immediately before use, adjusting the pH at 9.5 with 17 g/L of $NaHCO_3$. LiOCl was purchased from Fluka AG, Buchs, Switzerland. The commercial solid should contain 30% of LiOCl. Repeated iodometric titrations of the batch used in this work showed an oxidant content of 19.6–20.5% as LiOCl.

Oxidations with Aqueous Sodium Hypochlorite. The reaction flask was charged with 15 mmol of substrate, 0.15 mmol of **2a** (or **2b**), 1.5 mmol of KBr, 50 mL of CH_2Cl_2, and 2 mL of H_2O and stirred. The appropriate amount of a 0.9 M solution of NaOCl at pH 9.5 (see Table I) was added in 5–10 min, maintaining the temperature in the range 10–15 °C with an ice bath. After 10 min the organic phase was separated and washed with 10 mL of 10% HCl containing 125 mg (0.75 mmol) of KI, 10 mL of 10% aqueous $Na_2S_2O_3$, and 10 mL of H_2O. After drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by column chromatography on silica gel. All of the isolated products showed physical and spectroscopic (IR, ^1H NMR) properties in agreement with previously reported data. Results are shown in Table I. For the oxidation of 1,10-undecanediol to 10-oxoundecancarboxylic acid (Table I, entry 6), the addition of 0.75 mmol of Aliquat 336 was required.

Oxidative Lactonization of 1,4-Butanediol and 1,5-Pentanediol. A mixture of 24 mmol of diol, 0.24 mmol of **2a** (or **2b**), 16.8 g (57.6 mmol) of 20% LiOCl, and 6.05 g (72 mmol) of $NaHCO_3$ in 50 mL of CH_2Cl_2 was vigorously stirred at room temperature over 30 min. The reaction mixture was filtered, and the solid was thoroughly washed with CH_2Cl_2. After drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by column chromatography (silica gel; petroleum ether–Et_2O). The products showed physical and spectroscopic properties identical with those reported for γ-butyrolactone and γ-valerolactone.

Registry No. **2a**, 95407-69-5; **2b**, 2564-83-2; PhCH(OH)CH(OH)Ph, 492-70-6; 1,4-$(OH)_2C_6H_4$, 123-31-9; $CH_3CH(OH)(CH_2)_8CH_2OH$, 10596-05-1; $HO(CH_2)_4OH$, 110-63-4; $HO(CH_2)_5OH$, 111-29-5; $HO(CH_2)_2N(Ts)(CH_2)_2OH$, 7146-67-0; PhC(O)CH(OH)Ph, 119-53-9; PhC(O)C(O)Ph, 134-81-6; 1,4-$(=O)_2C_6H_4$, 106-51-4; $CH_3CH(OH)(CH_2)_8CHO$, 38199-58-5; $CH_3C(O)(CH_2)_8CHO$, 36219-78-0; $\overline{C(O)CH_2CH_2CH_2O}$, 96-48-0; $\overline{C(O)CH_2CH_2CH_2CH_2O}$, 542-28-9; $\overline{CnO)CH_2N(Ts)CH_2CH_2O}$, 91134-36-0; NaOCl, 7681-52-9; LiOCl, 13840-33-0; 10-oxoundecanoic acid, 676-00-6.

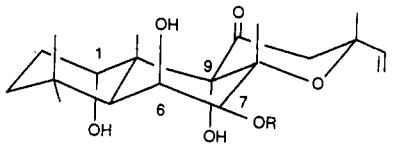
Regioselective Acylations of 7-Desacetylforskolin[1]

Raymond W. Kosley, Jr.,* and Robert J. Cherill

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

Received December 19, 1988

Forskolin (**1a**) is a diterpenoid, isolated from the roots of *Coleus forskohlii*.[2] Several total syntheses of forskolin have recently been reported.[3] During the course of an investigation of the physiological effects of forskolin analogues, it was of interest to prepare 1-esters (axial) and 7-esters (equatorial) of 7-desacetylforskolin (7-DAF, **1b**). It is known from the work of Eliel[4] and others[5] that equatorial alcohols are more reactive with respect to acylation than their axial counterparts. Consistent with these



1a R = $COCH_3$

1b R = H

observations is the report[6] that treatment of 7-DAF (**1b**) with propionic anhydride in pyridine provides predominately the 7-ester, the product of acylation of the equatorial 7-hydroxyl group rather than acylation of the axial 1-hydroxyl group.[7]

We found, however, that treatment of 7-DAF (**1b**) with bromoacetyl bromide and dimethylaniline in dichloromethane at 0–5 °C effected acylation exclusively on the *axial* 1-hydroxyl to provide, after treatment with morpholine, the 1-(amino ester) **2** in 73% yield (Scheme I). In contrast, treatment of **1b** with 4-morpholinoacetic acid[8] in the presence of DCC and 4-(dimethylamino)pyridine (DMAP)[9] (Scheme I) effected predominately acylation on the equatorial 7-hydroxyl to provide the 7-(morpholinoacetyl ester) **3** in 45% yield (64% based on recovered **1b**) in addition to 10% of the 1-(morpholinoacetyl ester) **2** and 15% of 7-desacetyl-1,7-bis(morpholinoacetyl)forskolin (**4**).

To confirm the structure of compound **2**, it was acylated with acetic anhydride/DMAP to provide 1-(morpholinoacetyl)forskolin (**5**) (Scheme II), which was identical by mp, IR, ^1H NMR, and MS with the product obtained by treating forskolin with bromoacetyl bromide/dimethylaniline, followed by morpholine (Scheme II).

The structure of **3** was confirmed by an independent synthesis employing a 1-hydroxyl-protected forskolin derivative. Seamon et al.[2] had prepared some forskolin analogues in which the 1-hydroxyl was protected as the 1-(*tert*-butyldimethylsilyl ether). However, the conditions required to cleave the *tert*-butyldimethylsilyl ether (fluoride or HF) are not compatible with some of the amino esters that comprised our targets. We chose, therefore, to protect the 1-hydroxyl as a 1,9-dimethylformamide (DMF) acetal[10,11] (Scheme III). Although DMF acetals of 1,2-diols have long been known[10] and 2-(dimethylamino)benzylidene and 1-(dimethylamino)ethylidene acetals have been used to protect sugars,[11] to our knowledge, the somewhat more stable DMF acetals have not been previously employed to protect 1,3-diols in rigid systems.[12] We found that treatment of forskolin (**1a**) with DMF dimethyl acetal provided forskolin-1,9–DMF acetal (**6**), the acetyl group of which was hydrolyzed with aqueous methanolic potassium carbonate to provide the 7-desacetylforskolin-1,9–DMF acetal (**7**) in 74% overall yield from forskolin.[13]

(1) Dedicated to Professor Hansgeorg Gareis on the occasion of his 60th birthday.

(2) For a review, see: Seamon, K. B.; Daly, J. W. *Adv. Cyclic Nucleotide Res.* **1986**, *20*, 1.

(3) (a) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115. (b) Hashimoto, S.-i.; Sakata, S.; Sonegawa, M.; Ikegami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670. (c) Corey, E. J.; Jardine, P. D. S.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672.

(4) Eliel, E. L.; Lukach, C. A. *J. Am. Chem. Soc.* **1957**, *79*, 5986.

(5) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959; pp 216–225, and references cited therein.

(6) Bhat, S. V.; Bajwa, B. S. Dornauer, H.; de Souza, N. J. *J. Chem. Soc., Perkin Trans. I* **1982**, 767.

(7) The 6- and 9-hydroxyl groups of 7-DAF **1b** are very much more hindered than the 1- and 7-hydroxyls; see: Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; deSouza, N. J.; Fehlhaber, H.-W. *Tetrahedron Lett.* **1977**, 1669–72.

(8) Remizov, A. L.; Khromov-Borisov, N. V. *Zh. Obshch. Khim.* **1953**, 794; *Chem. Abstr.* **1954**, *48*, 3908.

(9) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(10) DMF acetals of 1,2-diols were first synthesized by Meerwein; see: Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060. Meerwein, H.; Florian, W.; Schön, N.; Stopp, G. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1.

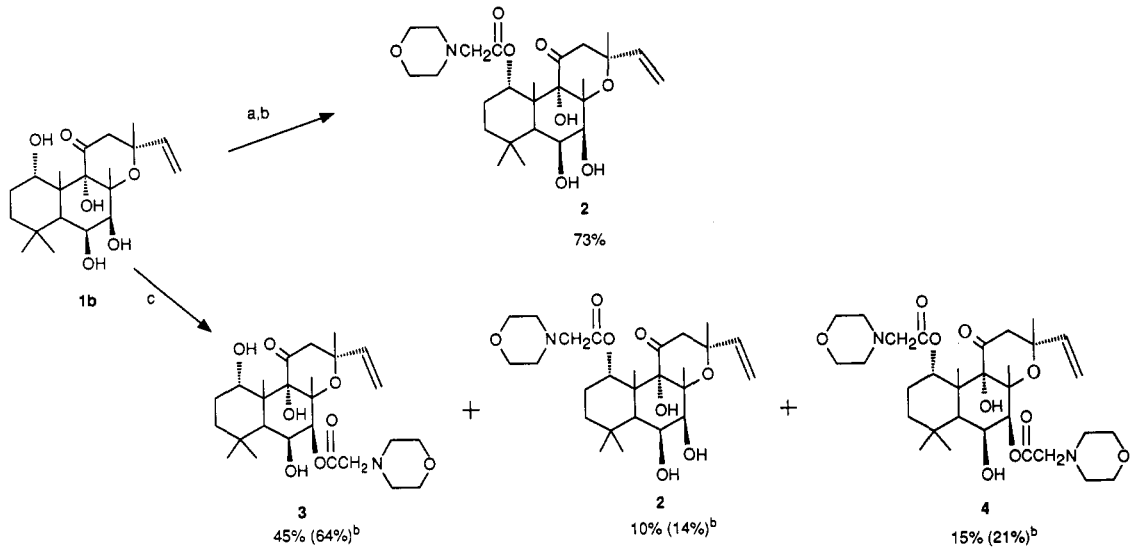
(11) Hanessian, S.; Moralioglu, E. *Can. J. Chem.* **1972**, *50*, 233.

(12) DMF acetals of 1,3-diols have been employed for the synthesis of unsaturated alcohols, see: Ackland, M. J.; Gordon, J. F.; Hanson, J. R.; Yeoh, B. L.; Ratcliffe, A. H. *J. Chem. Soc., Chem. Commun.* **1987**, 1756.

(13) The yield of 7-DAF-1,9–DMF acetal, **7**, was slightly higher if **6** was not isolated.

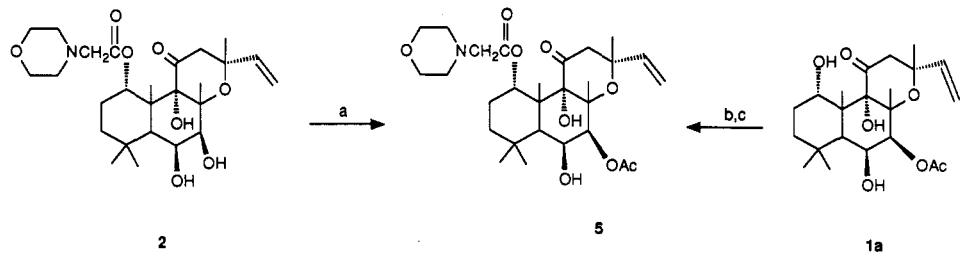
0022-3263/89/1954-2972$01.50/0

Scheme I[a]



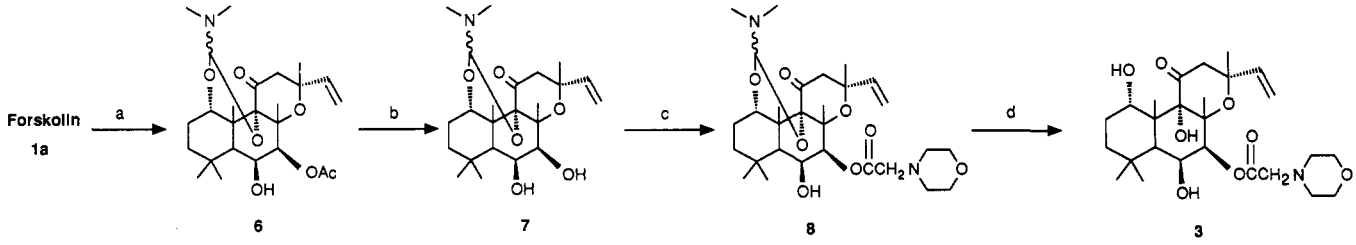
[a] (a) Bromoacetyl bromide, dimethylaniline, dichloromethane; (b) morpholine, dichloromethane/ethyl acetate; (c) morpholineacetic acid, DCC, DMAP, dichloromethane. [b] Based on recovered starting material.

Scheme II[a]



[a] (a) Acetic anhydride, DMAP, dichloromethane; (b) bromoacetyl bromide, dimethylaniline, dichloromethane; (c) morpholine, dichloromethane, ethyl acetate.

Scheme III[a]



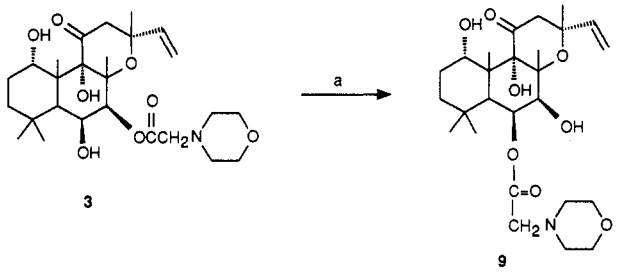
[a] (a) Dimethylformamide dimethyl acetal, neat; (b) saturated aqueous potassium carbonate/methanol; (c) morpholinoacetic acid, DCC, DMAP, dichloromethane; (d) 5/4/1 methanol/acetic acid/water.

Reaction of **7** with 4-morpholinoacetic acid in the presence of DCC and DMAP provided the 7-(morpholinoacetyl ester) **8**, which upon hydrolysis with methanol/acetic acid/water of the 1,9-DMF acetal group, gave a compound (**3**, Scheme III) identical by mp, IR, ^{1}H NMR, and MS with the major product of treatment of **1b** with 4-morpholinoacetic acid, DCC, and DMAP (Scheme I). The 1,9-DMF acetal protecting group has proven to be useful in a variety of synthetic manipulations involving forskolin and its derivatives. Forskolin-1,9-DMF acetals are stable to neutral and basic conditions, as well as to chromatography on silica gel, employing organic hydroxylic solvents.

To further establish the structures of compounds **2** and **3**, we elected to prepare 6-(morpholinoacetyl)forskolin (**9**) (Scheme IV). Precedent existed[6] for the migration of the acetyl moiety from the 7- to the 6-position of forskolin using alumina. We found that treatment of the 7-(morpholinoacetyl ester) **8** with lithium bis(trimethylsilyl)amide in THF provided the desired 6-(morpholinoacetyl) compound **9** (Scheme IV).

In conclusion, employing the methodology described above, one can regioselectively acylate the 1-, 6-, or 7-hydroxyl of 7-desacetylforskolin (**1b**). The observation that acylation of 7-DAF (**1b**) using bromoacetyl bromide/dimethylaniline is highly regioselective for the more sterically hindered axial 1-hydroxyl as opposed to the less sterically

Scheme IV[a]



[a] (a) Lithium bis(trimethylsilyl)amide, THF.

hindered equatorial 7-hydroxyl is unexpected and of potential synthetic utility.

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The structures of all compounds are supported by their IR (Pye Unicam SP3-200), ^{1}H NMR (Varian XL 200; chemical shifts are reported in δ units relative to TMS as internal standard in $CDCl_3$), and mass (Finnigan 4023; electron impact (EI) at 70 eV or chemical ionization (CI) using methane) spectra. Elemental analyses were performed by either Micro Tech Laboratories, Skokie, IL, or Oneida Research Services, Inc., Whitesboro, NY, and results are within ±0.4% of the theoretical values unless otherwise noted. Analytical TLC was performed on silica gel 60F-254 plates (EM). Flash chromatography was performed on silica gel 60 (230–400 mesh) (EM). All reactions were carried out under a dry nitrogen atmosphere.

7-Desacetylforskolin (1b). Forskolin (**1a**) (50 g, 122 mmol) was dissolved in a solution of 1.9 L of 4/1 methanol/saturated aqueous potassium carbonate and stirred for 2 h at 50–55 °C after which 625 mL of water was added to the warm solution. The mixture was cooled to room temperature, allowed to stand for 20 h, and filtered to provide **1b** (29.4 g, 65.6%). Recrystallization from cyclohexane/ethyl acetate provided analytically pure material, mp 170–171 °C [lit.[7] mp 177–180 °C]; IR ($CHCl_3$) 3024, 1720, 1104, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.41 (s, 6 H, 2 CH_3), 1.65 (s, 3 H, CH_3), 2.10 (d, 1 H, H-5) ($J_{6,5}$ = 3 Hz), 2.50 (d, 1 H, H-12) (J = 17 Hz), 3.18 (d, 1 H, H-12) (J = 17 Hz), 4.14 (d, 1 H, H-7) (J = 4 Hz), 4.48 (m, 1 H, H-6), 4.63 (m, 1 H, H-1), 4.99 (d, 1 H, H-15) (J = 11 Hz), 5.21 (d, 1 H, H-15) (J = 17 Hz), 6.13 (dd, 1 H, H-14), (J = 10, 11 Hz); MS (CI) m/z (relative intensity) 369 (M^+ + 1, 2.6), 351 (40), 333 (79), 315 (55), 237 (100), 219 (67). Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.76. Found: C, 64.91; H, 8.44.

7-Desacetyl-1-(morpholinoacetyl)forskolin (2). To a stirred solution of 1.0 g (2.72 mmol) of **1b** in 10 mL of dichloromethane was added 0.380 mL (3.01 mmol) of dimethylaniline, after which the solution was cooled in an ice bath. To the mixture at 0–5 °C was added dropwise a solution of 0.24 mL (0.560 g, 2.77 mmol) of bromoacetyl bromide in 10 mL of dry dichloromethane. The solution was stirred at 0–5 °C for 1 h and poured into cold sodium bicarbonate/water/dichloromethane, and the organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to provide a blue oil.

The oil was dissolved in 10 mL of dichloromethane and added dropwise to a solution of 1 mL of morpholine in 10 mL of ethyl acetate at 0–5 °C. Following addition, the solution was stirred at room temperature for 1 h and worked up as above. The resulting oil was flash chromatographed on silica gel (eluent 40% ethyl acetate/hexanes) to provide **2** (0.99 g, 73%). Recrystallization from ethyl acetate/cyclohexane provided a colorless solid: mp 174–175 °C; IR ($CHCl_3$) 3023, 1750, 1722, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 2.14 (d, 1 H, H-5) (J = 2 Hz), 2.49 (m, 5 H, CH_2NCH_2, H-12), 2.97 (d, 1 H, H-12) (J = 17 Hz), 3.10 (s, 2 H, $COCH_2N$), 3.72 (m, 4 H, CH_2OCH_2), 4.25 (d, 1 H, H-7) (J = 4 Hz), 4.50 (m, 1 H, H-6),[14] 4.95 (d, 1 H, H-15) (J = 10 Hz), 5.20 (d, 1 H, H-15) (J = 17 Hz), 5.53 (m, 1 H, H-1), 6.12 (dd, 1 H, H-14) (J = 10, 11 Hz); MS (EI, 18 eV) m/z (relative intensity) 496 (M^+, 2.5), 146 (33), 100 (100). Anal. Calcd for $C_{26}H_{41}NO_8$: C, 63.01; H, 8.34; N, 2.83. Found: C, 62.96; H, 8.42; N, 2.87.

7-Desacetyl-7-(morpholinoacetyl)forskolin (3), 2, and 7-Desacetyl-1,7-bis(morpholinoacetyl)forskolin (4). To a stirred solution of 0.5 g (1.36 mmol) of **1b**, 246 mg (1.35 mmol) of morpholinoacetic acid hydrochloride,[8] and 175 mg (1.43 mmol) of DMAP in 5 mL of dichloromethane was added 279 mg (1.35 mmol) of DCC. The mixture was stirred at room temperature for 1.5 h, filtered, diluted with dichloromethane, washed twice with sodium bicarbonate and once with water, dried (Na_2SO_4), filtered, and concentrated to an oil. The oil was purified by flash chromatography on silica gel (eluent 15%, 20%, 30%, and 40% acetone/hexanes) to provide **1b** (0.15 g), **3** [0.302 g, 44.8% (64%)[15]], **2** [0.069 g, 10.2% (14.6%)[15]], and **4** [0.12 g, 15.2% (21.8%)[15]]. Compound **3** was recrystallized from hexane/ethyl acetate to provide analytically pure material: mp 200–202 °C; IR ($CHCl_3$) 3023, 1748, 1720, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3) 1.44 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 2.22 (d, 1 H, H-5) (J = 2 Hz), 2.46 (d, 1 H, H-12) (J = 18 Hz), 2.67 (m, 4 H, CH_2NCH_2), 3.20 (d, 1 H, H-12) (J = 18 Hz), 3.34 (s, 2 H, $COCH_2N$), 3.78 (m, 4 H, CH_2OCH_2), 4.50 (m, 1 H, H-6),[16] 4.60 (m, 1 H, H-1), 4.96 (d, 1 H, H-15) (J = 11 Hz), 5.26 (d, 1 H, H-15) (J = 17 Hz), 5.55 (d, 1 H, H-7) (J = 4 Hz), 5.95 (dd, 1 H, H-14) (J = 11, 11 Hz); MS (CI) m/z (relative intensity) 496 (M^+ + 1, 52), 146 (100). Anal. Calcd for $C_{26}H_{41}NO_8$: C, 63.01; H, 8.34; N, 2.83. Found: C, 63.34; H, 8.57; N, 3.02. Compound **4** was pale yellow oil: IR ($CHCl_3$) 3023, 1748, 1720, 1120 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 1.05 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3) 2.01–2.83 [m, 10 H, H-5, 2 × (CH_2NCH_2), H-12], 2.99 (d, 1 H, H-12) (J = 17 Hz), 3.03 (d, 2 H, $COCH_2N$) (J = 2 Hz), 3.35 (s, 2 H, $COCH_2N$), 3.75 [m, 8 H, 2 × (CH_2OCH_2)], 4.53 (m, 1 H, H-6), 4.92 (d, 1 H, H-15) (J = 10 Hz), 5.25 (d, 1 H, H-15) (J = 17 Hz), 5.51 (m, 1 H, H-1), 5.65 (d, 1 H, H-7) (J = 4 Hz), 5.92 (dd, 1 H, H-14) (J = 11, 11 Hz); MS (CI) m/z (relative intensity) 624 (M^+ + 1, 6.0), 623 (M^+, 48), 478 (18), 146 (100). Anal. Calcd for $C_{32}H_{50}N_2O_{10}$: C, 61.71; H, 8.09; N, 4.50. Found: C, 62.00; H, 8.23; H, 4.25. Compound **2** was recrystallized from ethyl acetate/cyclohexane to provide material identical by mp, IR, NMR, and MS with that prepared by treatment of **1b** with bromoacetyl bromide/dimethylaniline followed by morpholine (see above). Anal. Calcd for $C_{26}H_{41}NO_8$: C, 63.01; H, 8.34; N, 2.83. Found: C, 62.96; H, 8.38; N, 2.79.

1-(Morpholinoacetyl)forskolin (5). To a stirred solution of 50 mg (0.101 mmol) of **2** in 0.5 mL of dry dichloromethane was added 11 mg (0.090 mmol) of DMAP. The reaction mixture was cooled to 0–5 °C and a solution of 0.011 mL of acetic anhydride in 0.5 mL of dichloromethane was added, after which the solution was allowed to warm to room temperature and stirred for 10 min. The mixture was poured into ice/water/ether, and the organic layer was separated, washed with water and brine, dried (Na_2SO_4), filtered and concentrated to an oil. The oil was purified by flash chromatography on silica gel (eluent 1/1 ethyl acetate/hexane) to provide **5** (35 mg, 64.5%). Recrystallization from cyclohexane/ethyl acetate provided analytically pure material: mp 174–175 °C; IR ($CHCl_3$) 3031, 1750, 1724, 1232, 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 2.18 (s, 3 H, $COCH_3$), 2.23 (br s, 1 H, H-5), 2.32–2.70 (m, 5 H, CH_2NCH_2, H-12), 2.98 (d, 1 H, H-12) (J = 17 Hz), 3.10 (br s, 2 H, $OCCH_2N$), 3.73 (m, 4 H, CH_2OCH_2), 4.49 (m, 1 H, H-6), 4.93 (dd, 1 H, H-15) (J = 10 Hz), 5.24 (dd, 1 H, H-15) (J = 17 Hz), 5.53 (m, 1 H, H-1),

(14) To confirm the chemical shift of proton H-6 (compound **2**) proton H-5 was irradiated at δ 2.14: the multiplet at δ 4.50 collapsed to a sharp doublet (J = 4 Hz).

(15) Based on recovered starting material.

(16) To confirm the chemical shift of proton H-6 (compound **3**), proton H-5 was irradiated at δ 2.22: the multiplet at δ 4.50 collapsed to a sharp doublet (J = 4 Hz).

5.57 (d, 1 H, H-7) (J = 4 Hz), 5.91 (dd, 1 H, H-14) (J = 11, 11 Hz); MS (EI) m/z (relative intensity) 583 (M^+, 6.3), 146 (40), 100 (100). Anal. Calcd for $C_{28}H_{43}NO_9$: C, 62.55; H, 8.06; N, 2.61. Found: C, 62.07; H, 8.05, N, 2.49.

1-(Morpholinoacetyl)forskolin (5). To a stirred solution of 2.0 g (4.88 mmol) of **1a** in 20 mL of dichloromethane was added 0.75 g (6.20 mmol) of dimethylaniline. The solution was cooled in an ice bath and a solution of 0.47 mL (1.09 g, 5.40 mmol) of bromoacetyl bromide in 20 mL of dichloromethane was added dropwise. The resulting blue solution was stirred in an ice bath for 1 h and poured into ice/dichloromethane/sodium bicarbonate, and the organic layer was separated, washed with water and brine, dried (Na_2SO_4), and concentrated to an oil.

The oil was dissolved in 20 mL of dichloromethane and added dropwise to a solution of 3 mL of morpholine in 20 mL of ethyl acetate in an ice bath. Following the addition the solution was stirred for 1 h in an ice bath and worked up as above to provide an oil. The oil was flash chromatographed on silica gel (eluent 25%, 50% ethyl acetate/hexanes) to provide **5** (2.12 g, 80.7%). Recrystallization from cyclohexane/ethyl acetate provided material that was identical by mp, IR, NMR, and MS with that prepared from **2**. Anal. Calcd for $C_{28}H_{43}NO_9$: C, 62.55; H, 8.06; N, 2.61. Found: C, 62.73; H, 8.14; N, 2.60.

Forskolin-1,9-Dimethylformamide Acetal (6). Forskolin (**1a**) (100 mg, 0.244 mmol) was dissolved in 1 mL of DMF dimethyl acetal and stirred for 20 h at 55 °C. The mixture was dissolved in ether, washed with water, dried (Na_2SO_4), filtered, and concentrated to an oil. The material was purified by flash chromatography on silica gel (eluent 3% methanol/dichloromethane) to provide **6** as an oil (85 mg, 79.1%): IR ($CHCl_3$) 2960, 1738, 1712, 1118, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 2.16 (s, 3 H, $COCH_3$), 2.28 (d, 1 H, H-5) (J = 2 Hz), 2.37–2.48 (d, 7 H, H-12, $N(CH_3)_2$), 2.87 (d, 1 H, H-12) (J = 16 Hz), 4.14 (m, 1 H, H-1), 4.49 (m, 1 H, H-6), 4.76 (s, 1 H, OCHN), 4.97 (dd, 1 H, H-15) (J = 11 Hz), 5.34 (dd, 1 H, H-15) (J = 17 Hz), 5.22 (d, 1 H, H-7) (J = 4 Hz), 5.82 (dd, 1 H, H-14) (J = 11, 10 Hz); MS (CI) m/z (relative intensity) 466 (M^+ + 1, 23), 421 (100), 315 (53). Anal. Calcd for $C_{25}H_{39}NO_7$: C, 64.49; H, 8.44; N, 3.01. Found: C, 64.69; H, 8.25; N, 3.09.

7-Desacetylforskolin-1,9-Dimethylformamide Acetal (7) (from 1a). A solution of 100 g (0.244 mol) of **1a** in 400 mL of DMF dimethyl acetal was stirred at 60–70 °C for 20 h. The solution was concentrated in vacuo and the residue dissolved in 400 mL of methanol to which was added a solution of 2 L of methanol and 600 mL of saturated potassium carbonate. The resulting mixture was stirred at 50–55 °C for 2 h after which was added 1.2 L of water. The mixture was allowed to stand overnight, filtered, and washed with methanol/water to provide **7** (76.6 g, 74.2%). The material was recrystallized from cyclohexane to provide colorless prisims, mp 144–147 °C: IR ($CHCl_3$) 2970, 1742, 1718, 1223, 1122 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05, (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 2.18–2.48 (m, 8 H, H-5, H-12, $N(CH_3)_2$), 2.88 (d, 1 H, H-12) (J = 16 Hz), 4.03 (d, 1 H, H-7) (J = 4 Hz), 4.13 (m, 1 H, H-1), 4.51 (m, 1 H, H-6), 4.74 (s, 1 H, OCHN), 4.98 (d, 1 H, H-15) (J = 11 Hz), 5.22 (d, 1 H, H-15) (J = 17 Hz), 5.97 (dd, 1 H, H-14) (J = 11, 10 Hz); MS (CI) m/z (relative intensity) 424 (M^+ + 1, 6.1), 423 (M^+, 35), 378 (100), 333 (61), 263 (54). Anal. Calcd for $C_{23}H_{37}NO_6$: C, 65.22; H, 8.81; N, 3.31. Found: C, 65.18; H, 8.76; N, 3.25.

7-Desacetyl-7-(morpholinoacetyl)forskolin-1,9-Dimethylformamide Acetal (8). To a stirred solution of 2.0 g (4.73 mmol) of **7**, 1.03 g (5.67 mmol) of morpholinoacetic acid hydrochloride, 1.15 g, (9.43 mmol) of DMAP, and 20 mL of dichloromethane was added 1.17 g (5.68 mmol) of DCC. The mixture was stirred for 20 h at room temperature after which an additional 1.17 g (5.68 mmol) of DCC and 1.15 g (9.43 mmol) of DMAP were added. The suspension was stirred for an additional 5 h after which were added 0.75 g of morpholinoacetic acid hydrochloride and 0.5 g (4.10 mmol) of DMAP. After being stirred for 20 h at room temperature, the suspension was filtered, diluted with dichloromethane, washed twice with sodium bicarbonate and once with water, dried (Na_2SO_4), filtered, and concentrated to an oil. The oil was purified by flash chromatography on silica gel (eluent 20% acetone/hexanes) to provide **8** (1.28 g, 49.3%), which crystallized on standing: mp 178–188 °C; IR ($CHCl_3$) 3023, 1756, 1723, 1122 cm^{-1}; ^1H NMR ($CHCl_3$) δ 1.02 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3), 2.27 (d, 1 H, H-5) (J = 2 Hz), 2.35–2.45 (m, 7 H, H-12, $N(CH_3)_2$), 2.64 (m, 4 H, CH_2NCH_2), 2.86 (d, 1 H, H-12) (J = 16 Hz), 3.31 (s, 2 H, $COCH_2N$), 3.75 (m, 4 H, CH_2OCH_2), 4.11 (br s, 1 H, H-1), 4.48 (br s, 1 H, H-6), 4.74 (s, 1 H, OCHN), 4.94 (dd, 1 H, H-14) (J = 10 Hz), 5.28 (d, 1 H, H-14) (J = 18 Hz), 5.45 (d, 1 H, H-7) (J = 4 Hz), 5.80 (dd, 1 H, H-15) (J = 10, 10 Hz); MS (CI) m/z (relative intensity) 551 (M^+ + 1, 1.1), 506 (100), 284 (40). Anal. Calcd for $C_{29}H_{26}N_2O_8$: C, 63.25; H, 8.42; N, 5.09. Found: C, 63.28; H, 8.37; N, 5.01.

7-Desacetyl-7-(morpholinoacetyl)forskolin (3). A solution of 300 mg (0.544 mmol) of **8** in 6 mL of methanol and 6 mL of 80% aqueous acetic acid was stirred for 48 h at room temperature. The solution was poured into ice/ethyl acetate/water, and the organic layer separated, washed twice with water and once with brine, dried (Na_2SO_4), filtered, and concentrated to an oil. The material was flash chromatographed on silica gel (eluent 20%, 30% ethyl acetate/hexanes) to provide **3** (0.173 g, 64.2%). Recrystallization from hexane/ethyl acetate provided analytically pure material identical by mp, IR, NMR, and MS with the compound prepared from esterification of **1b** with DCC, DMAP, and morpholinoacetic acid (see above). Anal. Calcd for $C_{26}H_{41}NO_8$: C, 63.01; H, 8.34; N, 2.83. Found: C, 63.16; H, 8.36; N, 2.67.

7-Desacetyl-6-(morpholinoacetyl)forskolin (9). To a stirred solution of 200 mg (0.404 mmol) of **3** in 4 mL of dry THF in an ice bath was added 0.41 mL of a 1 M solution of lithium bis(trimethylsilyl)amide in THF. The solution was stirred at 0–5 °C for 1 h and allowed to warm to room temperature, after which it was poured into ice/water, extracted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), and concentrated to an oil. The oil was purifed by flash chromatography on silica gel (eluent 40, 50, 60% ethyl acetate/hexanes) and the product-containing fractions were combined and concentrated to provide **9** (61 mg, 30.5%). Recrystallization from ethyl acetate provided analytically pure material: mp 199–204 °C; IR ($CHCl_3$) 3023, 1748, 1720, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 2.36 (d, 1 H, H-5) ($J_{6,5}$ = 2 Hz), 2.53 (d, 1 H, H-12) (J = 17 Hz), 2.54 (m, 4 H, CH_2NCH_2), 3.19 (s, 2 H, $COCH_2N$), 3.21 (d, 1 H, H-12) (J = 17 Hz), 3.74 (m, 4 H, CH_2OCH_2), 4.30 (d, 1 H, H-7) (J = 4 Hz), 4.66 (m, 1 H, H-1), 5.00 (d, 1 H, H-15) (J = 11 Hz), 5.19 (d, 1 H, H-15) (J = 17 Hz), 5.93 (m, 1 H, H-6), 6.12 (d, 1 H, H-14) (J = 11, 11 Hz); MS (CI) m/z (relative intensity) 496 (M^+ + 1, 100), 478 (28), 146 (29). Anal. Calcd for $C_{26}H_{41}NO_8$: C, 63.01; H, 8.34; N, 2.83. Found: C, 63.29; H, 8.61; N, 3.11.

Acknowledgment. We thank Anastasia Linville, Dana Hallberg, and Marc Agnew for spectra data and Drs. Helen H. Ong, Richard C. Allen, Nicholas J. Hrib, and Gregory M. Shutske for helpful discussions.

Registry No. **1a**, 66575-29-9; **1a** (1-bromoacetate), 120385-34-4; **1b**, 64657-20-1; **1b** (1-bromoacetate), 120385-33-3; **2**, 120385-29-7; **3**, 108211-64-9; **4**, 120385-30-0; **5**, 120385-31-1; **6**, 105575-66-4; **7**, 105535-42-0; **8**, 120385-32-2; **9**, 111124-64-2; $(CH_3)_2NCH(OCH_3)_2$, 4637-24-5.

π-Facial Selectivity in Norbornenobenzoquinone–Tropone Cycloaddition

Goverdhan Mehta* and Srinivasa Rao Karra

School of Chemistry, University of Hyderabad, Hyderabad 500 134, India

Received December 15, 1988

During the recent past, cycloaddition chemistry of tropone has been extensively investigated from mechanistic as well as synthetic perspectives.[1] Tropone has been

0022-3263/89/1954-2975$01.50/0