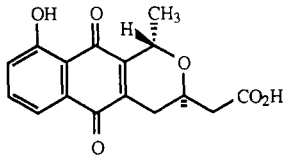
As a result of the sophisticated detection and isolation procedures developed by Omura[1] and others, the family of biologically active pyranoquinones continues to grow rapidly. As a consequence of their interesting structures and useful activity, several synthetic approaches have already appeared.[2] Its members include the antimycoplasmal antibiotics frenolicin B (**1**)[3] and nanaomycin A (**2**),[4] the antifungal agent kalafungin (**3**),[5] the antibiotics medermycin (**4**)[6] and mederrhodin (**5**),[7] and the novel C-glycoside SCH 38519 (**6**),[8] which inhibits the growth of Gram-negative and Gram-positive microorganisms. It is clear from an examination of their structures depicted below that the primary difference lies in the substitution pattern on the naphthoquinone subunit. Since an acid such as **2** can be converted into a lactone in high yield under mild conditions,[4] our interest in developing a common intermediate for the synthesis of all of these natural products led us to embark on the preparation of quinone **7**, wherein X could be a phenylthio group or a bromide or chloride.

A direct route to **7** coupled with the annulation methodology developed by Rapoport[9] could provide a general synthesis of **1**–**6**. The key to solving this problem came from our earlier report[2] that the reaction of naphthoquinones with electron-rich dienes in a Diels–Alder reaction followed by a fluoride-induced retro-Claisen reaction afforded excellent yields of advanced intermediates for the synthesis of pyranoquinones. Ester **8a** was available from acetylbenzoquinone via the one-pot Diels–Alder–retro-Claisen (DARC) reaction in 91% yield (Scheme I).

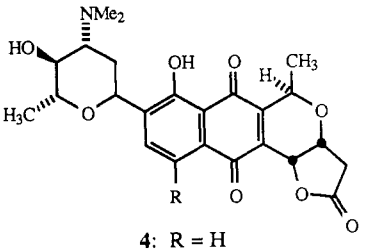
Bromination of *o*-hydroxyacetophenones using bromine/$TiCl_4$ has been shown to be selective for bromination



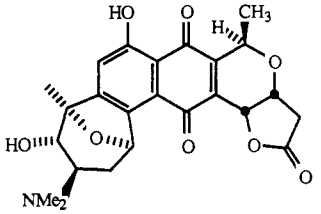
1: R = Pr
3: R = Me



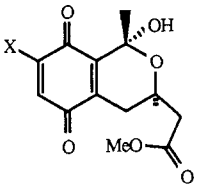
2



4: R = H
5: R = OH



6



7

ortho to the phenol.[10] Bromination of **8a** with 1 equiv of bromine afforded *only* bromophenol **8b**, as evidenced by TLC and the proton NMR of the unpurified material. Support for the regiochemical assignment came from an NOE study of the methyl ether of **8b**. Irradiation of the methyl group of the ether did not cause an enhancement of the aromatic ring proton, which is consistent with the structure of **8b**. Interestingly, bromination and oxidation with 2 equiv of bromine and $TiCl_4$ in methylene chloride at 0 °C afforded quinone **9** in 82% yield, presumably via the intermediacy of bromophenol **8b**. Initially, quinone **9** was treated with 1-methoxy-1-(trimethylsilyloxy)butadiene at −78 °C to afford a complex product mixture as evidenced by thin-layer chromatography. Fortunately, reductive removal of the hydroxyl group provided the quinone **10**, which did react in 34% yield to yield **11**, an advanced intermediate in our previous synthesis of nanaomycin A.[2]

In summary, the sequence **8a** → **9** → **10** produces a common intermediate by which the more complex pyranonaphthoquinones can be prepared. Since highly oxygenated dienes are readily available,[9] this extremely convergent approach will permit the direct synthesis of biologically active analogues and may also aid in the structure identification of quinone natural products.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes–ethyl acetate solvent mixtures for TLC. The purity of all title compounds was determined to be >90% by proton NMR and/or elemental analysis.

Methyl (4-Acetyl-2,3-dihydro-5-hydroxybenzofuran-2-yl)acetate (8a). To a solution of acetylbenzoquinone (2.30 g, 15.3 mmol) in 60 mL of dry CH_2Cl_2 at −78 °C was added 1-(*tert*-butyldimethylsilyloxy)-1-methoxybutadiene (6.52 g, 30.6 mmol). The solution was stirred at −78 °C for 30 min and then allowed to warm to ambient temperature for 1 h. The solution

(1) Omura, S. *Microbiol. Rev.* **1986**, *50*, 259–279.
(2) For leading references to syntheses of pyranoquinone antibiotics, see: Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273. Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1568 and references therein.
(3) Omura, S.; Tsuzuki, K.; Iwai, Y. *J. Antibiot.* **1985**, *38*, 1447.
(4) Omura, S.; Tanaka, H.; Okada, Y.; Marumo, H. *J. Chem. Soc., Chem. Commun.* **1976**, 320.
(5) Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454.
(6) Ogura, H.; Furuhata, K. *Abst. 9th Int. Congr. Heterocyclic Chem.* **1983**, 114.
(7) Hopwood, D. A.; Malpartida, F.; Kieser, H. M.; Ikeda, H.; Duncan, J.; Fujii, I.; Rudd, B. A. M.; Floss, H. G.; Omura, S. *Nature (London)* **1985**, *314*, 642.
(8) Hegde. V. R.; King, A. H.; Patel, M. G.; Puar, M. S.; McPhail, A. T. *Tetrahedron Lett.* **1987**, *28*, 4485.
(9) Bauman, J. G.; Hawley, R. C.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1569.
(10) Cresp, T. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Chem. Commun.* **1972**, 214.

0022-3263/90/1955-1105$02.50/0