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.

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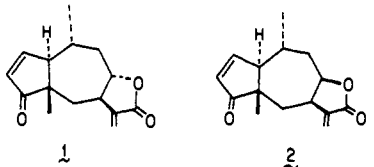
Total Synthesis of Pseudoguaianolides: (±)-Aromaticin and (±)-Aromatin

Sir:

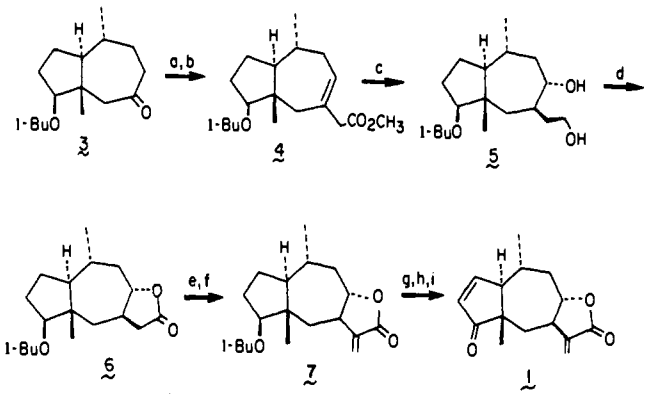
We report herein the first total synthesis of aromaticin (**1**) and aromatin (**2**), isolated from the Chilean plant *Helenium*



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-

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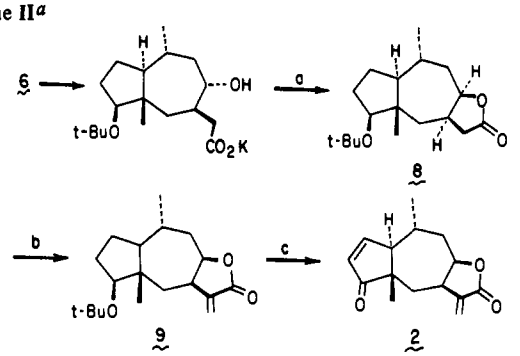
Scheme II[a]



[a] (a) excess CH_3SO_2Cl, $(C_2H_5)_3N$, THF; aqueous NaOH; (b) Stiles reagent, then CH_2O, $(C_2H_5)_2NH$, CH_3CO_2H;[21] (c) Scheme I, steps g–i.

nation[15] (in 75% crude yield) provided crystalline (±)-**1**, mp 178–181 °C, which was identical in all respects except for optical rotation with authentic (+)-**1**, by TLC, ^1H NMR, IR and MS.[16]

Having rigorously characterized (±)-**1**, we returned to **6** and undertook regiospecific C-8 epimerization of the latter, to gain access to aromatin (**2**) as well (Scheme II). The dried potassium salt of hydrolyzed **6** (KOH-CH_3OH) was reacted with excess mesyl chloride and triethylamine in tetrahydrofuran (sulfene-generating conditions[17]), so as to favor C-8 *hydroxyl activation*,[18] necessary for inversion, at least competitively with carboxyl activation,[19] which normally predominates during arenesulfonylation[20] (and promotes lactonization with stereochemical retention[20]). The crude mixed anhydride-C-8 mesylate so produced was treated directly with aqueous sodium hydroxide, resulting in quantitative isolation of crude **8**:[6b] IR (neat) 1780, 1200 cm^{-1} (~85% inversion, based on NMR integration of C-8 proton signals, at δ 4.8 in **8** and 4.2 in **6**). The latter was treated with Stiles reagent, whereupon *un*carboxylated residual **6** was removed by extraction, followed by Mannich alkylation-decarboxylation according to Parker and Johnson.[21] The cis-fused methylenelactone **9**[6b] [mp 95–97 °C; IR (neat) 1760, 1660 cm^{-1}], preparable in 50% yield from **6** (three steps), was then converted into **2** using the same reactions[13,15] employed in the **7** → **1** transformation. During this series, crystalline 2,3-dihydroaromatin[6b] (2,3-dihydro-**2**) was obtained in high purity, mp 113–114 °C, and shown to be devoid of 2,3-dihydro-**1** (by NMR). The yield of (±)-**2**, mp 125–126 °C, was ~35% for five steps beginning with **9**, and the ^1H NMR spectrum was identical with that reported[3b] for (−)-**2**.

These accomplishments, with some steps yet to be refined, are cause for optimism in our continuing efforts to synthesize even more complex members of the fascinating pseudoguaianolide family and we shall report on these matters in due course.

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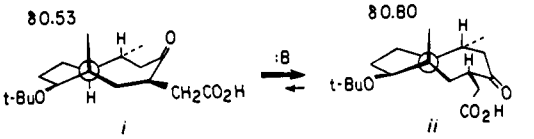
References and Notes

(1) Romo, J.; Joseph-Nathan, P.; Diaz, F. *Tetrahedron*, **1964**, *20*, 79–85.
(2) For recent accomplishments in the total synthesis of helenanolides, see: Ohfune, Y.; Grieco, P. A.; Wang, C.-L., J.; Majetich, G. *J. Am. Chem. Soc.* **1978**, *100*, 5946–5948. Grieco, P. A.; Ohfune, Y.; Majetich, G. *Tetrahedron Lett.* **1979**, *35*, 3265–3268. Grieco, P. A.; Ohfune, Y.; Majetich, G. *J. Org. Chem.* **1979**, *44*, 3092–3093. Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 7626–7627. Kok, P.; de Clerq, P. J.; Vande walle, M. E. *J. Org. Chem.* **1979**, *44*, 4553–4557.
(3) (a) Romo, J.; Romo de Vivar, A. *Fortschr. Chem. Org. Naturst.* **1967**, *25*, 90–130. (b) Yoshioka, H.; Mabry, T. J.; Timmerman, B. N. "Sesquiterpene Lactones"; University of Tokyo Press: Tokyo, 1973.
(4) Lansbury, P. T.; Serelis, A. K. *Tetrahedron Lett.* **1978**, *22*, 1909–1912.
(5) Lansbury, P. T.; Hangauer, D. G., Jr. *Tetrahedron Lett.* **1979**, *38*, 3623–3626.
(6) (a) Satisfactory elemental analyses and (b) ^1H NMR and infrared spectral data consistent with the assigned structure were obtained for this compound.
(7) Varech, D.; Jacques, J. *Bull. Soc. Chim. Fr.* **1969**, 3505–3515.
(8) The presumption that **6** possessed the proper relative configuration for preparing **1** was initially verified as follows. Ruthenum tetroxide oxidation (Lee, D. G.; van den Engh, M. In "Oxidation in Organic Chemistry", Trahanovsky, W. S., Ed.; Academic Press: New York, 1973; Part B, pp 177–227) of **5** or the cyclic ether derived from **5** via intramolecular alkoxide displacement upon the primary monotosylate gave not only the expected **6** (~40%) but also the keto acid **i** (~40%), mp 119–120 °C. Since the C-7 side chain in acid **i** would not epimerize during RuO_4 oxidation,[9] the only chair conformation that relieves diaxial compression between β-oriented substituents at C-5 and C-7 is that in which the C-5 methyl is highly shielded (δ 0.53 ppm). As anticipated, DBN epimerized **i** to the keto acid **ii**,[6b] mp



85–87 °C, whose α-oriented C-7 side chain allows population of the alternate chair conformation in which the C-5 methyl signal "shifts back" to δ 0.80 ppm.
(9) (a) Butterworth, R. F.; Overend, W. G.; Williams, N. R. *Tetrahedron Lett.* **1968**, 3239–3242. (b) Wheeler, J. W.; Oh, S. K.; Benfield, E. F.; Neff, S. E. *J. Am. Chem. Soc.* **1972**, *94*, 7589–7590. (c) Branca, S. J.; Smith, A. B., III *J. Org. Chem.* **1977**, *42*, 1026–1030.
(10) (a) Grieco, P. A. *Synthesis* **1975**, 67–82. (b) Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715–6717. (c) Patterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, 993–996.
(11) Herrmann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711–712.
(12) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918–920.
(13) Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312–4313.
(14) Bohlmann, F.; Mahanta, P. K. *Phytochemistry* **1979**, *18*, 887–888.
(15) Grieco, P. A.; Ohfune, Y.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 7393–7395.
(16) Experimental details for all stages in the synthesis of **1** are provided in the Ph.D. Dissertation of D. G. Hangauer, Jr., SUNY at Buffalo, 1980.
(17) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195–3196.
(18) The DEADCAT reaction (cf. Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284–1285) has found use for forming γ-butyrolactones with hydroxyl inversion when the functional groups are *geometrically prevented* from rapid lactonization. However, even when the potassium salt of hydrolyzed **6** is neutralized in situ, relactonization takes precedence over attempted DEADCAT reaction, and no detectable **8** is produced.
(19) It is likely that carboxylate attack on *sulfene*[17] is *reversible*, while attack on hydroxyl and zwitterion collapse via proton transfer is irreversible. This speculation seems valid, since mesylation in pyridine gives a 1:1 mixture of **8** and recovered **6**.
(20) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000–2006.
(21) Parker, W. H.; Johnson, F. *J. Org. Chem.* **1973**, *38*, 2489–2496.
(22) Allied Chemical Corporation Predoctoral Fellow, 1979–1980.

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X-ray Structural Analysis of $H_3[Rh_4(bridge)_8Cl][CoCl_4]_4 \cdot nH_2O$. The Photoactive Species in the Production of Hydrogen from Aqueous Solutions

Sir:

The photochemical production of hydrogen gas from aqueous solutions has recently been an extremely active research area. Several hydrogen producing systems have been designed and investigated by different workers.[1] The central point in these investigations has been the determination of the mechanism for hydrogen formation from photogenerated precursors. As an aid to illucidating the mechanism of photochemical hydrogen production in the $Rh_2(bridge)_4^{2+}$ (bridge

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