cable in terms of solvation of the cationic electrophile as well as the carboxylate by the protic reaction component.

Additional studies of our system and related systems will be necessary before the mechanisms of acyl transfer to carboxylate ions in dipolar aprotic solvent becomes fully understood. Obviously, problems such as determination of the rate-limiting step in the reaction as well as the catalytic importance of leaving-group stabilization (i.e., by neighboring-group participation) will have to be addressed. Nevertheless, the present studies clearly demonstrate that, under appropriate conditions, carboxylate ions can effectively function as nucleophilic catalysts in hydrolytic reactions.

Acknowledgments. We warmly thank the Research Corporation and Boston College for financial assistance.

Reference and Notes

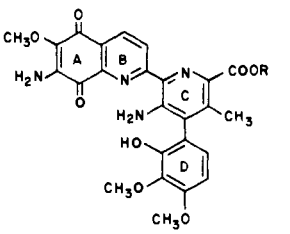
(1) Presented in part at the International Symposium on Physical Organic Chemistry, Chemical Institute of Canada, Toronto, Canada, Aug 6–9, 1979.
(2) M. L. Bender in "Bioorganic Chemistry", Vol. I, E. E. van Tamelen, Ed., Academic Press, New York, 1978, pp 19–57.
(3) (a) W. N. Lipscomb, *Acc. Chem. Res.*, **3**, 81 (1970); (b) E. T. Kaiser and B. L. Kaiser, *ibid.*, **5**, 219 (1972); (c) M. F. Dunn, *Struct. Bonding (Berlin)*, **23**, 61 (1975).
(4) (a) H. Brockerhoff and R. G. Jensen, "Lipolytic Enzymes", Academic Press, New York, 1974, pp 197–266; (b) R. A. Deems and E. A. Dennis *J. Biol. Chem.*, **250**, 9008 (1975).
(5) The absorption of the crown ether in the 220–240-nm region prevented us from monitoring the changes in the absorption of the carboxylic functions.
(6) (a) Hydrolysis of the mixed anhydride by "traces of water" under the reaction conditions could readily be ruled out by complete absence of *o*-toluate ion in the product solution, as determined by thin layer chromatographic comparison with an authentic sample of sodium *o*-toluate. For this purpose the acyl transfer reaction was carried out by stepwise addition (in small portions) of 1 equiv of *p*-nitrotoluate to 10 mL of 0.1 M crown ether solvated potassium acetate. The resulting solution was then added to 2 mL of freshly distilled aniline. The product solution was spotted on thin layer chromatographic plates and run against independently prepared acetanilide, *o*-toluylanilide, and sodium *o*-toluate. Absolutely no *o*-toluate was observed, and only small amounts of acetanilide were obtained. Significantly we found no traces of *o*-toluylanilide and the major component was the ester *p*-nitrophenyl *o*-toluate. (b) Direct observation of the mixed anhydride intermediate was possible by taking the IR spectrum of a sample of the acyl transfer product solution in acetonitrile. The long-wavelength carbonyl peak observed at 1765 cm^{-} (absent in the spectra of the individual starting materials) strongly suggests the presence of *o*-toluylacetate (iii).
(7) (a) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); (b) P. G. Gassman, P. G. Hodgson, and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976).
(8) Finely powdered potassium and sodium hydroxide as well as the corresponding methoxides were suspended in dry acetonitrile solution of 0.14 M 18-crown-6 and 15-crown-5, respectively. The mixtures were stirred at room temperature for several days. Using *p*-nitrophenol as indicator we found no ^{-}OH or $^{-}OCH_3$ ions in solution. Under similar conditions tetramethylammonium hydroxide readily deprotonated the indicator.
(9) It is now well recognized that the rate-determining step of hydrolytic acyl transfer reactions may vary depending on the system; changes in the solvent and the nucleophile may be involved. While in aqueous solution hydrolysis of aromatic esters by hydroxide ion the formation of the tetrahedral intermediate is rate limiting (ref 2, p 21), in case of aminolysis of esters in nonprotic media the collapse of the tetrahedral intermediate is the slow step; cf. F. M. Menger and A. C. Vitale, *J. Am. Chem. Soc.*, **95**, 4931 (1973), and F. Rivetti and U. Tonellato, *J. Chem. Soc., Perkin Trans. 2*, 1176 (1977).
(10) (a) J. Drenth, C. M. Enzing, K. H. Kalk, and J. C. A. Vessies, *Nature (London)* **264**, 373 (1976); (b) D. S. Sigman and G. Mooser, *Annu. Rev. Biochem.*, **44**, 889 (1975).

Joseph Hajdu,* Georgianna M. Smith
Department of Chemistry, Boston College
Chestnut Hill, Massachusetts 02167
Received August 20, 1979

Total Synthesis of Streptonigrin

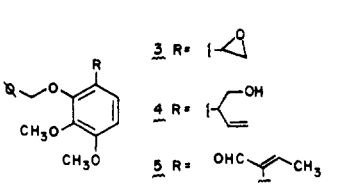
Sir:

Streptonigrin (**1**), a metabolite of a few species of *Streptomyces* and *Actinomyces*,[1,2] has been found quite effective in treatment of a variety of human tumors, although its high toxicity has precluded general clinical use.[3] Considerable work on elucidation of the biosynthesis[4] and the mechanism of action[5] of streptonigrin has recently been described. Many reports have also appeared[6,7] concerning synthesis of analogues of **1** and on model studies directed toward the synthesis of streptonigrin itself. We now describe the first total synthesis of this unique heterocyclic natural product.

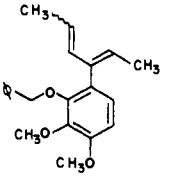


1 R = H **2** R = CH_3

2-Benzyloxy-3,4-dimethoxybenzaldehyde[8] was converted into epoxide **3** [$(CH_3)_3SI$, Me_2SO, NaH, −10 °C; 99%][9] which without purification was added to vinylmagnesium bromide (THF, 0 °C, 1 h) to give alcohol **4** in 97% yield. Oxidation of **4** with CrO_3–pyridine in methylene chloride, followed by brief treatment of the crude reaction product with dilute HCl, gave the conjugated unsaturated aldehyde **5**: 79%; IR (film) 2720, 1690, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (3 H, d, J = 7 Hz), 6.85 (1 H, d, J = 7 Hz), 9.5 (1 H, s).

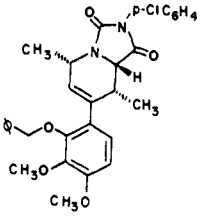


3 R =
4 R =
5 R =

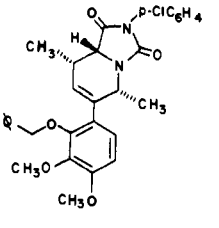


6

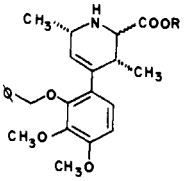
Treatment of aldehyde **5** with 1 equivalent of triphenylphosphonium ethylide (THF, −78 °C), followed by addition of 1 equivalent each of *n*-butyllithium and *t*-BuOK in *t*-BuOH (Schlosser procedure[10]), afforded diene **6** (75%) as an inseparable mixture of trans and cis isomers (~2.5:1, respectively, as estimated by NMR). This diene mixture was heated with 1-(*p*-chlorophenyl)-4-methoxyhydantoin (**7**)[11] (xylene, reflux, 72 h) to give an inseparable mixture of the desired Diels–Alder adduct **8** along with regioisomer **9**, in a ratio of ~3:1, respectively. We have never been able to get this cycloaddition reaction to go to completion, and thus routinely recycled unreacted diene **6**. The total yield of adducts **8** and **9** after one recycle was 56% and could be somewhat improved by further recycling.[12]



8



9



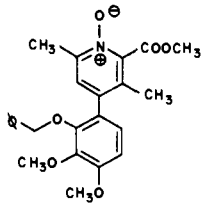
10 R = H
11 R = CH_3

The mixture of adducts **8** and **9** was hydrolyzed with $Ba(OH)_2$ (dioxane–H_2O, reflux, 24 h) to give a mixture of

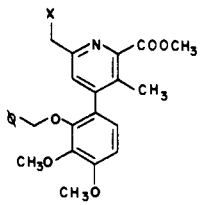
0002-7863/80/1502-3962$01.00/0

amino acid **10** and the corresponding regioisomeric compound derived from **9**. This mixture could be esterified ($SOCl_2$, CH_3OH, reflux, 12 h) to afford **11** containing some of the isomeric methyl ester. The crude mixture of amino esters was aromatized (5% Pd/C, toluene, reflux, 15 h) to afford the desired pyridine **12** [20% from the initial mixture of adducts **8** and **9**; IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 2.2 (3 H, s), 2.5 (3 H, s), 3.88, 3.90, 3.93 (3 H each, s), 4.8 (2 H, s), 6.7 (2 H, s), 6.8–7.2 (6 H, m)] and only a trace of the isomeric pyridine derived from **9**. It is not presently clear just why so little of the undesired pyridine is produced in the aromatization step.

N-Oxide **13** was prepared by treatment of pyridine **12** with *m*-chloroperbenzoic acid (CH_2Cl_2, room temperature; 100%). Upon heating with acetic anhydride (120 °C, 2 h) compound **13** was converted into acetate **14** [93%; mp 89–90 °C; IR ($CHCl_3$) 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (3 H, s), 2.25 (3 H, s), 4.9 (2 H, s), 5.25 (2 H, s)], which upon stirring at room temperature with K_2CO_3 in anhydrous methanol produced alcohol **15** (mp 128–128.5 °C). This alcohol was next trans-



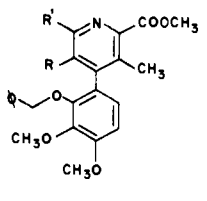
13



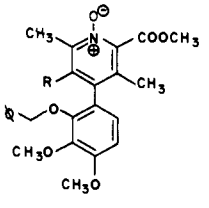
12 X = H
14 X = $OCOCH_3$
15 X = OH
16 X = Cl
17 X = 

formed into the chloride **16** ($SOCl_2$/benzene; mp 121–122 °C) which was alkylated with *N*-cyanomethylpyrrolidine (Me_2SO, 43 °C) to form quaternary salt **17**. Without isolation, **17** was treated first with *t*-BuOK in THF/Me_2SO (2:1) at −12 °C (deoxygenated argon, 10 min) and then with oxalic acid in THF/H_2O (2:1) at reflux to yield aldehyde **18**:[7b,13] 35% from acetate **14**; NMR ($CDCl_3$) δ 2.1, 2.75 (3 H each, s), 5.05 (2 H, s), 9.5 (1H, s).

Oxidation of **18** with pertrifluoroacetic acid (CH_2Cl_2, Na_2HPO_4, room temperature) led to *N*-oxide **19** (100%) which was further oxidized with $KMnO_4$ in acetone–H_2O (2:1) at room temperature giving carboxylic acid **20** (100%). Application of the Yamada modification[14] of the Curtius rearrangement to acid **20** [$(PhO)_2PON_3$, NEt_3, C_6H_6, reflux, 1 h, followed by H_2O, reflux, 0.5 h] afforded amine **21** in 74% yield. This compound was heated in acetic anhydride (120–125 °C, 2 h) and the crude product was hydrolyzed (K_2CO_3, dry CH_3OH, room temperature, 1.5 h) to yield alcohol **22** (68%). Oxidation of **22** with activated MnO_2 in chloroform at room temperature led to amino aldehyde **23**: 100%; IR ($CHCl_3$) 3500, 3350, 1720, 1675 cm^{-1}; NMR ($CDCl_3$) δ 2.2 (3 H, s), 4.95 (2 H, s), 10.2 (1 H, s).



18 R = CHO, R' = CH_3



19 R = CHO

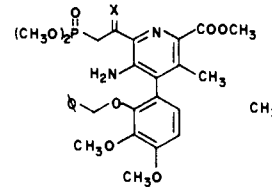
22 R = NH_2, R' = CH_2OH

20 R = COOH

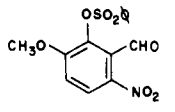
23 R = NH_2, R' = CHO

21 R = NH_2

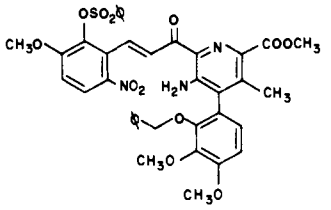
Hydroxyphosphonate **24** was formed by treatment of aldehyde **23** with $LiCH_2PO(OCH_3)_2$ in THF/HMPA (−78 °C; 46%) and oxidation of **24** with activated MnO_2 ($CHCl_3$, room temperature) provided ketophosphonate **25** (95%). This ketophosphonate was condensed with the known[15,16] nitroaldehyde **26** (KH, C_6H_6, room temperature, 2 h) to give nitrochalcone **27** (65%). Reductive cyclization of **27** with sodium hydrosulfite (CH_3OH–H_2O, reflux, 2 h)[15] led to the tetracyclic compound **28** in 90% yield and removal of the sulfonate protecting group was achieved with $NaOCH_3$ in dry methanol (40 °C, 40 min; 90%) yielding the A-ring phenol **29**.



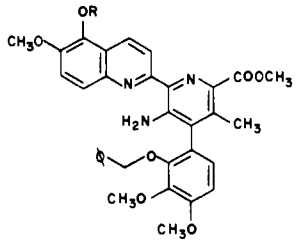
24 X = H, OH
25 X = O



26



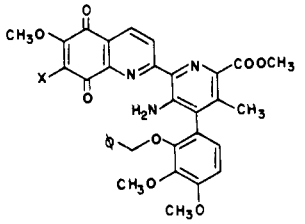
27



28 R = SO_2
29 R = H

Fremy's salt[17] oxidation of phenol **29** (CH_3OH–H_2O, room temperature, 10 min) cleanly produced quinolinequinone **30**: 90%; NMR ($CDCl_3$) δ 2.2 (3 H, s), 4.9 (2 H, AB quartet, J = 11 Hz), 6.3 (1 H, s), 6.8 (2 H, AB quartet, J = 8.5 Hz), 8.5 (1 H, d, J = 8.6 Hz), 9.0 (1 H, d, J = 8.6 Hz). This compound was transformed into the aminoquinone **31** (30%) by sequential treatment with (1) iodine azide/CH_3CN;[7c] (2) NaN_3/ DMF, room temperature, 15 min; and (3) sodium hydrosulfite/ CH_3OH–H_2O, reflux, 1 h[15] [NMR ($CDCl_3$) δ 2.2 (3 H, s), 4.9 (2 H, AB quartet, J = 11 Hz), 6.8 (2 H, AB quartet, J = 8.5 Hz)]. Our synthetic material was identical (IR, ^1H NMR, TLC, mass spectrum) with an authentic sample of compound **31** prepared from streptonigrin.[18]

Debenzylation of **31** was effected with anhydrous $AlCl_3$ ($CHCl_3$, room temperature, 1 h; 80%) to give streptonigrin methyl ester (**2**) which was identical with an authentic sample.[18] Hydrolysis of the ester group of **2** with 28% aqueous NH_4OH (room temperature, 4 days; 40%) afforded synthetic streptonigrin (**1**) indistinguishable from the natural product.



30 X = H
31 X = NH_2

Acknowledgments. We are extremely grateful to the National Science Foundation for support of this project on Grants MPS-75-01558 and CHE-78-19916. We acknowledge frequent helpful discussions with Professors R. W. Franck and S. J. Gould, and thank Dr. R. Minard and Mr. A. Freyer for determining mass spectra and NMR spectra, respectively, of our synthetic intermediates.

References and Notes

(1) Isolation: Rao, K. V.; Cullen, W. P. *Antibiot. Annu.* **1959–1960**, 950. Brazhnikovo, H. G.; Ponomarenko, V. I.; Kovsharova, I. N.; Kruglyak, E. B.; Prashlyakova, V. V. *Antibiot. (Moscow)* **1968**, *13*, 99.
(2) Structure: (a) Rao, K. V.; Biemann, K.; Woodward, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2532. (b) Chiu, Y.-Y.; Lipscomb, W. N. *Ibid.* **1975**, *97*, 2525.
(3) "USA–USSR Monograph, Methods of Development of New Anticancer Drugs", National Cancer Institute Monograph 45, DHEW Publication No. (NIH) 76–1037, 1977. Driscoll, J. S.; Hazard, G. F.; Wood, H. B.; Goldin, A. *Cancer Chemother. Rep.* **1974**, *4*, Part 2, 1.
(4) Gould, S. J.; Chang, C. C. *J. Am. Chem. Soc.* **1980**, *102*, 1702. Gould, S. J.; Chang, C. C.; Darling, D. S.; Roberts, J. D.; Squillacote, M. *Ibid.* **1980**, *102*, 1707.
(5) Cone, R.; Hasan, S. K.; Lown, J. W.; Morgan, A. R. *Can. J. Biochem.* **1976**, *54*, *219*. *Lown, J. W.; Sim. S. Ibid.* **1976**, *54*, 446, and references cited.
(6) For a review see Hibino, S. *Heterocycles* **1977**, *6*, 1485.
(7) (a) Kim, D.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 121. (b) *Ibid.* **1978**, *43*, 125. (c) Kende, A. S.; Naegely, P. C. *Tetrahedron Lett.* **1978**, 4775. (d) Wittek, P. J.; Liao, T. K.; Cheng, C. C. *J. Org. Chem.* **1979**, *44*, 870. (e) Rao, K. V.; Kuo, H.-S. *J. Heterocycl. Chem.* **1979**, *16*, 1241.
(8) Kametani, T.; Kozuka, A.; Tanaka, S. *Yakugaku Zasshi* **1970**, *90*, 1574. An improved preparation of this compound will be reported in the full paper.
(9) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(10) Schlosser, M.; Christmann, K. F. *Justus Liebigs Ann. Chem.* **1967**, *708*, 1. See also Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327.
(11) Ben-Ishai, D.; Goldstein, E. *Tetrahedron* **1971**, *27*, 3119.
(12) Regioisomer **8** was anticipated to be the major cycloadduct based upon detailed model studies of some similarly substituted dienes.[7a] The relative configurations assigned to **8** and **9** have not actually been determined, but are written as shown by analogy with these closely related model systems. We believe that some of the cis diene **6** slowly isomerizes thermally to the corresponding *trans* isomer during the long reflux period and thus actually contributes to the total yield of cycloaddition products. Compounds resulting from direct cycloaddition of model cis dienes to **7** were never observed during preliminary studies.[7a]
(13) Sanders, E. B.; Secor, H. V.; Seeman, J. I. *J. Org. Chem.* **1978**, *43*, 324.
(14) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203; *Tetrahedron* **1974**, *30*, 2151; *Chem. Pharm. Bull.* **1974**, *22*, 1398.
(15) Hibino, S.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 232.
(16) Reid, W.; Schiller, H. *Chem. Ber.* **1952**, *85*, 216.
(17) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229. We thank Professor L. Hegedus for providing us with a modified procedure for preparation of Fremy's salt.
(18) Compound **32** was prepared from natural streptonigrin by treatment with refluxing CH_3OH/boron trifluoride etherate[19] and was subsequently converted into benzyl ether **31** with benzyl bromide/K_2CO_3/acetone–THF/KI, room temperature, 3 days. We thank Dr. Nazir Khatri for his help with these experiments and Dr. John Douros (NCI) for supplying us with authentic streptonigrin.
(19) Kadaba, P. K. *Synthesis* **1972**, 628.
(20) Fellow of the A. P. Sloan Foundation, 1975–79; Recipient of a Research Career Development Award (HL-00541) from the National Institutes of Health, 1975–1980. Correspondence should be addressed to The Pennsylvania State University.

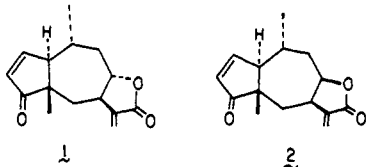
Fatima Z. Basha, Satoshi Hibino, Deukjoon Kim
Walter E. Pye, Tai-Teh Wu, Steven M. Weinreb*[20]
Departments of Chemistry
Fordham University, Bronx, New York 10458,
and The Pennsylvania State University
University Park, Pennsylvania 16802

Received January 25, 1980

Total Synthesis of Pseudoguaianolides: (±)-Aromaticin and (±)-Aromatin

Sir:

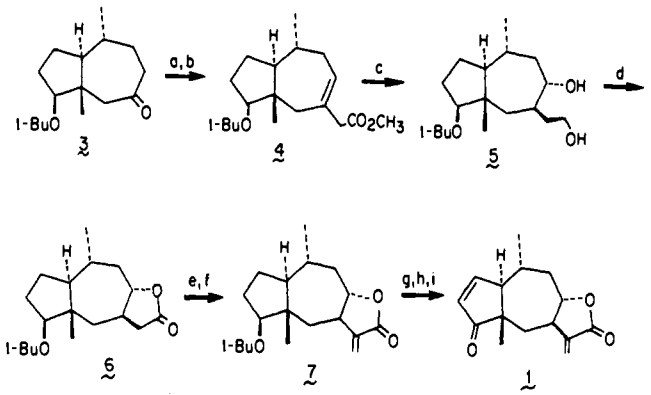
We report herein the first total synthesis of aromaticin (**1**) and aromatin (**2**), isolated from the Chilean plant *Helenium*



1 **2**

aromaticum (Hook) Bailey,[1] which are members of the helenanolide group[2] of pseudoguaianolides[3] characterized by an α-oriented methyl group at C-10.[3] To prepare for this undertaking, we had previously developed an expeditious route to properly functionalized bicyclo[5.3.0]decenone precursors,[4] in which the proper relative configurations at carbons 1, 5, and 10 were subsequently established.[5] These efforts afforded the key intermediate **3**, whose transformation into (±)-aromaticin (and subsequently (±)-aromatin) is outlined in Scheme I.

Scheme I[a]



3 **4** **5** **6** **7** **1**

[a] (a) LDA, $(CH_3)_3SiCH_2CO_2CH_3$, THF, −78 → 25 °C; (b) LDA–HMPA, THF, −78 °C, then CH_3CO_2H; (c) BH_3–THF, −78 → 25 °C, H_2O_2, OH^-; (d) Pt, O_2, H_2O–acetone; (e) LDA–HMPA, $BrCH_2OCH_3$, −78 → −5 °C; (f) 3 equiv of KO-*t*-Bu, 1 equiv of H_2O, THF; (g) TFA, 0 °C, 3 h, then NaOH/*i*-PrOH–H_2O, 25 °C, 2 h; (h) PCC, CH_2Cl_2; (i) C_6H_5SeCl, EtAc, HCl, then $NaIO_4$, THF–H_2O, 25 °C, 7 h.

Our regio- and stereoselective lactone annelation commenced with carbanion attack at C-7 in **3** (methyl trimethylsilylacetate and LDA; quantitative yield). Once the acrylate side chain had been introduced, deconjugation toward C-8 was cleanly achieved by protonolysis of the kinetic dienolate resulting from LDA-induced proton abstraction at the less hindered γ position (→ **4**). The stage was then set for the crucial hydroboration of **4**,[6] wherein two additional chiral centers can be correctly introduced if regiospecific attack by a borane occurs from the α face of the molecule, via a chair rather than twist-boat conformation. Complete hydroboration of the hindered double bond in **4**, at the low temperatures chosen to ensure maximum stereoselectivity, could only be achieved with borane itself; this, in turn, left no choice but to allow unavoidable ester reduction[7] to occur as well, affording diol **5**, as a 4:1 stereoisomeric mixture, in 95% yield after oxidative workup. Purified **5**,[6] mp 114–115 °C, was selectively oxidized (Pt/O_2) to yield the required[8] lactone **6**,[6] mp 88.5–89 °C, in 45% overall yield (four steps) from **3**: IR (neat) 1780, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2 (C-8 H, br m), 3.4 (C-4 H, br m).

α-Methylenation of **6** was achieved in two steps (Scheme I), surely one of the more direct approaches for solving this ubiquitous problem in natural products synthesis.[10] After alkylation[11] of **6** with methoxymethyl bromide, "unsolvated" potassium *tert*-butoxide–potassium hydroxide in THF[12] was used to effect methanol elimination *and* saponification, so as to generate the acrylate *anion* which is presumably more protected from nucleophilic destruction than the corresponding acid or lactone. Quenching the basic solution in dilute acid afforded crude **7**[6b] [IR (neat) 1765, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00 (1 H, d, J = 3 Hz), 5.26 (1 H, d, J = 3 Hz)], which was directly subjected to deblocking and oxidation of the C-4 alcohol, according to Marshall.[13] This afforded 2,3-dihydroaromaticin (2,3-dihydro-**1**), mp 123–124 °C, in ~20% overall yield from **6** (five steps). (+)-2,3-Dihydroaromaticin has recently been isolated from *Telekia speciosa*[14] and we were pleased to find the 100-MHz ^1H NMR spectrum and the mass spectrum (70 eV) of our synthetic material to be in excellent agreement with the detailed spectral data provided.[14] Insertion of the 2,3 double bond via selenylation and selenoxide elimi-

0002-7863/80/1502-3964$01.00/0