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

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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 (\pm) -Fredericamycin A

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The 1982 report¹ of the unusual structure 1 and exceptional anticancer activity of fredericamycin A has generated considerable attention.^{2,3} We now report the synthesis of (\pm) -fredericamycin Α.

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

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(7) Prepared (96% overall) in three steps (NaH, CH₃OCH₂Cl, THF; LiAlH₄, THF; t-BuSiMe₂Cl, imidazole, DMF), from 4-hydroxyindan-1-one which is available (88%) by a modification of the known⁸ AlCl₃-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,

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F. Ann. 1906, 349, 45-60.
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lateral¹³ 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 CH₂CH₂NMe₂,¹⁵ and OC(=O)NHMe¹⁶) was also unavailing. Attempts to carry the benzylic anion forward in a latent form $(2a, X^2 = Br \text{ or } SnMe_3)$ 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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^{34, 1389-1401. (}c) Warnick-Pickle, D. J.; Byrne, K. M.; Pandey, R. C.;
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White, R. J.; Misra, R.; Pandey, R. C. Biochemistry 1985, 24, 478-486.
(2) Chem. Eng. News. 1982, Aug 16, p 27; 1983, Sept 19, pp 36-37.
(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.,
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 ⁽⁶⁾ Compare: Poindexter, G. S. J. Org. Chem. 1982, 47, 3787-3788.
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⁽¹⁹⁾ Herscovici, J.; Antonakis, K. J. Chem. Soc., Chem. Commun. 1980, 561-562.

Scheme I



Scheme II^a



^a(a) Ac₂O, BF₃·Et₂O, 60 °C; (b) MeOH/HCl; (c) MeI, K₂CO₃, acetone; (d) PhCH₂Br, K₂CO₃, acetone; (e)¹² 10 equiv of MeOOCCH₂CH₂COOMe, 20 equiv of NaN(TMS)₂, THF, 0 °C; (f) NaOH, aqueous MeOH, THF; (g) Ac₂O, Δ .

nature of the indenyl anion 3b leads to regio*antispecific 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) (\rightarrow **13**) and the steric bulk of the Me₃Si group then directs **4** to the desired terminus of the allylic system with substantial (\sim 5.5:1) regioselectivity affording **14** [desilylation occurs during the workup (CH₃OH 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} unrecnogized impurity (Misra,^{1a} R., personal communication).

Scheme III^a



^a (a)¹⁷ MeI, Ag₂CO₃, C₆H₆, sonicate 5 days; (b) 2.1 equiv of *t*-BuLi, -78 °C, 15 min; 1.05 equiv of Me₃SiCl, 0.2 equiv of Et₃N; 1.05 equiv of anhydride 4, 1.0 equiv of NaN(TMS)₂, 0.5 h, -78 °C; MeOH (-78 → +40 °C); (c) Ac₂O, NaOAc, THF, 20 °C, 20 min; (d) DiBAL, CH₂Cl₂, -78 °C, 15 min; quench with K₂CO₃/MeOH, -78 → +20 °C (effects aldol^{18b}); (e) PDC, activated 4A molecular sieves,¹⁹ CH₂Cl₂, pyridine; (f) H₂, Pd/C, EtOH; air; (g) aq HCl/THF; (h) CH₃CH= CHCH=PPh₃²⁰, 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.

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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**₂CH₂COOMe, 106-65-0; CH₃CH=CHCH=PPh₃, 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, CDCl₃) 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), 4.98 (2 H, s), 5.10 (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), 3.60 (2 H, s), 5.00 (1 H, d, s), 4.93 (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 (1 H, s), 7.50 (1 H, s), 7.50 (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), 4.93 (1 H, d, s), 6.32 (1 H, s), 7.50 (1 H, s), 7.50 (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).