Enantioselective Total Synthesis of Miroestrol†

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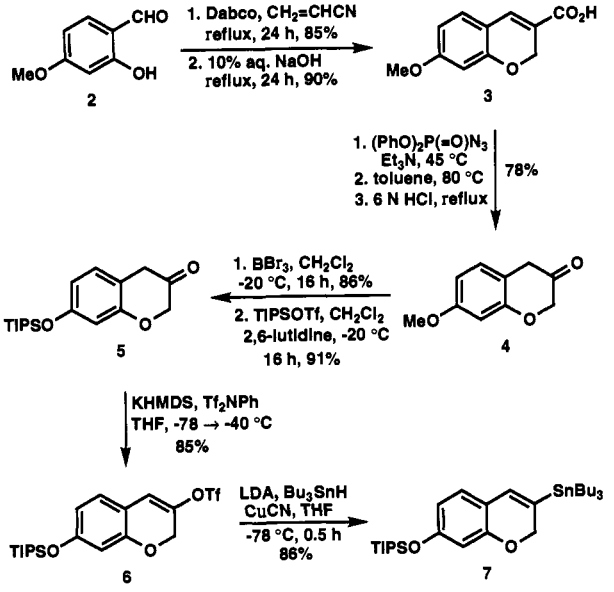
The Thai medicinal plant *Pueraria mirifica* (Thai *kwao keur*), which has a fascinating history in the folk medicine of southeast Asia, contains the unusual estrogenic phenol miroestrol (**1**), first isolated more than fifty years ago.[1-4] The assignment of structure (without absolute configuration) was made in 1960 on the basis of X-ray diffraction studies.[5] The synthesis of miroestrol has remained since that time as a classical unsolved problem, despite a number of attempts.[6] Reported herein is the first total synthesis of **1** by a route which is enantioselective and convergent. The ring system was constructed by a novel transannular double cation-olefin cyclization which, surprisingly, may also be involved in the biosynthesis.

On the basis of the large positive optical rotation of miroestrol, $[\alpha]_D^{17}$ +300°,[4b] and the octant rule for ketones, it seemed likely that the absolute configuration is that expressed by **1**, and this became the ultimate synthetic target. The retrosynthetically derived plan of synthesis led to the bicyclic vinylstannane **7** and the α-bromo-α,β-enone **13** as key intermediates.

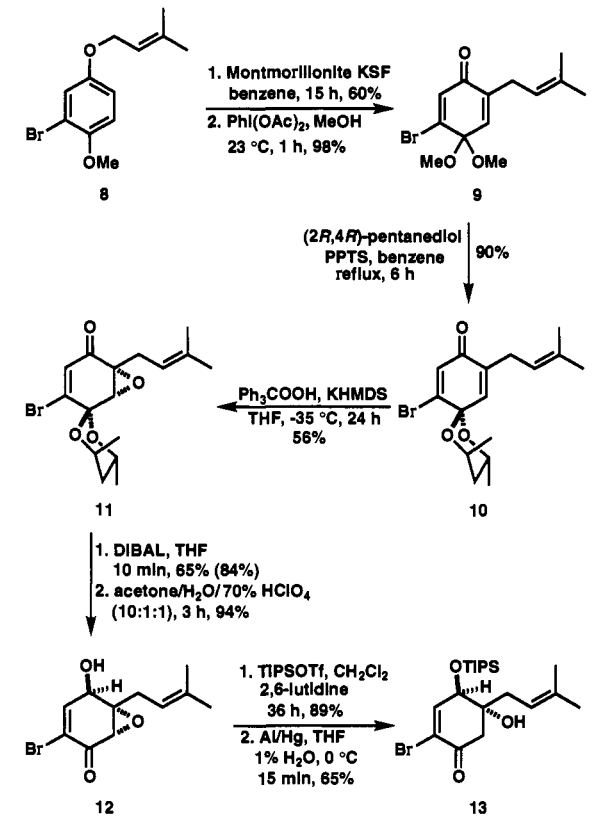
The bicyclic acid **3**, mp 201–203°, was prepared from 4-methoxysalicylaldehyde (**2**) by sequential O-cyanoethylation, aldol cyclization and hydrolysis of cyano to carboxyl (all reaction and mp temperatures in °C) (Scheme I). Conversion of **3** to the acyl azide,[7] Curtius rearrangement, and acid-catalyzed hydrolysis of the resulting vinyl isocyanate provided ketone **4**.[8] Demethylation of **4** (to form a phenolic ketone, mp 148–149°) followed by silylation with tri-*i*-propylsilyl (TIPS) triflate gave the silyl ether-ketone **5**. Reaction of the enolate **5** with the Hendrickson-McMurry reagent[9,10] afforded the corresponding conjugated enol triflate **6** which underwent coupling with the cuprate reagent[11] from tri-*n*-butylstannyllithium and CuCN to form the key vinylstannane **7**.

The α-bromo-α,β-enone component **13** was prepared starting from 3-bromo-4-methoxyphenol,[12] which was converted quantitatively by etherification to **8** with prenyl bromide-potassium carbonate in acetone at 23° for 12 h (Scheme II). Montmorillonite KSF clay[13] catalyzed the rearrangement of **8** to an *ortho* prenyl phenol which upon oxidation with $PhI(OAc)_2$ at 23° for 1 h

Scheme I



Scheme II



afforded the quinone monoketal **9**. Transketalization of **9** with (2*R*,4*R*)-pentane-2,4-diol yielded the chiral ketal-dienone **10**, $[\alpha]_D^{23}$ +43° (c = 1.5, $CHCl_3$).[14] Epoxidation of **10** with tritylhydroperoxide using potassium hexamethyldisilazide as base catalyst occurred with 85:15 diastereoselectivity favoring epoxide **11**, $[\alpha]_D^{23}$ +164° (c = 1.3, $CHCl_3$), R_f 0.54 (silica gel tlc with 4:1 hexane-ether), over the diastereomer, $[\alpha]_D^{23}$ −72° (c = 0.9, $CHCl_3$), R_f 0.44. After chromatographic separation pure **11** was isolated in 56% yield from **10**.[15] Reduction of epoxy ketone

† Dedicated to Her Royal Highness Princess Chulabhorn of Thailand on the Occasion of her 36th birthday.

(1) For an interesting account of the history of miroestrol, see: Cain, J. C. *Nature* **1960**, *188*, 774.

(2) First isolation: Schoeller, W.; Dohrn, M.; Hohlweg, W. *Naturwissenschaften* **1940**, *28*, 532.

(3) Biological studies: (a) Vatna, S. *Thai. Sci. Bull.* **1934**, *4*, 3. (b) Jones, H. E. H.; Pope, G. S. *J. Endocrinol.* **1960**, *20*, 229. (c) Pope, G. S.; Grundy, H. M.; Jones, H. E. H.; Tait, S. A. S. *J. Endocrinol.* **1958**, *17*, xv.

(4) Chemical studies: (a) Butenandt, A. *Naturwissenschaften* **1940**, *28*, 533. (b) Bounds, D. G.; Pope, G. S. *J. Chem. Soc.* **1960**, 3696.

(5) Structure: Taylor, N. E.; Hodgkin, D. C.; Rollett, J. S. *J. Chem. Soc.* **1960**, 3685.

(6) See, for example: (a) Weigele, M. *Diss. Abstr. B* **1965**, *26*, 6245. (b) Van Rheenen, V. H. *Diss. Abstr. B* **1966**, *27*, 1103. (c) Minard, R. D. *Diss. Abstr. B* **1969**, *30*, 133. (d) Miyano, M.; Dorn, C. R. *J. Org. Chem.* **1972**, *37*, 268. (e) Findlay, J. A.; Mebe, P.; Stern, M. D.; Givner, M. L. *Can. J. Chem.* **1980**, *58*, 1427.

(7) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6023.

(8) Wise, L. D.; DeWald, H. A.; Hawkins, E. S.; Reynolds, D. M.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A. *J. Med. Chem.* **1988**, *31*, 688.

(9) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

(10) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 4607.

(11) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795.

(12) Irvine, F. M.; Smith, J. C. *J. Chem. Soc.* **1927**, 74.

(13) Dauben, W. G.; Cogen, J. M.; Behar, V. *Tetrahedron Lett.* **1990**, *31*, 3241.

(14) The conformation of this ketal–dienone is indicated to be that shown in **10** by the observance of positive NOE effects in the 500-MHz ^1H NMR spectrum of **10** between the dienone β-H and *cis* axial CH_3 (2%) and carbinol C–H (9%) protons.

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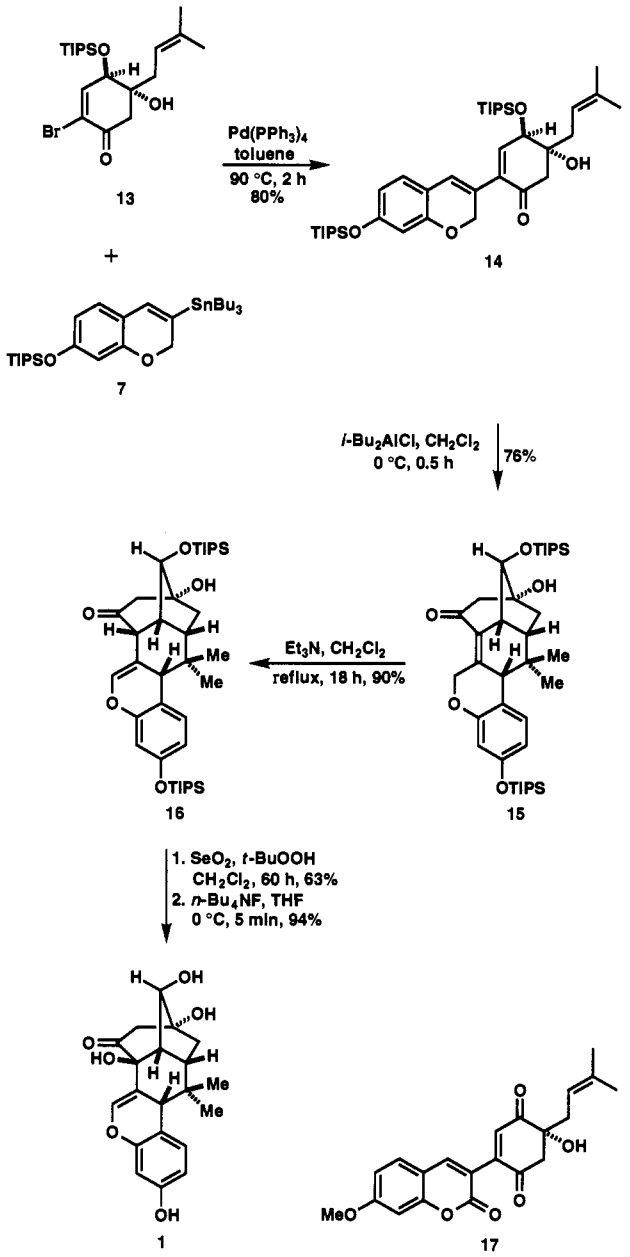
Scheme III



11 with diisobutylaluminum hydride afforded after chromatography the corresponding allylic alcohol, $[\alpha]_D^{23}$ +85° (c = 1, $CHCl_3$), R_f 0.34 (silica gel tlc with 3:1:1 hexane-ether-CH_2Cl_2), in 65% yield along with 31% of the diastereomeric alcohol, $[\alpha]_D^{23}$ −8° (c = 1.2, $CHCl_3$), R_f 0.27. The minor diastereomer was oxidized to **11** and reduced to provide an additional amount of the major isomer (total yield with one recycle, 84%), which upon deketalization gave **12**. Silylation of **12** and epoxide cleavage with aluminum amalgam[16] furnished **13**, $[\alpha]_D^{23}$ −82° (c = 1, $CHCl_3$).

The coupling of the key components **7** and **13** proceeded smoothly in the presence of a Pd(0) catalyst to form the tricyclic ketone **14**, $[\alpha]_D^{23}$ −28° (c = 0.8, $CHCl_3$) (Scheme III). At 0° in the presence of diisobutylaluminum chloride this ketone was rapidly and cleanly transformed into the isomeric pentacyclic ketone **15**, mp 145.5–147°, $[\alpha]_D^{23}$ + 119° (c = 0.7, $CHCl_3$). This highly efficient reaction, which generates the bridged ring system of miroestrol in a single step, may be regarded as a transannular double cation-olefin cyclization in which the initiation step is coordination of the catalytic Lewis acid to the α,β-enone carbonyl followed by transannular linkage of the enone β-carbon and the double bond of the prenyl unit. The resulting tertiary carbocation then attaches to the benzylic carbon of the chromene unit to form the second new ring in **15**. Alternatively the conversion **14** → **15** may be viewed as a Lewis acid catalyzed transannular Diels–Alder reaction of an unusual type (inverse electron demand) with an electron-rich dienophile and an electron-deficient diene component. As anticipated, the formation of **15** from **14** was not observed under thermal Diels–Alder conditions, which led only to complex decomposition. Treatment of the α,β-enone **15** with triethylamine resulted in isomerization to the thermodynamically more stable β,γ-enone **16**, mp 95–96°, $[\alpha]_D^{23}$ +153° (c = 0.7, $CHCl_3$). The destabilization of ketone **15** relative to the β,γ-isomer **16** is partly due to a twisting about the O=C—C_α bond in **15** which rotates the O=C and α,β-C=C π-orbitals to an angle of *ca* 70° and removes most of the π-conjugation. Oxidation of **16** with selenium dioxide produced the corresponding α-hydroxy-β,γ-enone, mp 138–139°, $[\alpha]_D^{23}$ +192° (c = 0.4, $CHCl_3$), which upon desilylation gave totally synthetic miroestrol, mp 265–267° (decomp), $[\alpha]_D^{23}$ +289° (c = 0.2, EtOH), [lit.[4b] mp 268–270° (decomp), $[\alpha]_D^{17}$ +301° (c = 1.1, EtOH)].

Although we could not locate an authentic sample of miroestrol, we were able to obtain *ca* 500 g of the dried root of *Pueraria mirifica* thanks to the generosity of Profs. Duang Buddhasukh and Yuthana Smitasiri of Chiang Mai University. Extraction of 200 g of this material with THF at 23° and chromatographic purification of the extract on silica gel (3 columns followed by preparative tlc) afforded 1.2 mg of miroestrol, which showed $[\alpha]_D^{23}$ +286° (c = 0.1, EtOH) and ^1H and ^{13}C NMR, mass, and IR spectra that were identical with those of synthetic **1**. The chromatographic mobilities of natural and synthetic **1** in several different solvent systems were also identical, as was mp behavior.

In the course of the isolation of **1** from *P. mirifica* we obtained *ca* 1 mg of another compound whose 500 MHz ^1H NMR spectrum was similar to that of the synthetic intermediate **14**. This new, unstable substance was identified as **17** by analysis of NMR and mass spectral data. If **17** is a biosynthetic precursor of miroestrol, the possibility arises that the biosynthesis of miroestrol might involve the same sort of cationic double annulation that served as a key step in the above described total synthesis of **1**, a rather interesting coincidence.

The series of reactions which leads from the simple starting materials **2** and **8** to miroestrol **1** includes several which require the special reaction conditions and reagents specified herein. In addition to the key double annulation process, **14** → **15**, other noteworthy transformations include **9** → **10**, **10** → **11**, **11** → **12**, **13** → **14** and **15** → **16** → **1**. A simpler version of this synthesis of **1** has been used to prepare (±)-**1** 3-methyl ether.

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Supplementary Material Available: Characterization data for compounds **3**–**17** and **1** (4 pp). Ordering information is given on any current masthead page.

(15) The stereochemistry of the predominating epoxide **11** corresponds to that expected for reaction of the more stable conformer of **10**.

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