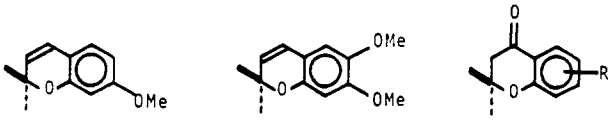
Novel Two-Step Pyrone to 4-Chromanone Transformation

Summary: A two-step synthesis of 4-chromanones has been developed on the basis of the decarboxylative dimerization of 4-methyl-6-hydroxy-2-pyrone followed by a decarboxylative Diels–Alder reaction.

Sir: The assemblage of chemical and pharmacological data on the benzopyrans is rich and well developed.[1] Interest in this broad class of compounds has been intensified by the recent discovery that certain naturally occurring Δ^3-chromenes (4*H*-1-benzopyrans), dubbed "precocenes", show biological activity as antiallatotropins (antijuvenile hormones).[2] The intriguing possibility exists that these compounds will form the basis for a new class of "natural" insecticides. Examples of the precocenes are 7-methoxy-2,2-dimethylchromene (**1**) and 6,7-dimethoxy-2,2-dimethylchromene (**2**). From a synthetic perspective the 4-chromanones, generalized as **3**, stand forth as direct and versatile precursors to the Δ^3-chromenes, in addition to their intrinsic worth as a significant structural subclass of the benzopyran natural products.[3] In light of this preamble, we report herein a versatile 4-chromanone synthesis marked by its novelty and brevity.



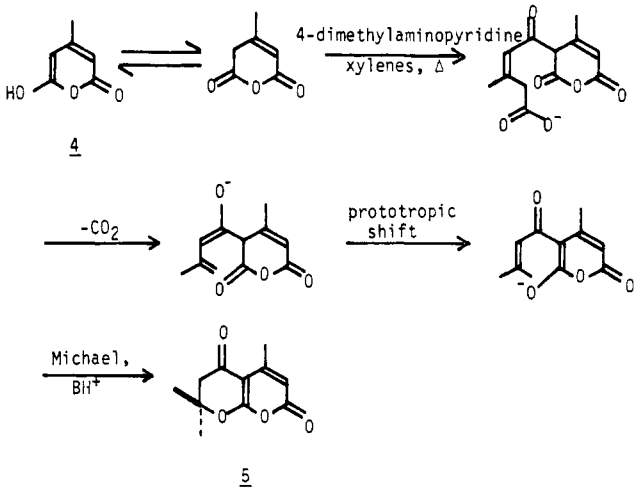
1 **2** **3**

The two-step synthetic access to 4-chromanones was presaged by the observation that 4-methyl-6-hydroxy-2-pyrone (**4**)[4] undergoes an amine-catalyzed decarboxylative dimerization (Scheme I). Specifically, treatment of the 2-pyrone with a catalytic amount of 4-(dimethylamino)-pyridine in refluxing xylenes gave in 42% yield the highly crystalline coumarochromanone **5** (mp 153 °C), which we christened "prechromanone". A mechanism for the formation of **5** is advanced in Scheme I.

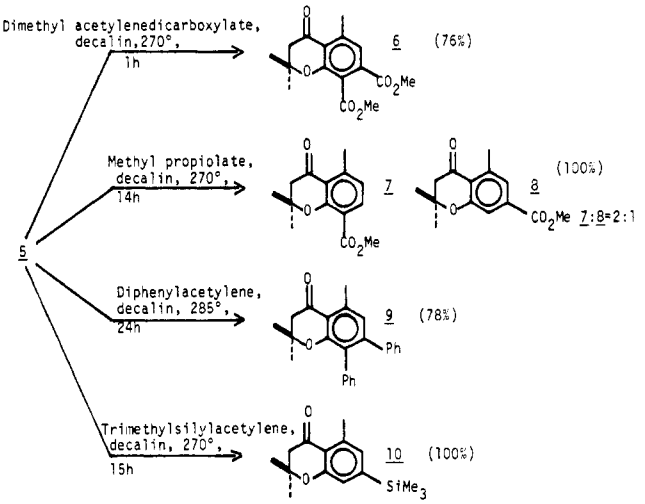
It was felt that the 2-pyrone moiety in **5** could be entered into partnership with an acetylenic dienophile to provide the desired 4-chromanones directly via a decarboxylative Diels–Alder reaction (Scheme II).[5] This intention was easily put to practice by heating "prechromanone" (**5**) in decalin solution with suitable dienophiles in sealed tubes. For example, dimethyl acetylenedicarboxylate served as a dienophilic coadjutor to provide in 76% yield the 4-chromanone **6** (mp 100–100.8 °C). Similarly, methyl propiolate gave in essentially quantitative yield a 2:1 mixture of the regioisomeric adducts **7** and **8**.[6] Diphenylacetylene entered the decarboxylative cycloaddition to yield the corresponding derivative **9**, mp 159–160 °C (78%). Finally, even trimethylsilylacetylene, which is regarded as a relatively feeble dienophile,[7] proved to be a superb substrate, generating quantitatively the single regioisomer **10**, mp 104.5–105.3 °C.[8]

In summary, this simple two-step synthesis offers direct and efficient access to a variety of 4-chromanones. Further studies on the scope, limitations, and application of this method are in progress and will constitute supervenient reports.[9,10]

Scheme I



Scheme II



(1) (a) Ellis, G. P., Ed. "Chromenes, Chromanones, and Chromones"; Wiley: New York, 1977. (b) Cambell, N. Rodd, E. H., Ed. "Chemistry of Carbon Compounds"; Elsevier: Amsterdam, 1959; Vol IVB, Chapter VIII. (c) Vandewalle, M. *Ind. Chim. Belg.* **1959**, *24*, 1037, 1207.

(2) (a) Bowers, W. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. *Science*, **1976**, *193*, 542. (b) Bowers, W. S. Centennial Meeting of the American Chemical Society, New York, NY, Apr 4–9, 1976; Abstract No. PEST 019. (c) Rodriguez, E. Second Chemical Congress of the North American Continent, San Francisco, CA, Aug 24–29, 1980; Abstract No. ORGN 213. (d) *Chem. Eng. News* **1976**, *54*(16), 19. (e) *Ibid.* **1980**, *58*(36), 42.

(3) Lockhart, I. M. "Chromenes, Chromanones, and Chromones"; Ellis, G. P., Ed.; Wiley: New York, 1977; pp 207–428.

(4) Bland, N., Thorpe, J. F. *J. Chem. Soc.* **1912**, 856.

(5) For reviews of 2-pyrones as Diels–Alder dienes, see: (a) Shusherina, N. P. *Russ. Chem. Rev. (Engl. Transl.)* **1974**, *43*, 10; (b) Shusherina, N. P.; Dmitrieva, N. D.; Luk'yanets, E. A.; Levina, R. Y. *Ibid.* **1967**, *36*, 175. For recent related applications, see: (c) Kozikowski, A. P.; Schmiesing, R. *Tetrahedron Lett.* **1978**, 4241; (d) Jung, M. E.; Lowe, J. A. *J. Chem. Soc., Chem. Commun.* **1978**, 95.

(6) This ratio was determined by ^{1}H NMR and GC analyses.

(7) Cunico, R. F. *J. Org. Chem.* **1971**, *36*, 929.

(8) The formation of only the 7-(trimethylsilyl)-4-chromanone **10** and of the mixture of regioisomeric esters **7** and **8** suggests that steric interaction between the acetylenic substituent and the geminal dimethyl moiety exerts significant influence on the regiochemical outcome.

(9) In the interest of readability, common names were utilized for compounds **5**–**10** in the text. Nomenclature for these structures consistent with Chemical Abstracts guidelines is as follows: **5**, 6,7-dihydro-4,7,7-trimethyl-2*H*,5*H*-pyrano[2,3*b*]pyran-2,5-dione; **6**, 2,3-dihydro-2,2,5-trimethyl-7,8-bis(carbomethoxy)-4*H*-1-benzopyran-4-one; **7**, 2,3-dihydro-2,2,5-trimethyl-8-(carbomethoxy)-4*H*-1-benzopyran-4-one; **8**, 2,3-dihydro-2,2,5-trimethyl-7-(carbomethoxy)-4*H*-1-benzopyran-4-one; **9**, 2,3-dihydro-2,2,5-trimethyl-7,8-diphenyl-4*H*-1-benzopyran-4-one; **10**, 2,3-dihydro-2,2,5-trimethyl-7-(trimethylsilyl)-4*H*-1-benzopyran-4-one.

(10) All compounds reported herein gave ^{1}H NMR, ^{13}C NMR, IR, and mass spectral and combustion analysis data consistent with the assigned structures.

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Registry No. 4, 67116-20-5; 5, 77224-28-3; 6, 77224-29-4; 7, 77224-30-7; 8, 77224-31-8; 9, 77224-32-9; 10, 77224-33-0; dimethyl acetylenedicarboxylate, 762-42-5; methyl propiolate, 922-67-8; diphenylacetylene, 501-65-5; (trimethylsilyl)acetylene, 1066-54-2.

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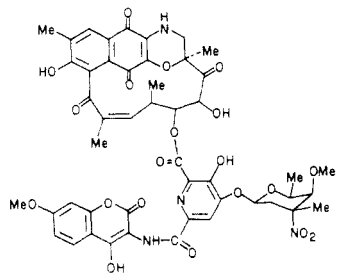
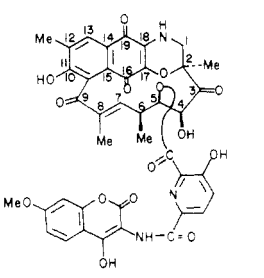
Studies Directed toward the Total Synthesis of the Rubradirin Antibiotics. 2. Synthesis of the Unique Morpholinonaphthoquinone Chromophore: A Lesson in Diels-Alder Regiocontrol by Diene Substituent Selection

Summary: A Diels-Alder approach to the aromatic/heterocyclic portion of the rubradirins is detailed.

Sir: Rubradirin and rubradirin B represent a unique class of ansamycin-related products. The structures of these compounds have been elucidated by a combination of NMR and X-ray methods.[1] The antibiotic rubradirin



Rubradirin

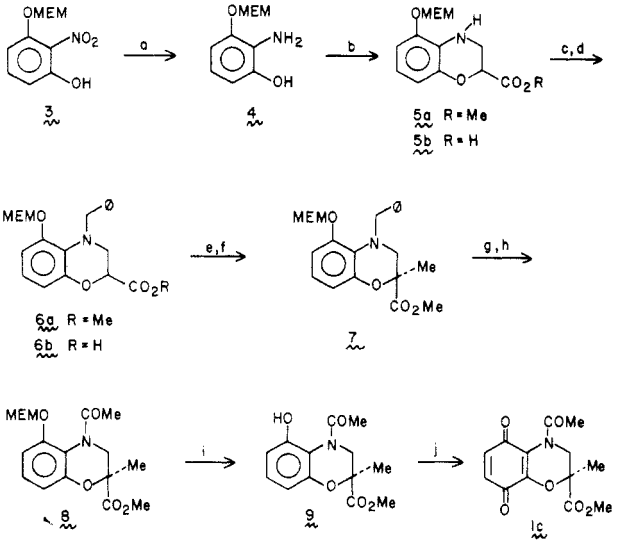


Rubradirin B
Absolute configuration 2S, 4S, 5R, 6S

interferes with ribosomal functions related to enzymatic peptide chain initiation. The aglycone of rubradirin retains moderate inhibitory activity toward ribosomal functions but also acts as an extremely potent inhibitor of RNAP. Rubradirin B, on the other hand, exclusively affects ribosomal functions, but to a smaller degree than rubradirin, and does not impair the function of RNAP at all.[2]

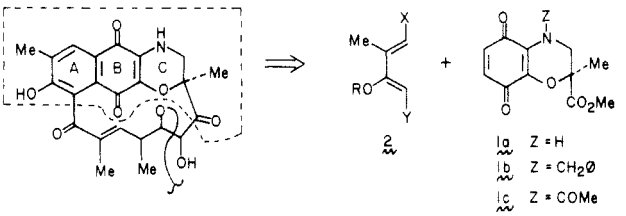
The promising biological activity of the products in combination with the unique structures has led us to embark on a program to design a total synthesis route to these materials. In accomplishing this objective, we have initially focused our attention on the preparation of the morpholinoquinone chromophore. Since, to our knowledge, only one such related compound has ever been prepared, this exercise in aromatic/heterocyclic chemistry posed a considerable challenge.[3] After some preliminary studies,[4] we

Scheme I. Preparation of the Morpholinoquinone 1c[a]



[a] (a) H_2, 10% Pd/C, $NaBH_4$, 2 N NaOH, 30 min, room temperature; (b) $BrCH_2CH(Br)CO_2Me$, K_2CO_3, acetone, Δ, 12 h; (c) $PhCH_2Cl$, NaI, K_2CO_3, acetone, 90 °C, 15 h (sealed tube); (d) 1:1:1 5% KOH-EtOH-THF, room temperature, 1 h; (e) (1) 4 equiv of LDA, THF, −50 °C, 2 h; (2) MeI, −50 °C to room temperature; (f) CH_2N_2, MeOH; (g) H_2, 10% Pd/C, HCl, PhH-EtOH, room temperature, 6 h; (h) Ac_2O, pyr, 110 °C, 5 h; (i) HCl gas, MeOH, 40 °C, 10 min; (j) Fremy's salt, 1/6 M KH_2PO_4, room temperature, 2 h.

decided that the best way to achieve access to this substructure was to consider preparing first the B, C portion, the morpholinoquinone **1**, and then to anneal this unit to



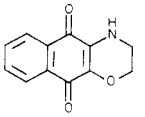
the ring A portion by a Diels-Alder reaction. An important regiochemical question would have to be addressed in this study, for the precise course of the cycloaddition reaction would depend on the nature of the substituents X and Y of the diene, and, most likely, on the type of Z group affixed to the dienophilic component.

The synthesis of **1** commenced with the readily available starting material 2-nitroresorcinol (**3**,[5] Scheme I). One of the phenolic groups was protected as its MEM ether,[6] and the nitro group was converted in quantitative yield to amine by palladium-catalyzed sodium borohydride re-

(1) (a) Hoeksema, H.; Lewis, C.; Mizsak, S. A.; Shiley, J. A.; Wait, D. R.; Whaley, H. A.; Zurenko, G. E. *J. Antibiot.* **1978**, *31*, 945. (b) Bhuyan, B. K.; Owen, S. P.; Dietz, A. *Antimicrob. Agents Chemother.* **1965**, 91. (c) Meyer, C. E. *Ibid.* **1965**, 97. (d) Hoeksema, H.; Chidester, C.; Mizsak, S. A.; Baczynskyj, L. *J. Antibiot.* **1978**, *31*, 1067. (e) Hoeksema, H.; Mizsak, S. A.; Baczynskyj, L. *Ibid.* **1979**, *32*, 773. (f) Mizsak, S. A.; Hoeksema, H.; Pschigoda, L. M. *Ibid.* **1979**, *32*, 771.

(2) Reusser, F. *J. Antibiot.* **1979**, *32*, 1186; *Biochemistry* **1973**, *12*, 1136.

(3) The parent system pictured below was made by treatment of 2-amino-3-aziridino-1,4-naphthoquinone with OH^- followed by HI: Casini, G.; Claudi, F.; Felici, M.; Ferrapi, M.; Grifantini, M. *Farmaco, Ed. Sci.* **1969**, *24*, 732.



(4) Kozikowski, A. P.; Sugiyama, K. and Springer, J. P. *Tetrahedron Lett.* **1980**, 3257.

(5) This compound was purchased from the Eastman Kodak Co. and used without further purification.

(6) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

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