A Novel Approach to Estranes by an Intramolecular Double Michael Reaction

Masataka Ihara,[a] Takako Takahashi,[a] Noriko Shimizu,[a] Yohhei Ishida,[a] Izumi Sudow,[a] Keiichiro Fukumoto,*[a] and Tetsuji Kametani[b]

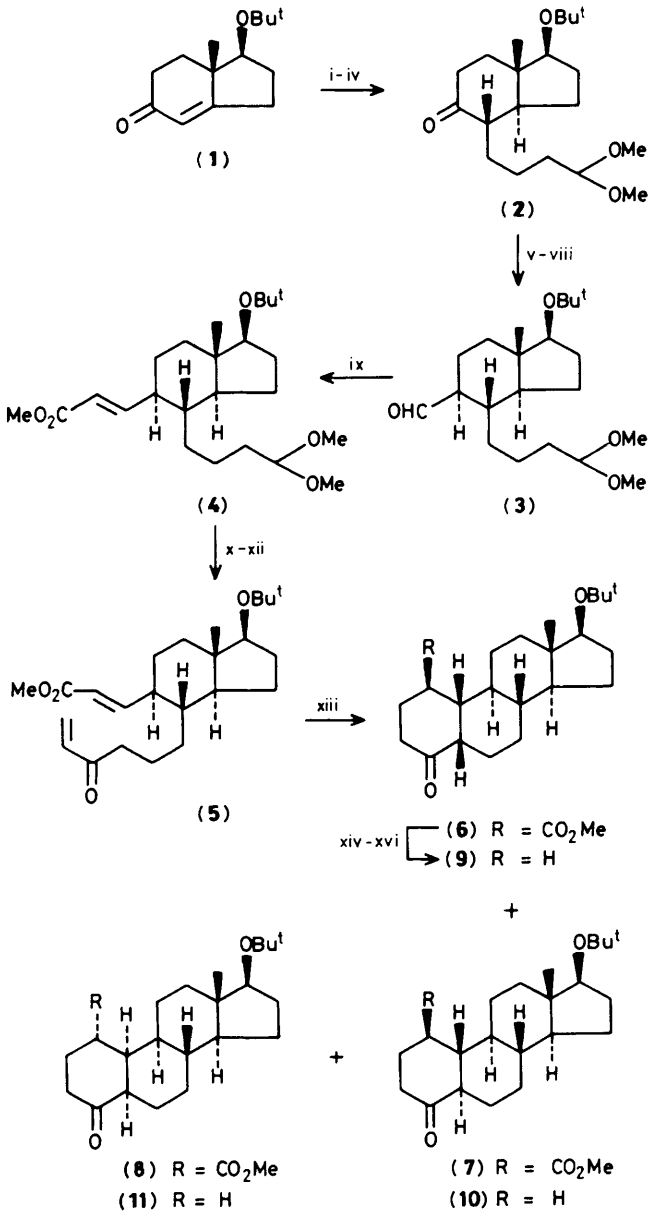
[a] *Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan*
[b] *Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan*

A new construction of the estrane ring system was achieved by intramolecular double Michael reaction of the α,β-unsaturated enone ester (**5**).

The development of a new method for assembly of the steroidal skeleton is a challenging problem owing to its medicinal importance. Recently we reported a synthesis of androgens *via* A/B-ring formation using an intramolecular Diels–Alder reaction.[1] Further investigation of the synthesis of the steroidal A/B ring system using an intramolecular double Michael reaction[2] led us to develop a new approach to estranes.

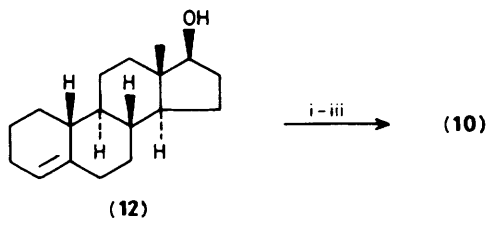
The optically active indanone (**1**)[3] was converted into the ketone (**2**) in four steps: condensation with 1,1-dimethoxy-4-bromobutane in the presence of sodium methylsulphinylmethide (53% yield), catalytic hydrogenation using 10% Pd–C, Collins oxidation of the epimeric alcohols, and epimerisation with NaOMe (64% overall yield for three steps). Wittig reaction (98% yield) followed by hydroboration–oxidation gave a mixture of two epimeric primary alcohols (95% yield), which was oxidised by Swern oxidation. After epimerisation with NaOMe, the aldehyde (**3**) was subjected to Wadsworth–Emmons reaction to afford the (*E*)-unsaturated ester (**4**) (86% overall yield for three steps) as the sole product. The ester (**4**) having the correct stereochemistry at the five chiral centres on the C/D-ring system was transformed into the enone (**5**) in three steps: deblocking with AcOH–H_2O (4 : 1) at 60 °C (98% yield), Grignard reaction, and oxidation with pyridinium dichromate in CH_2Cl_2 (81% overall yield for two steps).

The vinyl ketone group of (**5**) was too reactive with lithium di-isopropylamide (LDA) or lithium hexamethyldisilazide to produce any desired product. However, heating (**5**) in the



Scheme 1. *Reagents:* i, $(MeO)_2CH[CH_2]_3Br$, $NaCH_2SOMe$; ii, H_2, 10% Pd–C; iii, CrO_3·2 pyridine; iv, NaOMe; v, Ph_3PMeBr, KH, $EtC(Me)_2OH$; vi, BH_3·Me_2S then H_2O_2, NaOH; vii, dimethyl sulphoxide (DMSO), $(COCl)_2$, Et_3N; viii, NaOMe; ix, $(MeO)_2POCH_2CO_2Me$, NaH; x, AcOH, H_2O; xi, CH_2=CHMgBr; xii, pyridinium dichromate; xiii, Me_3SiCl, Et_3N, $ZnCl_2$, heat then 10% $HClO_4$, tetrahydrofuran; xiv, $(Bu^i)_2AlH$; xv, DMSO, $(COCl)_2$, Et_3N; xvi, $(Ph_3P)_3RhCl$, heat.

presence of Me_3SiCl, Et_3N, and $ZnCl_2$[4] in toluene in a sealed tube at 160 °C for 12 h followed by acidic treatment gave three tetracyclic compounds (**6**), (**7**), and (**8**) (57% yield) in a ratio of *ca.* 1:2:1. The compound (**6**), m.p. 145—146 °C, $[\alpha]_D^{27}$ +13.6° (*c* 1.0, $CHCl_3$), c.d.[θ] −657° (297 nm) (MeOH), was easily purified by silica gel column chromatography, but (**7**) and (**8**) were inseparable. They were converted into three estran-4-ones (**9**), (**10**), and (**11**) in three steps: reduction with $(Bu^i)_2AlH$ (86% yield), Swern oxidation (98% yield), and decarbonylation using $(Ph_3P)_3RhCl$[5] in refluxing xylene (59—79% yield). Separation of (**10**) and (**11**) was achieved by h.p.l.c. The major product, m.p. 76—79 °C, showing a large negative Cotton effect[6], c.d. [θ] −4900° (292 nm) (MeOH),



Scheme 2. *Reagents:* i, *m*-chloroperbenzoic acid; ii, BF_3·Et_2O; iii, $(CH_3)_2C$=CH_2, BF_3·Et_2O, H_3PO_4.

was identical with the 5α, 10β-estran-4-one (**10**), m.p. 76—79 °C, c.d. [θ] −4930° (292 nm) (MeOH), which was prepared from (+)-17β-hydroxyester-4-ene (**12**)[7] in three steps; epoxidation with *m*-chloroperbenzoic acid, rearrangement with BF_3·Et_2O, and protection with isobutene in the presence of BF_3·Et_2O and H_3PO_4. The compound (**9**) was readily epimerised with NaOMe to (**10**), while the ketone (**11**) was intact under the basic conditions. Therefore the structure of (**9**), m.p. 104—107 °C, c.d. [θ] −478° (300 nm) (MeOH), was determined as an 5β,10β-estran-4-one. The 5α,10α-stereochemistry of (**11**), m.p. 60—62 °C, was deduced by the negative Cotton effect, c.d. [θ] −2092° (292 nm) (MeOH).

The above annulation of the α,β-unsaturated ester (**5**) was carefully studied by t.l.c. during the reaction and it was observed that (**5**) was initially converted into a tetracyclic ketone, which was then gradually transformed into a mixture of silyl enol ethers. A similar result was observed in our synthesis of pentalenic acid.[8] Therefore we predicted that the cyclisation would not be an intramolecular Diels–Alder reaction of the siloxydiene but a tandem conjugate addition. The configuration at the C-1 position of the compounds (**6**)—(**8**) were tentatively assigned from the assumption that the stereochemistry of the (*E*)-α,β-unsaturated ester was retained during the reaction.

Thus a new route to the estran-4-ones, useful intermediates in the synthesis of medicinally important steroid hormones,[9] was achieved.

Received, 30th March 1987; Com. 407

References

1 M. Ihara, I. Sudow, K. Fukumoto, and T. Kametani, *J. Org. Chem.*, 1985, **50**, 144; *J. Chem. Soc., Perkin Trans. 1*, 1986, 117.
2 M. Ihara, M. Toyota, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 2167; M. Ihara, M. Tsuruta, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1985, 1159; M. Ihara, M. Toyota, M. Abe, Y. Ishida, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1543; M. Ihara and K. Fukumoto, *J. Synth. Org. Chem. Jpn.*, 1986, **44**, 96 and references cited therein.
3 R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott, and P. A. Wehri, *J. Org. Chem.*, 1975, **40**, 675.
4 S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, 1974, **96**, 7807; R. L. Snowden, *Tetrahedron*, 1986, **42**, 3277; M. Ihara, T. Kirihara, A. Kawaguchi, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 4541.
5 M. C. Baird, J. T. Mague, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc. A*, 1967, 1347; K. Ohno and J. Tsuji, *J. Am. Chem. Soc.*, 1968, **90**, 99.
6 M. P. Hartshorn, D. N. Kirk, and W. Klyne, *Tetrahedron Lett.*, 1965, 89.
7 M. S. de Winter, C. M. Siegmann, and S. A. Szpilfogel, *Chem. Ind.*, 1959, 905.
8 M. Ihara, M. Katogi, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1987, 721.
9 D. P. Strike, D. Herbst, and H. Smith, *J. Med. Chem.*, 1967, **10**, 446.