182. The Enantioselective Synthesis of 3-Methoxy-1,3,5(10)-estratrien-11,17-dione by a Thermal Intramolecular Cycloaddition Reaction[1])

Preliminary Communication

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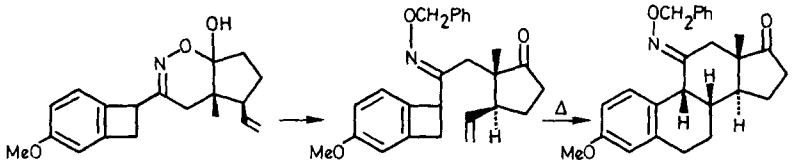
Summary

The enantiomerically pure (+)-3-methoxy-1,3,5(10)-estratrien-11,17-dione **11** (with *trans-anti-trans* configuration) was synthesized in a highly stereocontrolled fashion from (±)-*t*-butyl 4-methoxy-1-benzocyclobutene carboxylate (**8**) and the (+)-carboxylic acid **6**, obtained from **4** in two steps, followed by one crystallization of the (+)-ephedrine salt. The key step **10** → **11** *(Scheme 2)* involves a thermal intramolecular cycloaddition reaction.

In continuation of our work on intramolecular *o*-quinodimethane cycloadditions[2]) [1] [2] a stereoselective synthesis of the racemic 3-methoxy-1,3,5(10)-9β-estratrien-11,17-dion-11-oxime-*o*-benzyl ether **3** (with *cis-anti-trans* configuration) *via* the intermediates **1** and **2** has been developed *(Scheme 1)* [3]. In view of the efficient and highly stereocontrolled preparation of **1** this synthesis compares favorably with other approaches to racemic estrone derivatives *via* benzocyclobutene-precursors [4].

Scheme 1

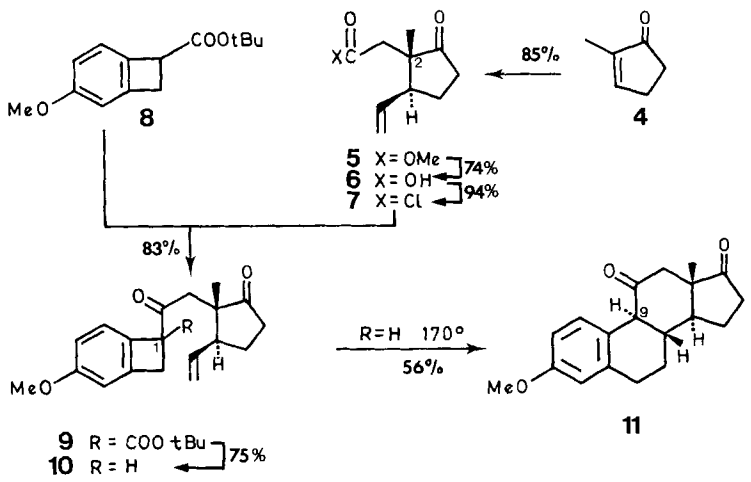


We now wish to report a related, even simpler and moreover enantioselective route to C(11) functionalized steroids as follows *(Scheme 2)*. Conjugate addition of lithium 3,3-dimethylbutynyl-vinylcuprate, followed by alkylation of the nonisolated

[1]) Presented in part by one of us *(W.O.)* at the Symposium on 'Strategy in Organic Synthesis', Wageningen, Holland, March 1978.

[2]) Reviews: [2].

Scheme 2



enolate adduct with methylbromoacetate[3]) [5] furnished a 6:1 mixture of the ester **5**[4]) and its C(2)-epimer in 85% yield.

Saponification of this ester mixture (0.02 N KOH in MeOH/H_2O 10:1, 21 h/20°), followed by one crystallization of the crude (±)-acid with (+)-ephedrine from ethyl acetate gave a salt (m.p. 166–169°, $[\alpha]_D^{22°} = +60.9°$ ($c = 0.55$, methanol)), which after treatment with hydrochloric acid afforded the enantiomerically pure (+)-acid **6**[4]) (oil, $[\alpha]_D^{22°} = +74.6°$ ($c = 0.67$, $CHCl_3$) in 74% yield (from crude (±)-**5**). Reaction of (+)-**6** with $(COCl)_2$ (3 mol-equiv. in dry CH_2Cl_2/0° to 20°) furnished the (+)-acid chloride **7**[4]) (b.p. 110° (bath)/0.01 Torr, $[\alpha]_D^{22°} = +71.3°$ ($c = 0.47$, $CHCl_3$) 94% yield). The racemic benzocyclobutenecarboxylic ester **8**[4]), prepared from the corresponding acid in 73% yield[5]) [9], was treated successively with lithium cyclohexylisopropylamide (1.05 mol-equiv.) and (+)-**7** (1.0 mol-equiv.) in THF at −78° [10] to give the diketoester **9**[4])[6]) in 83% yield.

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[3]) 2-Methyl-2-cyclopentenone [6] (20.5 mmol) was added at −70° to a solution of lithium 3,3-dimethylbutynyl cuprate [7] (prepared from *t*-butylacetylene [8], 20.4 mmol) in ether/THF 9:1 (130 ml). Then the mixture was successively allowed to warm to −10°, cooled to −30° and transferred by argon pressure over a 10 min period to a stirred and cooled (−18°) solution of methyl bromoacetate (178 mmol) in HMPT/ether 2:1 (150 ml). After warming of the resulting solution to 20° over a 2 h period, stirring for 18 h and subsequent shaking with sat. aq. NH_4Cl/ether and distillation of the dried and evaporated ether solution gave **5** (b.p. 57–58°/0.04 Torr, 85%).

[4]) The IR. and ^{1}H-NMR. spectra (100 MHz) and MS. of this compound are in agreement with the assigned structure.

[5]) A solution of 4-methoxybenzocyclobutene-1-carboxylic acid [4a,b] (15 mmol) in acetonitrile (8 ml) was added to the reaction mixture, obtained from DMF (6 ml) and oxalylchloride (22 mmol) in acetonitrile (4 ml) at −20°. After addition of pyridine (6 ml) and *t*-butyl alcohol (50 mmol) at −30° to −20° the mixture was warmed to 20°, to give after work-up and distillation **8** (b.p. 160° (bath)/0.01 Torr), 73%). We thank Dr. *P. Stadler*/Sandoz AG for kindly communicating to us this esterification method prior to publication [9].

[6]) 1:1-Mixture of C(1)-epimers which is of little synthetic relevance since the chirality of C(1) is lost in the thermal opening of the benzocyclobutene **10** [1,2].

Removal of the COO*t*Bu-group from **9** [a) CF_3COOH/0°, b) DMF/pyridine 30:1, 90°/30 min] furnished the 1,4-diketone **10**[4])[6]) in 75% yield. An alternative route to racemic **10** involves treatment of **1** with ceric ammonium nitrate (2 mol-equiv.) in MeOH/H_2O 9:1 (20°, 5 h, 32% yield)[7]).

After heating a solution of **10** (0.33 mmol) in decane (10 ml) under a pure argon atmosphere at 150° for 12 h the optically pure (+)-3-methoxy-1,3,5(10)-estradien-11,17-dione **11**[4]) (with *trans-anti-trans* configuration) (m.p. 180–192°, $[\alpha]_D^{22°} = +387°$ ($c = 0.5$, $CHCl_3$)) crystallized directly from the cooled reaction mixture (52%). The mother liquor gave, after chromatography (SiO_2) and crystallization, another crop of pure **11** (total yield of **11**: 56%) followed by a small amount of its *cis-anti-trans*-C(9)-epimer (5% yield). The synthetic (+)-**11** was shown to be identical with an authentic sample[8]) by chiroptic, spectral, chromatographic and mixed m.p. evidence. It thus appears that during the reaction **10** → **11** the intermediate *trans*-quinodimethane [1] [2] adds preferentially in an *exo* mode to the vinyl group as opposed to the exclusive *endo* addition observed in the transformation **2** → **3**[9]). Accordingly the correct induction of all three chiral centers in the key step **10** → **11** of this convergent synthesis, together with the selective functionalizability of the C(11)-carbonyl group in **11** to give physiologically active products [12], nicely exemplifies the utility of intramolecular *o*-quinodimethane cycloadditions.

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[7]) The feasibility of the cleavage **1** → **10** has been demonstrated in context with another synthetic target [11].

[8]) We are indebted to Dr. *M. G. Buzzolini*, Sandoz Inc., Hannover, N.J. for kindly providing chiral 3-methoxy-1,3,5(10)-estratrien-11,17-dione-17-ethyleneacetal, which by acetal cleavage (0.9N $HClO_4$ in THF/H_2O 3.5:1.5/20°/18 h) gave **11** of natural origin $[\alpha]_D^{22°} = +364°$ $c = 0.5$, $CHCl_3$).

[9]) For related possibilities of directing intramolecular cycloadditions towards either *endo*- or *exo*-products see [2].