of coordination in individual proteins. (3) Effects on the proximal histidine associated with the R ⇄ T quaternary conformation influence the five-coordinated sites.

Acknowledgment. We express our sincere thanks to Prof. James Hyde and Dr. William Antholine for allowing us to perform the Q-band ESR measurements at the National Biomedical ESR Center at Milwaukee, WI. We also thank Dr. Periannan Kuppusamy for valuable suggestions.

Registry No. NiHbA, 82029-96-7; CuHbA, 82029-94-5; CuHbS, 82030-03-3; Ni, 7440-02-0; Cu, 7440-50-8; L-histidine, 71-00-1.

Communications to the Editor

Synthesis of (±)-Fredericamycin A

T. Ross Kelly,* Naohito Ohashi,
Rosemary J. Armstrong-Chong, and Stephen H. Bell

Department of Chemistry, Boston College
Chestnut Hill, Massachusetts 02167

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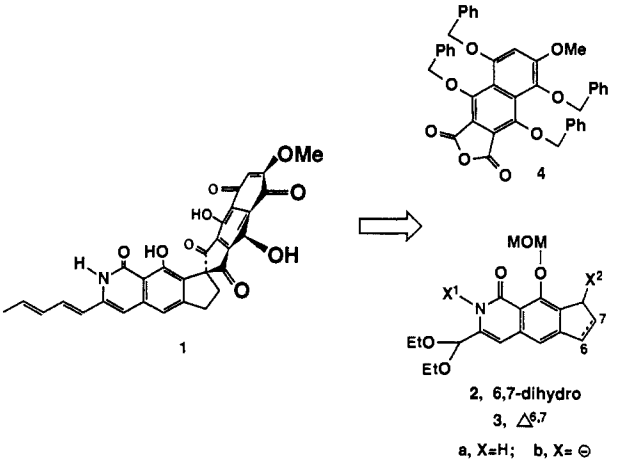
The 1982 report[1] of the unusual structure **1** and exceptional anticancer activity of fredericamycin A has generated considerable attention.[2,3] We now report the synthesis of (±)-fredericamycin A.

The synthetic strategy was to first construct synthons for the top and bottom units of **1** and to then effect their coupling in conjunction with elaboration of the spiro center, a process which was envisaged to commence with acylation of **2a** by **4**. Synthesis of **2a** was achieved (Scheme I) by three consecutive metalation reactions which serve to annelate the pyridone ring onto the methoxymethyl ether (**5**) of commercially available 4-indanol. Anhydride **4** was secured by the route outlined in Scheme II. Both **2a** and **4** are routinely prepared in 5–10-g batches.

It had been our hope that the MOM group in **2a** might facilitate



lateral[13] metalation of the adjacent benzylic carbon to give **2b**, thereby setting the stage for condensation with **4**. Unfortunately, lateral metalation of **2a** could not be achieved. Replacement of the MOM group with other possible activating groups (e.g., MEM,[14] $CH_2CH_2NMe_2$,[15] and OC(=O)NHMe[16]) was also unavailing. Attempts to carry the benzylic anion forward in a latent form (**2a**, X^2 = Br or $SnMe_3$) foundered due to the instability of intermediates.

In contrast to indane **2a**, indene **3a** [also regularly prepared (Scheme I) on a 5–10-g scale] could be converted in high yield to the corresponding anion **3b** under carefully defined conditions (3.2 equiv of *t*-BuLi, THF, −78 °C, 30 min) and **3b** is smoothly acylated by **4**. But while use of **3a** in place of **2a** solves the metalation problem, a new complication is introduced: the allylic

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(3) For reports of model studies on the construction of the spiro system of **1**, see: (a) Rama Rao, A. V.; Reddy, D. R.; Deshpande, V. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1119–1120. (b) Parker, K. A.; Koziski, K. A., Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181–2182. (c) Kende, A. S.; Ebetino, F. H.; Ohta, T. *Ibid.* **1985**, *26*, 3063–3066. (d) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 4723–4724. (e) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Ibid.* **1985**, *26*, 4725–4726. (f) Braun, M.; Veith, R. *Ibid.* **1986**, *27*, 179–182. (g) Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1986**, *51*, 749–752. (h) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878–888. For another approach to a bottom-half synthon for **1** see: Parker, K. A.; Breault, G. A. *Tetrahedron Lett.* **1986**, *27*, 3835–3838.

(4) (a) For a leading reference, see: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935–1937. (b) See also: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1–360.

(5) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312.

(6) Compare: Poindexter, G. S. *J. Org. Chem.* **1982**, *47*, 3787–3788. Diethoxyacetonitrile was obtained from Chemical Dynamics Corp.

(7) Prepared (96% overall) in three steps (NaH, CH_3OCH_2Cl, THF; $LiAlH_4$, THF; *t*-$BuSiMe_2Cl$, imidazole, DMF), from 4-hydroxyindan-1-one which is available (88%) by a modification of the known[8] $AlCl_3$-catalyzed isomerization of dihydrocoumarin.

(8) Loudon, J. D.; Razdan, R. K. *J. Chem. Soc.* **1954**, 4299–4303.

(9) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

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(12) Compare Homeyer, A. H.; Wallingford, V. H. *J. Am. Chem. Soc.* **1942**, *64*, 798–801.

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(14) Ellison, R. A.; Kotsonis, F. N. *J. Org. Chem.* **1973**, *38*, 4192–4196.

(15) Amupitan, J.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1978**, 852–853. Köster, F.-H.; Wolf, H. *Tetrahedron Lett.* **1981**, *22*, 3937–3940.

(16) Compare ref 4a.

(17) Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040–4044.

(18) (a) For reviews of the synthesis of spiro compounds, see: Krapcho, A. P. *Synthesis* **1974**, 383–419; **1976**, 425–444; **1978**, 77–126. (b) A similar reduction/aldol sequence has been reported: Holland, H. L.; MacLean, D. B.; Rodrigo, R. G. A.; Manske, R. F. H. *Tetrahedron Lett.* **1975**, 4323–4326. We thank Prof. Rodrigo for bringing the similarity of this reaction to our attention. (c) To date putative one-step conversions of **17** to **19** (e.g., with methoxide) have failed.

(19) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561–562.

(20) Bohlmann, F.; Mannhardt, H.-J. *Chem. Ber.* **1956**, *89*, 1307–1315.

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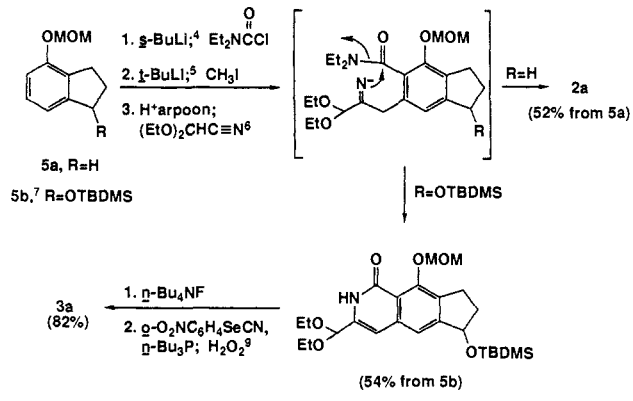
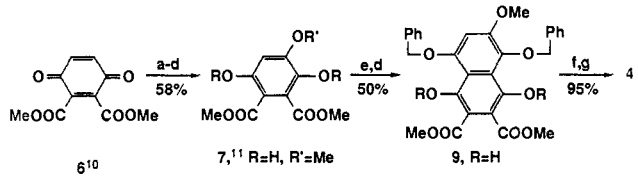
Scheme I

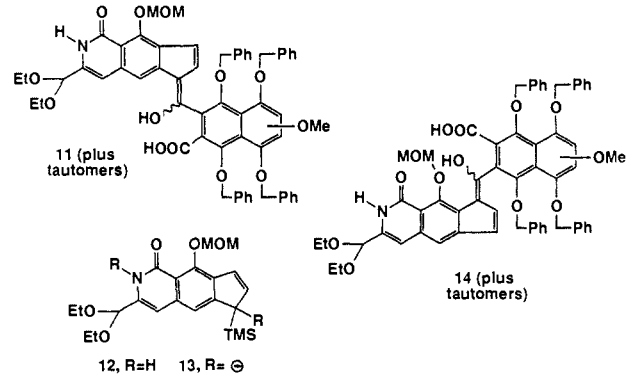


Scheme II[a]



[a] (a) Ac_2O, $BF_3{\cdot}Et_2O$, 60 °C; (b) MeOH/HCl; (c) MeI, K_2CO_3, acetone; (d) $PhCH_2Br$, K_2CO_3, acetone; (e)[12] 10 equiv of $MeOOCCH_2CH_2COOMe$, 20 equiv of $NaN(TMS)_2$, THF, 0 °C; (f) NaOH, aqueous MeOH, THF; (g) Ac_2O, Δ.

nature of the indenyl anion **3b** leads to regio*anti*specific reaction of **3b** with **4** to give exclusively **11**. The production of **11** rather

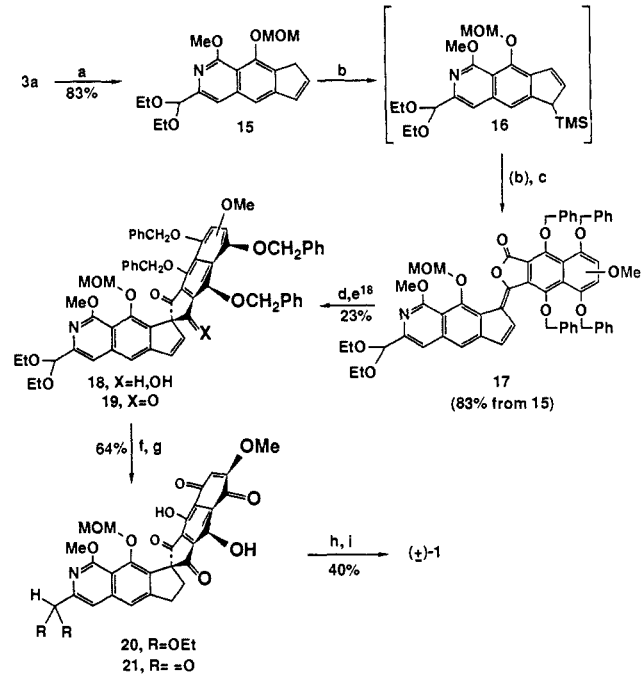


than its desired regioisomer offered little cause for celebration, but it nonetheless ultimately proved possible to exploit the seemingly adverse regiochemical propensity of **3b**, for reacting **3b** with TMSCl cleanly gives **12**. Without workup, **12** can be deprotonated in situ (1.2 equiv of *t*-BuLi, −78 °C, 30 min) (→**13**) and the steric bulk of the Me_3Si group then directs **4** to the desired terminus of the allylic system with substantial (~5.5:1) regioselectivity affording **14** [desilylation occurs during the workup (CH_3OH quench)].

Keto acid **14** can be carried forward to fredericamycin A, but better yields and complete regiospecificity are realized by enlisting quinoline **15** in place of quinolone **3a** as outlined in Scheme III. The conversion of **19** to **20** merits special note since in one operation (78%) the indene double bond is saturated, the four benzyl ethers (but not the benzylic acetal) are cleaved, and simply upon opening the hydrogenation vessel to the air, oxidation of the pale yellow hydrogenation product to the deep red naphthopurpurin **20** occurs. The synthetic fredericamycin A produced via Scheme III is identical in all appropriate respects with natural **1** by direct comparison.[21,22]

(21) The reported[1b] UV/vis spectrum of **1** contains peaks at 756 (sh) and 784 nm; in our hands neither natural nor synthetic **1** gives rise to these peaks. The extraneous peaks are due to an initially[1b] unrecognized impurity (Misra,[1a] R., personal communication).

Scheme III[a]



[a] (a)[17] MeI, Ag_2CO_3, C_6H_6, sonicate 5 days; (b) 2.1 equiv of *t*-BuLi, −78 °C, 15 min; 1.05 equiv of Me_3SiCl, 0.2 equiv of Et_3N; 1.05 equiv of anhydride **4**, 1.0 equiv of $NaN(TMS)_2$, 0.5 h, −78 °C; MeOH (−78 → +40 °C); (c) Ac_2O, NaOAc, THF, 20 °C, 20 min; (d) DiBAL, CH_2Cl_2, −78 °C, 15 min; quench with K_2CO_3/MeOH, −78 → +20 °C (effects aldol[18b]); (e) PDC, activated 4A molecular sieves,[19] CH_2Cl_2, pyridine; (f) H_2, Pd/C, EtOH; air; (g) aq HCl/THF; (h) CH_3CH=CHCH=PPh_3[20], THF; (i) NaBr, *p*-TsOH, MeOH, 60 °C.

Efforts to refine the synthesis of **1** and to prepare analogues for biological screening and mechanism of action studies are under way.

Acknowledgment. We thank the National Cancer Institute for support of this project (Grant CA37054). We are grateful to Dr. M. Suffness (NCI) for a sample of natural **1**, Dr. R. C. Pandey for invaluable information, Drs. V. Snieckus, H. Gschwend, and R. Misra[1a] for helpful discussions, and Ruth Pryor, Brian McKinnon, and Peggy Pitts for assistance in the preparation of intermediates.

Registry No. 1, 104438-52-0; **2a**, 104422-93-7; **2a** (6-OTBMS), 104422-95-9; **2a** (6-OH), 104423-06-5; **3a**, 104422-96-0; **4**, 104423-00-9; **5a**, 104422-92-6; **5b**, 104422-94-8; **7**, 103548-65-8; **8**, 104422-97-1; **9**, 104422-98-2; **10**, 104422-99-3; **11**, 104422-88-0; **12**, 104423-01-0; **14**, 104422-89-1; **15**, 104423-02-1; **17**, 104422-90-4; **18**, 104422-91-5; **19**, 104423-03-2; **20**, 104423-04-3; **21**, 104423-05-4; $MeOOCCH_2CH_2COOMe$, 106-65-0; CH_3CH=CHCH=PPh_3, 56374-57-3; 4-hydroxyindan-1-one, 40731-98-4.

(22) All compounds gave spectra consistent with the structures assigned. Satisfactory combustion analyses were obtained for a plurality of intermediates; mp's of crystalline solids are **2a**, 127–128 °C; 6-hydroxy-**2a**, 151–153 °C; **3a**, 123.5–124 °C; **4**, 166–168 °C dec; **7**, 149–151 °C; **8**, 149–150 °C; **10**, 150–151 °C; **15**, 66–67 °C; **21**, 174–175.5 °C dec. ^1H NMR (300 MHz, $CDCl_3$) of key compounds: **3a**, δ 1.28 (6 H, t, *J* = 7 Hz), 3.67 (3 H, s), 3.50–3.75 (6 H, m), 5.28 (2 H, s), 5.38 (1 H, s), 6.55 (1 H, s), 6.80 and 6.90 (2 × 1 H, each apparent dt, *J* = 5, 2 Hz), 7.32 (1 H, s), 8.60 (1 H, br s); **4**, δ 3.86 (3 H, s), 4.85 (2 H, s), 5.17 (2 H, s), 5.18 (2 H, s), 5.27 (2 H, s), 6.93 (1 H, s), 7.20–7.52 (20 H, m); **15**, δ 1.28 (6 H, t, *J* = 7 Hz), 3.64 (2 H, apparent t, *J* = 2 Hz), 3.66 (s, 3 H), 3.66–3.82 (4 H, m), 4.12 (3 H, s), 5.19 (2 H, s), 5.49 (1 H, s), 6.73 and 6.90 (2 × 1 H, each apparent dt, *J* = 2, 5 Hz), 7.49 (1 H, s), 7.51 (1 H, s); **19**, δ 1.27 (6 H, t, *J* = 7 Hz), 2.95 (3 H, s), 3.60–3.75 (4 H, m), 3.86 (3 H, s), 4.04 (3 H, s), 4.82 (1 H, d, *J* = 10 Hz), 4.93 (1 H, d, *J* = 10 Hz), 4.98 (2 H, s), 5,10–5.40 (6 H, m), 5.49 (1 H, s), 6.39 (1 H, d, *J* = 5 Hz), 6.94 (1 H, s), 7.10 (1 H, d, *J* = 5 Hz), 7.12–7.60 (20 H, m), 7.50 (1 H, s), 7.55 (1 H, s); **21**, δ 2.58 (2 H, apparent t, *J* = 7 Hz), 2.99 (3 H, s), 3.50 (2 H, apparent t, *J* = 7 Hz), 4.01 (3 H, s), 4.11 (3 H, s), 4.83 (2 H, s), 6.32 (1 H, s), 7.66 (1 H, s), 7.88 (1 H, s), 10.02 (1 H, s), 12.58 (1 H, s), 13.22 (1 H, s).