# 291. A Highly Stereoselective Synthesis of C(11)-Functionalized Aromatic Steroids by an Intramolecular Benzocyclobutene-Olefin -Cycloaddition

Preliminary Communication

by **Wolfgang Oppolzer, Martin Petrzilka** and **Kurt Bättig**
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

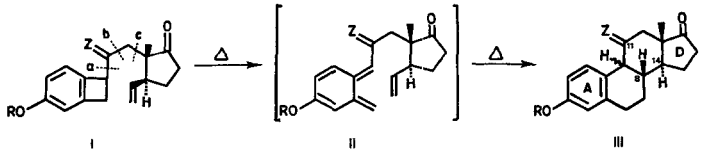
(8. XI. 77)

*Summary*

The racemic *cis-anti-trans*-steroids **9** to **11** have been synthesized in a highly stereoselective manner starting from 4-methoxybenzocyclobutene carboxylic acid *via* the key step **8** → **9**. (*cf. Scheme 2*).

The total synthesis of steroids is a continuing challenge for the organic chemist. From 1939 up to the present numerous often exciting and even some practical routes to this pharmaceutically important class of compounds have been developed[1]). Based on our pioneering work on intramolecular quinodimethane cycloadditions [6–8] a new approach to this skeleton *via* the generalized sequence I → II → III (*Scheme 1*)

*Scheme 1*




I II III

appeared feasible. Consideration of models of all four possible transitions states for the intramolecular cycloaddition of II, points towards kinetically favoured formation of adducts III with *anti*-disposed H–C(8) and H–C(14), caused by steric interactions of the angular methyl group. In addition, one may expect [7] that the *trans*- or *cis*-B, C-ring fusion in III will be controlled by the influence of a $sp^3$- or $sp^2$-carbon functional group C = Z on the *endo*/*exo* mode of the addition II → III. In fact, highly stereoselective formation of *trans-anti-trans* products has been observed in a related

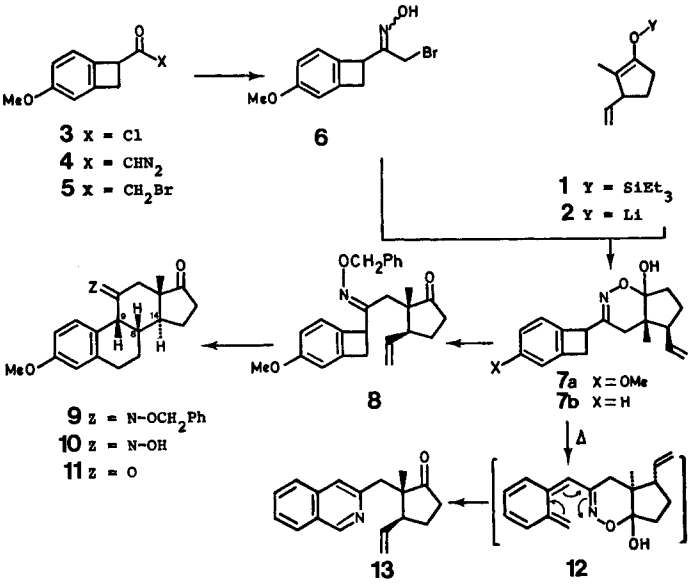
[1]) Reviews: [1–5].

approach to D-homoestrone [9], in earlier work in our laboratory[2]) [7] and in a very recent application of *Scheme 1*[3]) [10][4]).

However, a major difficulty encountered in the preparation of I is the joining of the readily accessible benzocyclobutene unit[5]) with the appropriately functionalized ring-D-building block[6]).

We now wish to report a new steroid synthesis according to *Scheme 1* which involves satisfactory access to I and leads to both unequivocal substitution of ring A and functionalization of position 11 in III. To this end it was decided to form the bond *c* in I by using the nucleophile-induced elimination-addition of an *α*-halooxime [15–17] (*Scheme 2*). The ring-D-precursor 1[7]) was prepared in 93% yield from 2-methylcyclopent-2-

*Scheme 2*




enone [18] by conjugate addition of lithium pentynyl-vinylcuprate [19] (1.3 mol-equiv. in the presence of 2.5 mol-equiv. of hexamethylphosphorous triamide in ether at $-60°$ to $-40°$) and quenching of the adduct with chlorotriethylsilane (1.0 mol-equiv. at

[2]) In this approach [7] the bond *a* of I was formed by *C*-acylation of a benzocyclobutene-1-carboxylic acid ester-enolate; we thank Dr. *G. Lenz* for preliminary experiments.

[3]) This elegant route to the stereoid skeleton [10] involves a cobalt-catalysed co-oligomerization of a 1,5-diyne with *bis*(trimethylsilyl)acetylene to a transient benzocyclobutene; however, oxygen-functionality has not yet been introduced specifically in position 3.

[4]) For another approach to the conversion II → III *via* a photo-enolization of an *o*-toluene-carbonyl compound see [11].

[5]) For approaches to benzocyclobutenes, see a review [12] and more recent works [13] [14].

[6]) Because of the reported inaccessibility of I, $Z=H_2$ [9] one of the above cited syntheses [9] was directed towards D-homoestrone; bond *c* was formed there by alkylation of a protected 2-methylcyclohexanone-enolate which proceeded in only 16% yield.

[7]) The IR. and $^1$H-NMR. spectra and MS. of this compound are in agreement with the assigned structure.

−78°). The corresponding electrophilic benzocyclobutene reaction partner **6**[7]) (m.p. 45–55°) was obtained in 98% overall yield through the sequence[8]) **3** → **4** → **5** → **6**. Combination of the two building blocks **2** and **6** was accomplished by *in situ*-cleavage of the silylether **1** (1.0 mol-equiv. of MeLi/THF/25°/2 h) to **2**, followed by slow addition of the bromooxime **6** (0.5 mol-equiv. over 45 min/THF/−75°) to give **7a**[7]), isolated in high yield by direct crystallization after work-up of the reaction mixture (ether/pentane, m.p. 110–120°, 77%)[9]). In previous model experiments **7b**[7]) was thermolysed (*o*-dichloro-benzene/160°/18 h) to give the isoquinoline **13**[7])[10]) (51%, presumably *via* an electrocyclization of the transient quinodimethane **12**[11])) rather than the desired steroid skeleton. Accordingly the hemiacetal **7a** was opened by selective *O*-benzylation (10 mol-equiv. of benzyl bromide/3 mol-equiv. of 4-dimethylaminopyridine/dry $CH_2Cl_2$/25°/15 h) to give the oxime ether **8**[7]) (oil, 53% to 70%) which on heating (*o*-dichlorobenzene/140°/6 h/argon) cyclized exclusively to the *cis-anti-trans*-steroid **9**[7]) (glass, 50%). It thus follows that the crucial kinetically controlled transformation **8** → **9** proceeds by a selective *endo*-addition of a quinodimethane intermediate II leading to the expected *anti*-arrangement of the hydrogens at C(8) and C(14)[12]). Hydrogenolysis of the benzyl ether (1 atm. $H_2$/Pd/C-10%/MeOH/25°/18 h) yielded the crystalline oxime **10**[7]) (m.p. 193–195°, 73%) which was cleaved [22] (excess ceric ammonium nitrate/MeOH/−30°/15 min) to the diketone **11**[7]) (m.p. 126–129°, 37%). The synthetic (±)-**11** shows $^1$H-NMR., IR. and mass spectra identical to those of an authentic sample obtained from 3-methoxy-1,3,5(10)-trien-11,17-dione 17-ethyleneacetal (by simultaneous acetal-cleavage and epimerization at C(9) with THF/conc. aq. HCl-solution 5:2/25°/17 h). The conversion of aromatic B,C-*cis*-fused 11-*oxo*-steroids to B,C-*trans*-fused steroids and the transformation of closely related derivatives of **11** to physiologically active products have been reported previously [23] [24].

[8]) The acid chloride **3**[7]) was prepared from 4-methoxybenzocyclobutene-1-carboxylic acid (accessible in 37% overall yield from 3-hydroxybenzaldehyde [9] [20]) with excess $SOCl_2$/20°/20 h in 88% yield. Reaction of **3** with $CH_2N_2$ (5 mol-equiv.) in ether/0°/15 min, then excess of 47% aq. HBr/0°/10 min yielded the crystalline bromoketone **5**[7]) (m.p. 86–87°) which was converted to the oxime **6**[7]) (mixture of *E* and *Z*-isomers) by reaction with $NH_2OH \cdot HCl$ (1.2 mol-equiv.), sodium acetate (1.2 mol-equiv.) in acetic acid/20°/18 h.

[9]) The reaction **2** + **6** → **7a** is the first reported substitution of a nonactivated enolate to an α-halooxime. Additions of other carbon-nucleophiles, such as *Grignard* reagents [15], enolates of 1,3-dicarbonyl compounds [15], dimethylcuprate [16] and 1-lithiobut-1-yne [17] to transient nitrosoolefins have been described previously. In the reaction described here, it appears that the adduct, formed initially from **2** and **6** gives the cyclic hemiacetal **7a** rather than a free 4-ketooxime. In model experiments direct trapping of the conjugate adduct of 2-methylcyclopent-2-enone and lithium pentynyl-vinylcuprate by the demethoxy analogue of **6**[7]) gave **7b**[7]), m.p. 127–135° in lower yield (53%) than the corresponding reaction of the lithium enolate **2**, prepared from **1** (79% yield of **7b**).

[10]) UV. ($CHCl_3$, $\lambda_{max}$ (nm)/log ε): 238/3.70, 258/3.60, 266/3.59, 310/3.32, 322/3.35.

[11]) For a similar thermal reaction of a benzocyclobutenon-oxime ether see [21].

[12]) The *trans-anti-trans*-oxime benzylether, (C(9)-epimer of **9**) prepared from the authentic 3-methoxy-1,3,5(10)-trien-11,17-dione 17-ethyleneacetal did not epimerize to **9** on heating (*o*-dichlorobenzene/140°/6 h) showing the kinetic nature of the stereochemical control in the reaction **8** → **9**; the *endo*-preference, observed here, (which contrasts to previously reported *exo*-additions II → III [7] [9] [10]) seems to depend on the oxime ether-substituent ($sp^2$-center as part of the bridge; for other examples see [7]).

Financial support of this work by the *Fonds National Suisse de la Recherche Scientifique*, *Sandoz Ltd*, Basel and *Givaudan SA*, Vernier is gratefully acknowledged. We are indebted to Dr. *J. Kalvoda*, *Ciba-Geigy AG*, Basel, Dr. *M. G. Buzzolini*, *Sandoz Inc.*, Hannover, N.J. and Dr. *G. Lenz*, *Searle Laboratories*, Chicago for kindly providing authentic samples of 11-oxo-estrone-derivatives. We also wish to thank Mr. *J. P. Saulnier* and Mrs. *F. Klöti* for careful $^1$H-NMR. and mass spectra measurements.

## REFERENCES

[1] *A. A. Akhrem & Y. A. Titov*, 'Total Steroid Synthesis', Plenum Press, N.Y. 1970.
[2] *D. Taub*, in 'The Total Synthesis of Natural Products'. Ed. J. ApSimon, Wiley 1973, Vol. 2, p. 641.
[3] *K. Nakanishi*, in 'Natural Products Chemistry'. Ed. *K. Nakanishi*, *T. Goto*, *S. Itô*, *S. Natori & S. Nozoe*, Academic Press, N.Y. Vol. 1, 1974, p. 421.
[4] *P. J. Sykes & J. S. Whitehurst*, in 'Terpenoids and Steroids'. Ed. *K. H. Overton* (Specialist Periodical Reports), The Chemical Society, London, Vol. 6, 1976, p. 276 and earlier volumes of this series.
[5] *W. S. Johnson*, Angew. Chem. *88*, 33 (1976); Angew. Chem. Int. Ed. Engl. *15*, 9 (1976).
[6] a) *W. Oppolzer*, J. Amer. chem. Soc. *93*, 3833 (1971); b) *93*, 3834 (1971); c) *W. Oppolzer & K. Keller*, ibid. *93*, 3836 (1971).
[7] *W. Oppolzer*, Angew. Chem. *89*, 10 (1977); Int. Ed. Engl. *16*, 10 (1977).
[8] *W. Oppolzer*, Synthesis, review in preparation.
[9] *T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama & K. Fukumoto*, J. Amer. chem. Soc. *98*, 3378 (1976); *T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, H. Matsumoto & K. Fukumoto*, ibid. *99*, 3461 (1977).
[10] *R. L. Funk & K. P. C. Vollhardt*, J. Amer. chem. Soc. *99*, 5483 (1977).
[11] *G. Quinkert*, Chimia *31*, 225 (1977).
[12] *I. L. Klundt*, Chem. Rev. *70*, 471 (1970).
[13] *R. J. Spangler, B. G. Beckmann & J. H. Kim*, J. org. Chemistry *42*, 2989 (1977).
[14] *P. Schiess & M. Heitzmann*, Angew. Chem. *89*, 485 (1977); Int. Ed. Engl. *16*, 469 (1977).
[15] *A. Dornow & H. D. Jordan*, Chem. Ber. *94*, 76 (1961).
[16] *E. J. Corey, L. S. Melvin, Jr. & M. F. Haslanger*, Tetrahedron Letters *1975*, 3117.
[17] *E. J. Corey, M. Petrzilka & Y. Ueda*, Tetrahedron Letters *1975*, 4343; Helv. *60*, 2294 (1977).
[18] *P. G. Gassman & J. M. Pascone*, J. Amer. chem. Soc. *95*, 7801 (1973).
[19] *E. J. Corey & D. J. Beames*, J. Amer. chem. Soc. *94*, 7210 (1972).
[20] *T. Kametani, Y. Kato, T. Honda & K. Fukumoto*, J. Amer. chem. Soc. *98*, 8185 (1976).
[21] *W. Oppolzer*, Angew. Chem. *84*, 1108 (1972); Angew. Chem. Int. Ed. Engl. *11*, 1031 (1972).
[22] *J. W. Bird & D. G. M. Diaper*, Canad. J. Chemistry *47*, 145 (1969).
[23] *J. S. Baran*, J. med. Chemistry *10*, 1188 (1967); *C. D. Liang, J. S. Baran, N. L. Allinger & Y. Yuh*, Tetrahedron *32*, 2067 (1976); *J. S. Baran, D. D. Langford, I. Laos & C. D. Liang*, ibid. *33*, 609 (1977).
[24] *J. H. Fried*, U.S. Patent 3, 408, 372 (1968); Chem. Abstr. *70*, P 68646r (1969).