177. The Enantioselective Synthesis of (+)-Estradiol from 1,3-Dihydrobenzo[c]thiophene-2,2-dioxide by Successive Thermal SO_2-Extrusion and Cycloaddition Reactions

Preliminary communication

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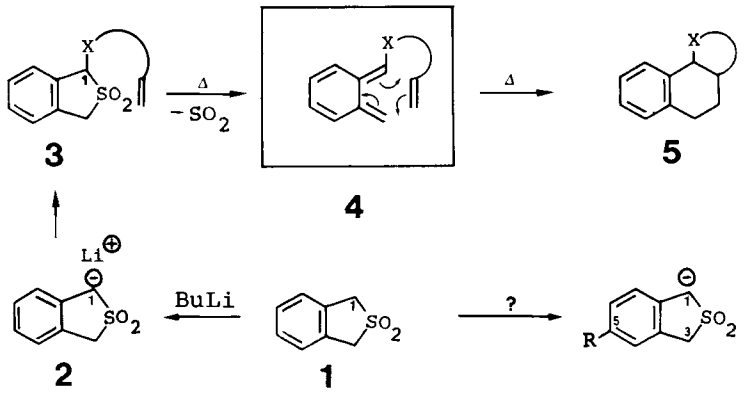
Summary

The optically pure steroid (+)-**15** has been synthesized from the easily accessible (+)-carboxylic acid **11** by a sequence of 7 steps in 50% overall yield. The key steps are the regioselective deprotonation/alkylation **7** + **13** → **14** and the thermal SO_2-extrusion/cycloaddition **14** → **15** *(Scheme 3)*. The compound (+)-**15** has been readily converted to the naturally occurring (+)-estradiol (**17**) in 60% yield.

In conjunction with our long-standing engagement with intramolecular cycloadditions of *o*-quinodimethanes [1], we have reported the deprotonation (**2**) and alkylation or acylation of benzo[c]thiophene dioxide (**1**) followed by thermolysis of the monosubstituted sulfones **3**, giving (*via* **4**) the polycyclic products **5** in good yields [2] *(Scheme 1)*. This evidence as well as independent work [3] indicates benzo[c]-thiophene dioxide (**1**) to be a useful functionalizable masked quinodimethane unit[1]). However, there remained the problem of how to direct the electrophilic introduction

Scheme 1



[1]) For fundamental work on the thermal SO_2-extrusion from **1** see [4].

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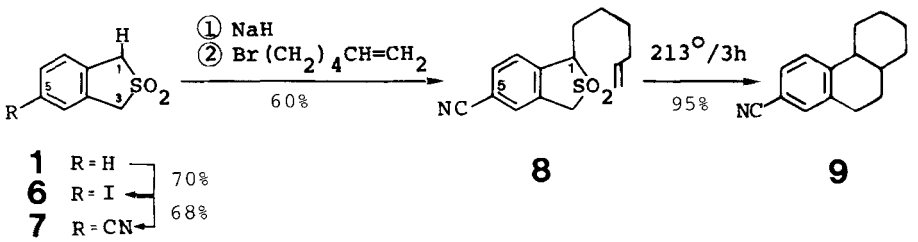
of the dienophile side chain selectively into position 1 of 5-substituted-1,3-dihydrobenzo[c]thiophene-2,2-dioxides. We now present a solution to this problem *(Scheme 2)* and its first application to the synthesis of a naturally occurring steroid *(Scheme 3)*.

With the idea of favoring selective deprotonation at C(1) by means of an electron-attracting substituent R in the *p*-position C(5), the nitrile **7** was prepared as follows: iodination of the readily available sulfone **1** [4] (Ag_2SO_4, I_2, conc. H_2SO_4, 16 h, 20°) [5] furnished the iodide **6**[2]) (m.p. 197–200°, 70%), which on iodide/cyanide exchange [6] (excess of NaCN supported on alumina, 0.1 mol-equiv. of $Pd(PPh_3)_4$, toluene, 100°, 3 h) gave the desired nitrile **7**[2]) (m.p. 157–159°, 68%). Successive treatment of **7** with sodium hydride and 6-bromo-1-hexene (THF/HMPA 6:1, −70°→+15°, 16 h) furnished exclusively the 1-substituted sulfone **8**[2]) (oil, dist. (bath) 210°/0.02 Torr, 60%[3]). Thermolysis of **8** in refluxing 1,2,4-trichlorobenzene for 3 h followed by crystallization of the evaporated solution gave the adduct **9**[2])[4]) (m.p. 77–90°) in nearly quantitative yield [7b].

Scheme 2



Having solved the problem of regioselective 1,5-functionalization of the sulfone **1** we examined the synthesis of (+)-estradiol (**17**). Exploiting the ready availability of the optically pure carboxylic acid (+)-**11** from **10** [1] [8] the properly functionalized ring D-unit **13** was prepared in the following way. Esterification of (+)-**11** with diazomethane in ether furnished the ketoester **12**[2])[5])[6]) (oil, dist. (bath) 105°/0.02 Torr, 98%). Successive stereoselective reduction of the keto group in **12** with $NaBH_4$ (MeOH, 0°, 45 min), silylation of the resulting alcohol with *t*-butyldimethylchlorosilane (imidazole, DMF, 80°, 4 h), reduction of the ester group with $LiAlH_4$ (ether, 20°, 1 h), tosylation of the primary alcohol with *p*-toluenesulfonyl chloride (pyridine, 25°, 4 h) and *Finkelstein* reaction (NaI, acetone, 60°, 16 h) gave after chromatography (SiO_2, hexane) the iodide **13**[2])[5]) (oil, 77% overall yield from **12**). The selective joining of the masked quinodimethane and the ring D-unit was

[2]) IR., ^{1}H-NMR. and MS. are in full agreement with the assigned structure.

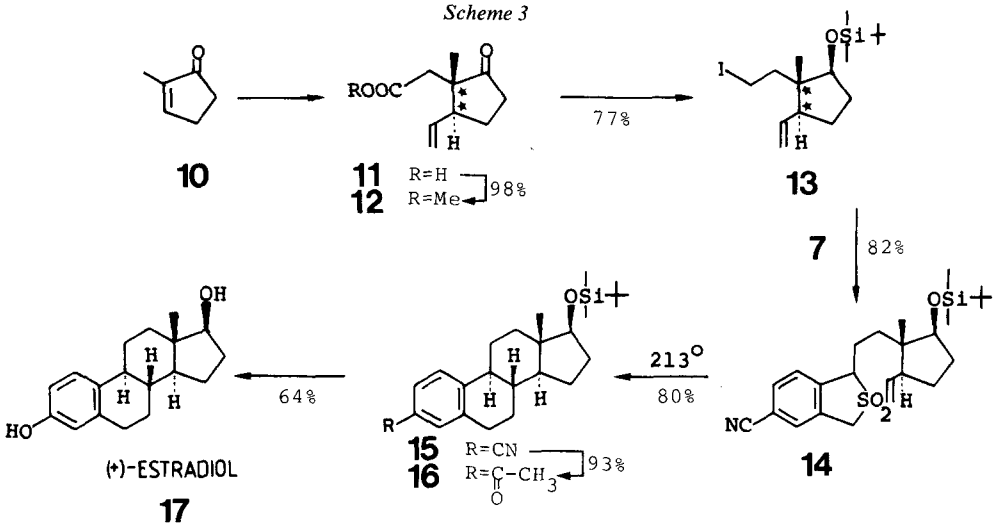
[3]) The easily accessible *N,N*-diethyl-1,3-dihydro-5-sulfonamidobenzo[c]thiophene-2,2-dioxide also underwent highly regioselective deprotonation and alkylation [7]. Although simple nitration of **1** afforded smoothly the corresponding 5-nitrobenzo[c]thiophene dioxide, subsequent treatment with various bases led only to intractable tars.

[4]) The ^{13}C-NMR. of the recrystallized compound **9** is in agreement with its *trans*-configuration.

[5]) The following compounds showed the indicated optical rotations $[\alpha]_D^{23°}$: **12**: +72.6° (c=0.74, $CHCl_3$); **13**: +27.2° (c=1.09, $CHCl_3$); **15**: +55.0° (c=0.65, $CHCl_3$); **16**: +52.3° (c=1.00, $CHCl_3$); **17**: +76.7° (c=0.58, MeOH).

[6]) The chiral purity of **12** was confirmed by ^{1}H-NMR. evidence using the chiral shift reagent tris-(3-trifluoroacetyl-*d*-camphorato)europium-III.

Scheme 3



accomplished by treatment of **13** with 2 mol-equiv. of the sulfone **7** in the presence of 2 mol-equiv. of sodium hydride (THF/HMPA 1:1, $-30° \rightarrow +20°$, 12 h, argon) to obtain **14**[2]) (oil, 1:1-mixture of diastereoisomers, 82% from **13**). Thermolysis of the olefinic sulfone **14** (15% solution in refluxing 1,2,4-trichlorobenzene, 3 h, argon) yielded smoothly after crystallization (hexane) the pure *trans-transoid-trans* steroid **15**[2])[5]) (m.p. 167–170°, 80%). The depicted configuration of **15** follows from its ultimate transformation to (+)-estradiol, carried out in the following way. Treatment of **15** with 1.4 mol-equiv. of methyllithium (ether, $-20°$, 5 min) and aqueous workup gave the methyl ketone **16**[2])[5]) (solid, 93%). *Baeyer-Villiger* oxidation of **16** (1.6 mol-equiv. of CF_3CO_3H, CH_2Cl_2, 20°, 1 h) followed by acidic cleavage of the resulting crude silyl ether-acetate MeOH/THF/2N HCl 1:1:1, 60°, 3 h) furnished after chromatography (SiO_2, toluene/ethyl acetate 4:1) and crystallization ($CHCl_3$/hexane) (+)-estradiol (**17**)[5]) (m.p. 178–179.5°, 64% from **16**). The synthetic (+)-**17** was shown to be identical with an authentic sample by chiroptic, spectral (IR., 360 MHz-^{1}H-NMR., MS.) and mixed m.p. evidence.

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