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SYNTHESIS OF THE RIFAMYCIN CHROMOPHORE

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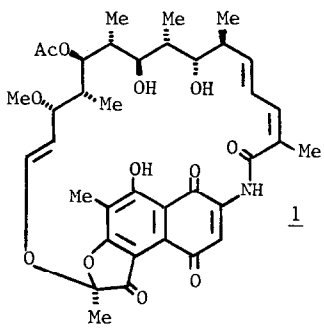
Summary: A regiospecific, Diels-Alder based synthesis of the naphthofuranone chromophore (2) of the rifamycins is described.

The family of macrolides known as the rifamycins (e.g. 1),[1] has attracted considerable synthetic interest recently. Most effort has focused on addressing the stereochemical problems embodied in the ansa bridge.[2] Construction of the naphthofuranone chromophore ring system itself (2), which is unique to the rifamycins, has received relatively scant attention: Kishi et al. have described a ca. 16-step synthesis of 3,[3] which was further elaborated during



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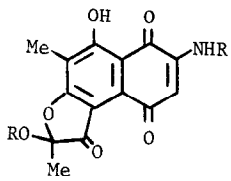

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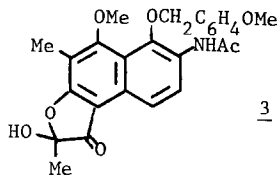
a, R=H
b, R=Ac



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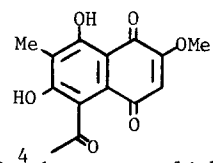

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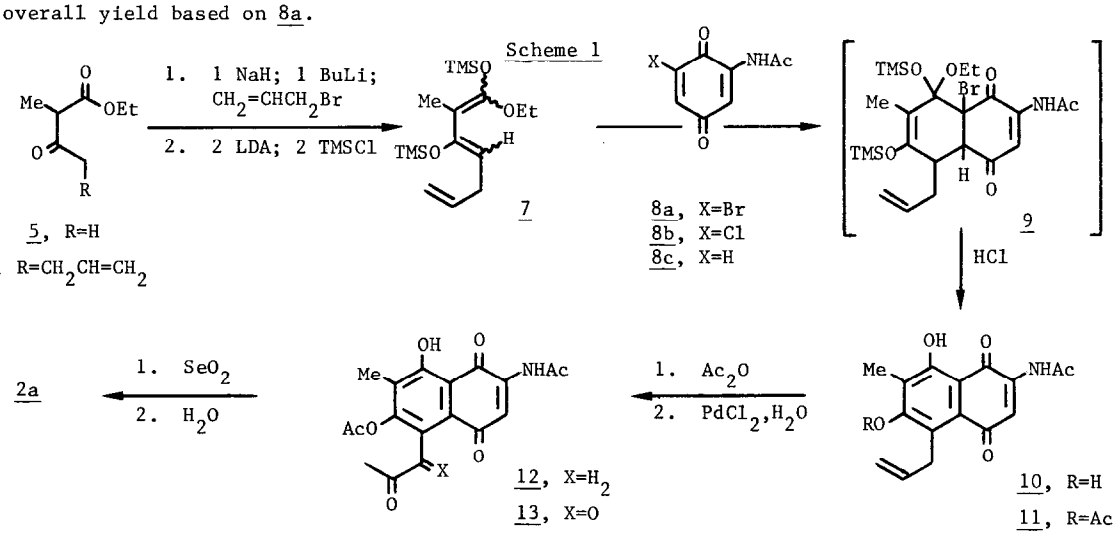
the final stages of their conquest[2a] of 1, and Parker and Petraitis[4] have accomplished a substantially shorter synthesis of the model compound 4.[5,10] We now report an efficient, regiospecific synthesis (Scheme 1) of the intact chromophore which affords 2a in 8 steps and 37% overall yield based on 8a.

Scheme 1



5, R=H
6, R=$CH_2CH=CH_2$

7

8a, X=Br
8b, X=Cl
8c, X=H

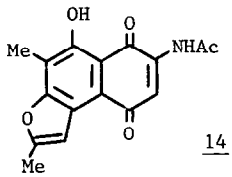
9

10, R=H
11, R=Ac

12, $X=H_2$
13, X=O

2a

Thus* reaction of 8a[8] with 2 equivalents of readily available diene 7 [prepared in 2 steps (89%) from ethyl 2-methylacetoacetate (5) using dianion technology] proceeds regiospecifically[9,10,11] to give the unstable adduct 9 which was directly transformed to 10 (73% from 8a). Attempts to oxidize the allyl sidechain of 10 were complicated by participation of the ortho hydroxy group [e.g., $Pd(OAc)_2$ oxidation[12a,b] of 10 gives 14 which could not be fruitfully elaborated]; but oxidation[12a,c] of the corresponding acetate 11 affords 12 in 76% yield. Selenium dioxide oxidation of 12 and hydrolysis provide the chromophore 2a (68%). The structure of 2a was confirmed by direct comparison with naturally derived 2a;[1b] the corresponding diacetyl[1b] derivatives (2b) are also identical.



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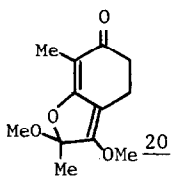

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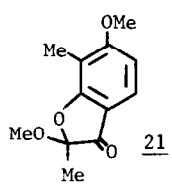

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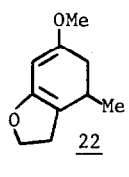

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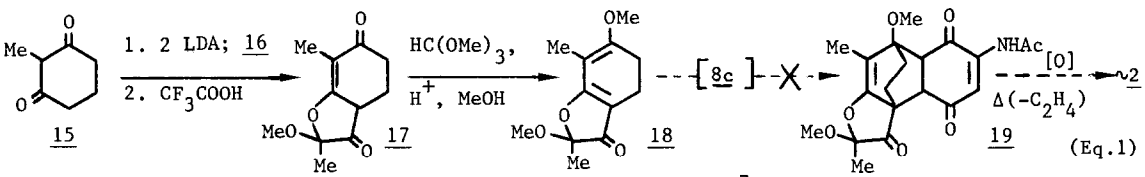
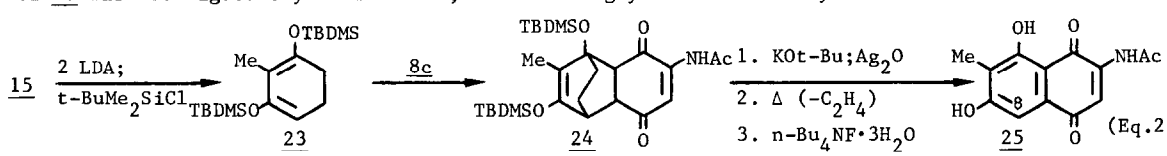
In an earlier approach to 2 the sequence outlined in Equation 1 was examined. Condensation of the dianion of 15 with methyl 2,2-dimethoxypropionate[14] (16) followed by intramolecular transketalization gives 17 (61% overall) which was converted to 18 (60%). The assignment of structure



(Eq.1)

18 rather than 20 to the dienone is supported by spectral data[7] and is strongly buttressed by dehydrogenation of 18 to 21. Unfortunately, 8c serves admirably for the oxidation of 18 to 21 and the formation of adduct 19 could not be induced either by varying reaction solvents or by using Lewis acid catalysis or ultrahigh pressure (8 kilobars in acetone).[15] Since both 22[16] and 23 (below) participate normally in Diels-Alder reactions and since 18 does not react with maleic anhydride, we attribute the lack of Diels-Alder reactivity of 18 to the electronic effects of the carbonyl group (18 can also be viewed as a vinylogous ester). Numerous attempts (e.g., reduction, ketalization, olefination, etc.) to mask the carbonyl group of 18 failed.

In contrast to 18, diene 23 adds to 8c virtually instantaneously at room temperature (Eq.2). Oxidation, thermolysis and desilylation afford 25 regiospecifically [although the regiochemistry of 25 was not rigorously established, it is strongly corroborated by the chemical shift (12.28) of the peri-OH resonance;[7,17] consideration of resonance and hydrogen bonding interactions[18] in 8c predicts the regiochemical outcome indicated]. Myriad attempts to append a pyruvoyl group to the C-8 carbon of 25 using both inter- and intramolecular stratagems were invariably unrewarding.



(Eq.2)

*See footnotes 6 and 7 for experimental details and spectral data, respectively.

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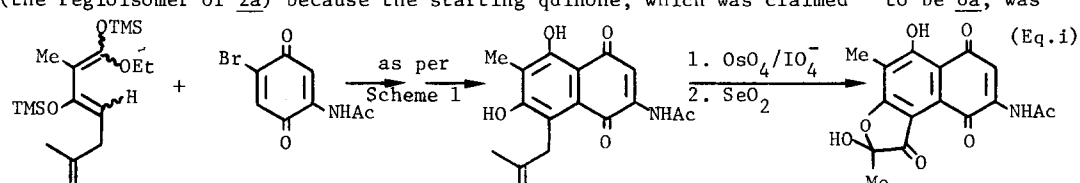
References and Notes

1. For leading references see a) V. Prelog and W. Oppolzer, Helv. Chim. Acta, 56, 2279 (1973) and adjoining papers and b) W. Kump and H. Bickel, ibid., 56, 2323 (1973) and adjoining papers. For reviews see inter alia c) W. Wehrli, Top. Curr. Chem. 72, 21 (1977) and d) K.L. Rinehart, Jr. and L.S. Shield, Prog. Chem. Org. Nat. Prod., 33, 231 (1976).
2. See inter alia a) Y. Kishi, Pure. Appl. Chem., 53, 1163 (1981) and reference 3 therein; b) H. Nakaoka and Y. Kishi, Tetrahedron, 37, 3873 (1981); c) S. Hanessian, J.-R. Pougny and I.K. Boessenkool, J. Am. Chem. Soc., 104, 6164 (1982); d) S. Masamune, B. Imperiali and D.S. Garvey, ibid., 104, 5528 (1982); e) M. Nakata, H. Takao, Y. Ikeyama, T. Sakai, K. Tatsuta and M. Kinoshita, Bull. Chem. Soc. Jpn., 54, 1749 (1981); f) E.J. Corey and D.A. Clark, Tetrahedron Lett. 21, 2045 (1980).
3. H. Nagaoka, G. Schmid, H. Iio and Y. Kishi, ibid., 22, 899 (1981).
4. K.A. Parker and J.J. Petraitis, ibid., 22, 397 (1981).
5. The rubradirins, which contain a napthoquinone system reminiscent of that in 1, have inspired a synthetic approach conceptually related to the route depicted in Scheme 1: A.P. Kozikowski, K. Sugiyama and E. Huie, ibid., 22, 3381 (1981). We thank Professor Kozikowski for experimental details.
6. a) Experimental (salient details). 5 → 6: 59.0 mmol 5 and 62.5 mmol NaH in 160 mL THF 15 min. at 0°C; then 60 mmol n-BuLi (hexane), 15 min at 0°; then 65 mmol CH_2=$CHCH_2Br$, 30 min at 5-15°; 3M HCl/ether workup; 90% yield, bp 67-68°/1.5 torr [general procedure: S.N. Huckin and L. Weiler, J. Am. Chem. Soc., 96, 1082 (1974)]. 6 → 7: add 22.6 mmol 6 to LDA (from 47.5 mmol diisopropylamine in 10 mL THF + 28.6 mL 1.66M BuLi in hexane); -78 → 0° → -78°; add 56.7 mmol Me_3SiCl, then 10 h at 20°; filter and concentrate → 6.7g 7 (99%, used crude). 7 + 8a → 10: 443 mg 8a + 1.13 g 7 in 4 mL MeCN 1 h at 20°; then add 4 mL 12 N HCl, stir 30 min at 20°; then add 10 mL 1:1 MeOH/H_2O, collect precipitate → 399 mg 10 (73%); anal. samp.[6b] (orange-red crystals from EtOAc) dec. 165∿168° without melting. 10 → 14: 172 mg 10, 10 mL HOAc, 130 mg $Pd(OAc)_2$ and 1 mL 80% t-BuOOH, 30 min at 20°C; triturate with H_2O → 161 mg (94%) 14 as a dark red solid mp 218-20°C (dec). 10 → 11: 230 mg 10, 9 mL Ac_2O, 0.26 mL pyridine at 20° (10 min); triturate with H_2O → 257 mg 11 (98%); anal. samp[6b] (dark orange crystals from MeOH) mp 158-9° (dec). 11 → 12: add 65 mg $PdCl_2$ to 121 mg 11 in 6 mL 5:47.5:47.5 H_2O/MeOH/THF; 6 h at 20°; dilute with 20 mL EtOAc and filter through NaH_2PO_4-deactivated silica gel; wash with H_2O; chromatograph on NaH_2PO_4-deactivated silica gel (95:95:10 EtOAc/pet. ether/MeOH) → 96 mg (76%) 12; anal. samp[6b] (dark yellow crystals from 5:1 cyclohexane/benzene) dec 166-70° without melting. 12 → 2a: 71 mg 12 and 23 mg SeO_2 heated 5 h at 90-95° in 10 mL DMF; H_2O/EtOAc workup; crude 13 stirred 12 h at 20° with 12 mL of a mixture of 1 g Na_2CO_3 and 100 mL 9:1 MeOH/H_2O; aq HOAc/CH_2Cl_2 workup; triturate with 1:1 $CHCl_3$/pet. ether → 39 mg pure 2a (68% from 12). 15 + 16 → 17: add 7.2 g 15 to 120 mmol LDA in 250 mL THF; -78° → 0°(0.5 h) → -78°; add 4.5 g (0.5 equiv) 16; 1.5 h at -78°, 0.75 h at 0°; aq tartaric acid/CH_2Cl_2 workup; concentrate; extract residue with CH_2Cl_2 (15 is insoluble); concentrate; dissolve in 20 mL $CDCl_3$ and add 1.5 mL CF_3COOH; ∿3 h at 20°; triturate with 100 mL ether → 3.79 g 17 (2 crops, 61% based on 16); anal. samp[6b] mp 167-9° (gas evolution) from EtOAc. 17 → 18: 600 mg 17 + 36 mL $HC(OMe)_3$ + 18 mL CH_3OH + 95 mg $TsOH \cdot 1H_2O$, reflux ∿1 h; aq $NaHCO_3$/CH_2Cl_2 workup; PLC (silica, 20:1 $CHCl_3$/EtOH) → 350 mg 18; mp 68-73° (hexane). 18 → 21: 64 mg 18 and 47 mg 8c 36 h at 55° in 0.5 mL acetone; PLC (silica, 20:1 $CHCl_3$/EtOH) → 32 mg 21; anal. samp.[6b] mp 128.5-129.5° from hexane. 15 → 23: dianion from 3.5 g 15 (as above); add 10.4 g TBDMS-Cl at -78°; → 20°; add 0.7 mL HMPA; 10 h; cold aq $NaHCO_3$/pet. ether workup → 10.4 g 23 (contains some monosilylated 15, used crude). 23 + 8c → 24: add 5 g crude 23 in 20 mL CH_2Cl_2 dropwise (20 min) to 2 g 8c in 40 mL CH_2Cl_2 at 20°; after 1 h concentrate and triturate with pet. ether → 4.3 g 24 (used crude). 24 → 25: to 4.1 g 24 in 250 mL THF at 0° add 1 g KOt-Bu; after 20 min add 5.4 g Ag_2O; after 30 min filter, aq. tartaric acid/CH_2Cl_2 workup → 4.1 g

oxidized 24; heat 1 g crude oxidized 24 neat 0.5 h at 125°; dissolve in 20 mL THF, add 2 eq n-$Bu_4NF \cdot 3H_2O$; 30 min at 20°; aq tartaric acid/ether workup; concentrate; triturate with ether → 347 mg 25 (67%), dec ∿160° without melting, b) a satisfactory combustion analysis was obtained for this compound.

7. Spectral data. 6: δ($CDCl_3$) 6.1-5.4 (1H,m), 5.1-4.8 (2H,m), 4.12 (2H,q,J=7Hz), 3.47 (1H,q, J=7Hz), 2.8-2.1 (4H,m), 1.26 (3H,d,J=7Hz), 1.21 (3H,t,J=7Hz). 7: δ($CDCl_3$) 6.0-5.5 (1H,m), 5.2-4.5 (3H,m), 4.15 and 3.80 (2H,q), 2.9-2.2 (2H,m), 1.67 (3H,s), 1.25 and 1.23 (3H,t, J=7Hz), 0.20 (9H,s), 0.14 (9H,s). 10: δ(CF_3CO_2H) 8.98 (1H,br s), 7.75 (1H,s), 5.9 (1H,m), 5.23-5.08 (2H,m), 3.99 (2H,br d,J≃5Hz), 2.50 (3H,s), 2.29 (3H,s). 14: δ($CDCl_3$) 12.21 (1H,s), 8.4 (1H,br s), 7.75 (1H,s), 7.44 (1H,s), 2.51 (3H,s), 2.44 (3H,s), 2.30 (3H,s). 11: δ(1:1 $CDCl_3$/DMSO-d_6) 12.65 (1H,s), 9.41 (1H,br s), 7.61 (1H,m), 5.05-4.7 (2H,m), 3.70 (2H,br d,J≃5Hz), 2.43 (3H,s), 2.23 (3H,s), 2.03 (3H,s). 12: δ($CDCl_3$) 12.47 (1H,s), 8.25 (1H,br s), 7.60 (1H,s), 4.04 (2H,s), 2.34 (3H,s), 2.32 (3H,s), 2.23 (3H,s), 2.10 (3H,s). 17: δ($CDCl_3$) 8.9 (1H,br s), 3.24 (3H,s), 2.6 (4H,m), 1.82 (3H,s), 1.70 (3H,s). 18: δ($CDCl_3$) 3.88 (3H,s), 3.25 (3H,s), 2.61 (4H,br s), 1.80 (3H,br s), 1.55 (3H,s); IR (CCl_4) 1720 cm^{-1}; UV (95% EtOH) 242 (5,600), 258 (7,700), 368 (13,000) (calc. 378). 21: δ($CDCl_3$) 7.52 (1H,d,J=9Hz), 6.64 (1H,d,J=9Hz), 3.92 (3H,s), 3.25 (3H,s), 2.13 (3H,s), 1.57 (3H,s); UV (abs EtOH) 214 (8,300), 233 (6,500), 288 (10,000) [284 calc: see A.I. Scott, "Interpretation of the Ultra-Violet Spectra of Natural Products," Pergamon, Oxford, 1964; p 336 (compound XCVII used for base value)], 324 (4,000). 23: δ($CDCl_3$) 4.60 (1H,m), 2.16 (4H,m), 1.68 (3H,s), 0.97 (18H,s), 0.14 (12H,s). 24: δ($CDCl_3$) 7.86 (1H,br s), 7.46 (1H,s), 2.99 (2H,m), 2.83 (1H,m), 2.16 (3H,s), 1.68 (4H,m), 1.42 (3H,s), 0.94 (9H,s), 0.88 (9H,s), 0.29 (3H,s), 0.16 (3H,s), 0.09 (6H,s). 25: δ(DMSO-d_6)12.2 (1H,s), 9.6 (1H,br s), 7.68 (1H,s), 7.26 (1H,s), 2.23 (3H,s), 2.09 (3H,s); MS 261 (M^+).
8. T. R. Kelly, A. Echavarren and M. Behforouz, submitted.
9. a) The utility of halo substituents for directing regiochemistry has been demonstrated by Brassard and associates: see J. Savard and P. Brassard, Tetrahedron Lett., 4911 (1979) and references therein. For other applications see b) footnote 6 in B.A. Pearlman, J.M. McNamara, I. Hasan, S. Hatakeyama, H. Sekizaki and Y. Kishi, J. Am. Chem. Soc., 103, 4248 (1981) and c) ref. 5.
10. a) Use of 8b[8] in place of 8a results in a less clean reaction and a lower yield of 10. Quinone 8c [F. Kehrmann and G. Bahatrian, Ber., 31, 2399 (1898)] appears (tlc) to undergo addition to 7 (in THF or CH_3CN at 20°) but we were unable to oxidize the adduct to 10. b) Use of freshly prepared 7 is essential; 7 rapidly deteriorates even on storage in the freezer and use of old samples of 7 results in substantial reduction of 8a/8b to the corresponding hydroquinones.
11. Due to an error in the literature we originally developed a synthesis (Equation i) of iv (the regioisomer of 2a) because the starting quinone, which was claimed[13] to be 8a, was



ii i iii (mp 162-4°) iv (dec 190-200°)

in fact[8] i (ii was prepared in a manner analogous to that employed for 7 using methallyl iodide. Use of ii in place of 7 in Scheme 1 was frustrated by intramolecular addition of the ortho OH to the olefinic grouping during the step corresponding to 9 → 10).
12. a) For a review see H. Mimoun, Angew. Chem. Int. Ed. Engl., 21, 734 (1982). b) compare ref. 9b. c) H. Mimoun, R. Charpentier, A. Mitschler, J. Fischer and R. Weiss, J. Am. Chem. Soc., 102, 1047 (1980).
13. G. Heller, W. Dietrich, T. Hemmer, H. Katzel, E. Rottsahl and P.G. Zambalos, J. prakt. Chem., 129, 211 (1931).
14. N.E. Hoffman and T.V. Kandathil, J. Org. Chem., 32, 1615 (1967).
15. We thank Professor W.G. Dauben and Dr. Stephen Peacock for conducting this experiment.
16. A. Murai, S. Sato and T. Masamune, J. Chem. Soc., Chem. Commun., 511 (1982).
17. In naphthoquinones with unnatural[11] regiochemistry the peri-OH resonance appears between 13 and 14δ while it appears between 11.5 and 13δ in compounds with natural regiochemistry.[7]
18. T. R. Kelly, Tetrahedron Lett., 1387 (1978).
19. Note added: After this manuscript was complete a similarly conceived approach to the chromophore of streptovaricin D was reported: B.M. Trost and W.H. Pearson, ibid., 24, 269 (1983).

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