CHEMISTRY LETTERS, pp. 783-786, 1987.

Synthesis of Heterosteroids. The First Synthesis of 11-Thiasteroids and a New Synthesis of 11-Oxasteroids[1]

Hiroshi SUGINOME,* Jian Bo WANG, and Shinji YAMADA
Organic Synthesis Division, Department of Chemical Process Engineering,
Faculty of Engineering, Hokkaido University, Sapporo 060

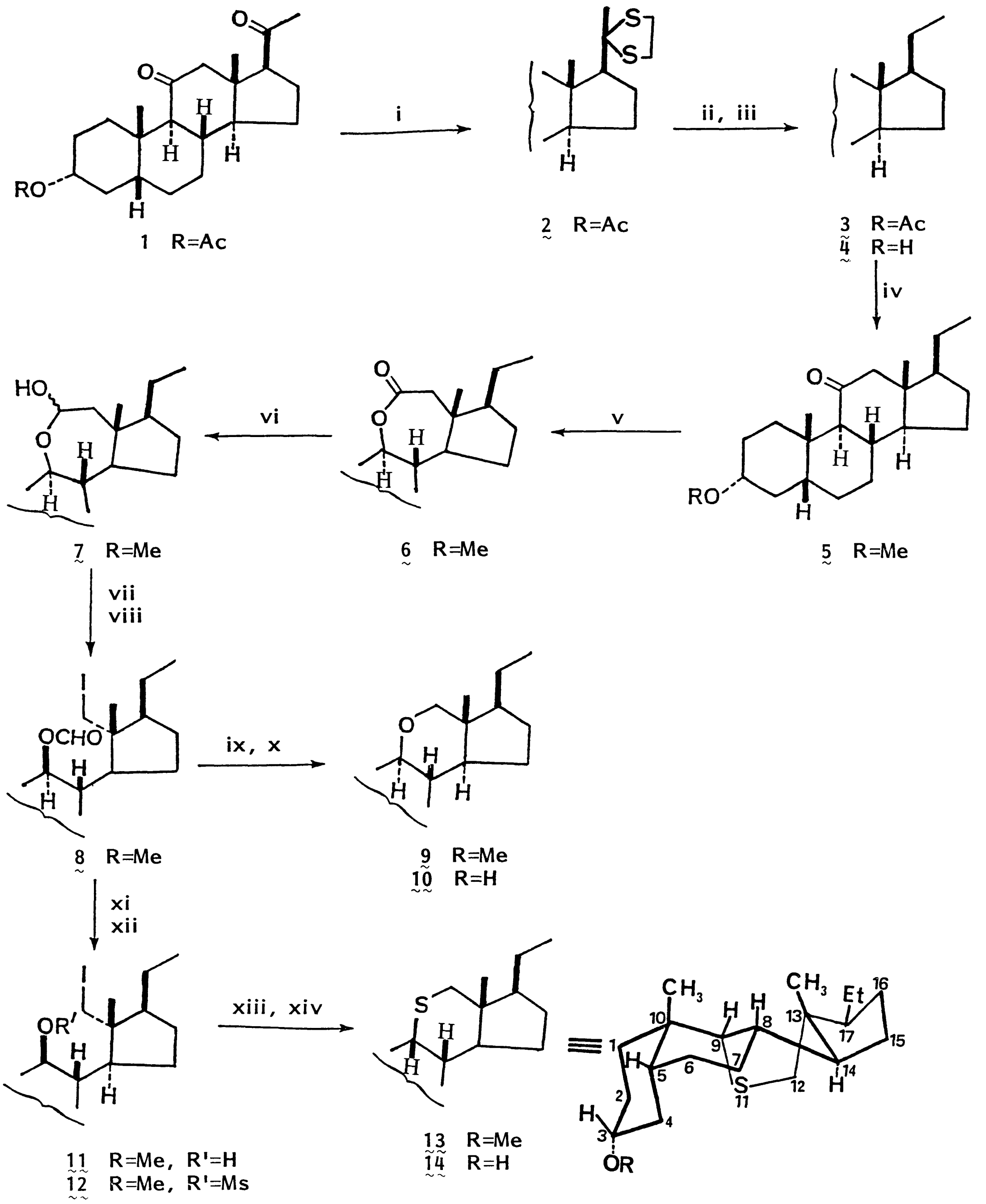
We report the syntheses of 3α-hydroxy-11-thia-5β,9β-pregnane, the first 11-thiasteroid, and 3α-hydroxy-11-oxa-5β-pregnane by the replacement of the 11-carbonyl group of 3α-hydroxy-5β-pregnane-11,20-dione acetate by a sulphur or an oxygen atom.

Among heteromodifications of steroids, the synthesis of 11-heterosteroids is of considerable importance since the replacement of carbon atom at position 11 of the steroidal framework by an oxygen atom has been shown to result in noteworthy improvements of the biological activity.[2]

The first synthesis of an 11-oxasteroid was achieved by Engel and his colleagues *via* 12 steps from hecogenin, employing the acidic cyclization of a 9,11-seco-C-nor-9,12-diol as the intermediate.[3,4] Planas and Bonet have recently reported the transformation of estrone into 11-oxaestradiol; this, again, was based on an acidic cyclization of another 9,11-seco-C-nor-9,12-diol, derived by dye-sensitized photooxygenation of a 1,3,5(10),9-estratetraene.[5] 11-Azasteroids were also synthesized by Engel and his colleagues[6] and later by Badanova and Pivnitskic.[7] There has, however, been no report so far on the synthesis of 11-thiasteroids.

We wish to report a new and efficient partial synthesis of 11-oxasteroids as well as the first synthesis of 11-thiasteroids by replacing the 11-carbonyl group of 3α-hydroxy-5β-pregnane-11,20-dione acetate (1) as the model substrate by an oxygen or a sulphur atom.

Thus, the 20-oxo group of commercially available 3α-hydroxy-5β-pregnane-11-dione acetate (1) was removed by the reduction of the thioketal group of the corresponding 20-thioketal derivative 2[8] with Raney Ni to give 3α-hydroxy-5β-pregnan-11-one acetate (3) in an almost quantitative yield. A basic hydrolysis of acetate 3 gave the corresponding 3α-ol 4;[9] this in turn gave 3α-methoxy-5β-pregnan-11-one (5) by methylation with methyl iodide-sodium hydride in THF in a yield of over 95%. The Baeyer-Villiger oxidation of ketone 5 with potassium persulphate in glacial acetic acid - concd sulphuric acid (3:0.5 in vol.) for 10 days at room temperature gave exclusively 3α-methoxy-11-oxa-*C*-homo-5β-pregnan-12-one (6)[10] (62%),[11] this was reduced with DIBAL to give a crystalline lactol 7[12] in a 98% yield. The lactol 7 was converted into the corresponding hypoiodite with a mercury(II) oxide-iodine reagent in benzene, after which the solution was subjected *in situ* to the photolysis previously reported by us,[13] to give a



Scheme 1. Reagents: i, $HSCH_2CH_2SH$, AcOH, $BF_3 \cdot Et_2O$, 20 °C, 8 h, 97%; ii, Raney Ni, dioxane, reflux, 100%; iii, KOH, MeOH, reflux, 2 h, 88%; iv, MeI, NaH, THF, 20 °C, 8 h, >95%; v, AcOH, concd H_2SO_4, $K_2S_2O_8$, 20 °C, 10 d, 62%; vi, DIBAL, toluene, -78 °C--28 °C, 5 h, 98%; vii, HgO, I_2, benzene; viii, hν, benzene, 3 h, 83%; ix, $NaBH_4$, THF, reflux, 48 h, 96%; x, Me_3SiI, $CHCl_3$, 20 °C, 12 h, 84%; xi, DIBAL, toluene, -78 °C- -20 °C, 90%; xii, CH_3SO_2Cl, pyridine, 20 °C, 79.8%; xiii, $Na_2S \cdot 9H_2O$, acetonitrilie, reflux, 4 d, 33%; xiv, Me_3SiI, $CHCl_3$, 20 °C, 12 h, 70%.

crystalline iodo formate **8**[14] in an 83% yield. Iodo formate **8** was cyclized cleanly to give 3α-methoxy-11-oxa-5β-pregnane (**9**)[15] with sodium borohydride in THF under reflux (96%). Finally, the treatment of oxasteroid **9** with trimethylsilyl iodide[16] in chloroform at room temperature for 12 h gave 3α-hydroxy-11-oxa-5β-pregnane (**10**)[17] in an 84% yield.

On the other hand, the formyloxy group of iodo formate **8** was reductively hydrolyzed with DIBAL in toluene at -78 °C to give an iodo alcohol **11** in a 90% yield. Mesylation of 9β-alcohol **11** by the standard method gave the corresponding mesylate **12**[18] in a 70.8% yield. A reflux of the acetonitrile solution of mesylate **12** containing sodium sulphide led to the first 11-thiasteroids, 3α-methoxy-11-thia-5β,10β-pregnane (**13**)[19] in a 33% yield, together with a by-product arising from the elimination. The corresponding 3α-hydroxy-11-thiasteroid **14**[20] was obtained in a 70% yield by the treatment of thiasteroid **13** with trimethylsilyl iodide in chloroform for 12 h.[21]

The 9α-configuration assigned to the oxasteroid **10** and the 9β-configuration assigned to the thiasteroid **14** were in accord with their NMR data ($J_{8,9}$=10.3 Hz and $J_{8,9}$=5.5 Hz). An inspection of the model of thiasteroid **14** with a 5β,9β-configuration indicates that the rings A and C adopt a chair and a boat conformation respectively while the rings A and C are folded back under the B-ring, as is shown in Fig. 1. The structure of this bend molecule with the 9β-configuration is further supported by the study of its nOe. Thus, irradiation of the signal due to the 19-H of thiasteroid **14** resulted in an enhancement of the signal of the 9β-H.

The synthesis of a number of other 11-heterosteroids along the lines of the present methodology is currently under active investigation.

We gratefully acknowledge financial support from the Japanese Ministry of Education and the Takeda Science Foundation.

References

1) Photoinduced Molecular Transformations. Part 85. Part 84, H. Suginome, H. Washiyama, and S. Yamada, Bull. Chem. Soc. Jpn., 60, 1071 (1987).

2) C. R. Engel, D. Mukherjee, M. N. R. Chowdhury, G. Ramani, and V. S. Salvi, J. Steroid Biochem., 6, 585 (1975).

3) C. R. Engel, R. C. Rastogi, and M. N. R. Chowdhury, Tetrahedron Lett., 1968, 2107; C. R. Engel, R. C. Rastogi, and M. N. R. Chowdhury, Steroids, 19, 1 (1972); C. R. Engel, S. Salvi, and M. N. R. Chowdhury, ibid., 25, 781 (1975); V. S. Salvi, D. Mukherjee, M. N. R. Chowdhury, and C. R. Engel, ibid., 26, 717 (1976).

4) For a paper of the participation of the 20-oxo-group in the acidic cyclization of intermediary 3,20-dioxo-9,11-seco-C-nor-5α-pregnane-9β,11-diol to an 11-oxasteroid in the Engel synthesis of 11-oxasteroids, see H. Nagano, T. Iwadare, and M. Shiota, J. Chem. Soc., Perkin Trans. 1, 1986, 2291.

5) T. Planas and J. J. Bonet, 11 IUPAC Symposium on Photochemistry, Lisbon, July-August, 1986, Abstr., p. 259.

6) C. R. Engel and S. Rakhit, Can. J. Chem., **40**, 2153 (1962); M. Gumulka, I. H. Ibrahim, Z. B.-Tomaszewski, and C. R. Engel, ibid., **63**, 766 (1984).

7) Y. P. Badanova and K. K. Pivniydkii, J. Gen. Chem. USSR, **41**, 242 (1971).

8) Mp 181-182 °C. U.S. Patent 3132160 (1964); Chem. Abstr., **61**, 4433h (1964), (mp 176-177°C).

9) Mp 158-161 °C. U.S. Patent 3132160 (1964); Chem. Abstr., **61**, 4434a (1964), (mp 153-154 °C).

10) Mp 127.5-129.0 °C; MS *m/z* 348 (M^+, 45.4%); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.67 (s, 18-H), 1.07 (s, 19-H), 2.43 (d, *J*=13.9 Hz, 12-H), 2.68 (d, *J*=13.9 Hz, 12-H), 3.20 (m, 3β-H), 3.36 (s, OMe), and 4.29 (d, *J*=9.5 Hz, 9α-H).

11) This is based on the converted ketone **5**. The yield of **6** in oxidation with MCPBA was 57%. To our knowledge, no successful formation of lactones by means of the Baeyer-Villiger oxidation of 11-ketosteroids has previously been reported and this seems to be the first example.

12) Mp 179.5-181 °C.

13) H. Suginome and S. Yamada, J. Org. Chem., **50**, 2489 (1985).

14) Mp 102-103 °C. MS *m/z* 349 [$(M-I)^+$, 0.3%].

15) MS *m/z* 320 (M^+, 27%), 288 [$(M-MeOH)^+$, 100]. ^{1}H NMR ($CDCl_3$) δ 0.72 (3H, s, 18-H), 1.02 (3H, s, 19-H), 3.09 (1H, d, *J*=9 Hz, 12-H), 3.13 (1H, d, *J*=9 Hz, 12-H), 3.35 (3H, s, OMe), and 3.86 (1H, d, *J*=10.3 Hz, 9α-H); Found: M^+, 320.2721. Calcd for $C_{21}H_{36}O_2$: M, 320.2715.

16) M. E. Jung and M. S. Lyster, J. Org. Chem., **42**, 3761 (1977).

17) Mp 139-140 °C. IR (Nujol) 3270, 1080, 1049, and 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.73 (3H, s, 18-H), 1.02 (3H, s, 19-H), 3.10 (1H, d, *J*=3 Hz, 12-H), 3.14 (1H, d, *J*=3 Hz, 12-H), 3.64 (1H, m, 3β-H), 3.88 (1H, d, *J*=10.3 Hz, 9α-H); MS *m/z* 306 (M^+, 91%), 191 (100). Found: C, 78.38; H, 11.14. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18.

18) Mp 107.5-109.0 °C. MS *m/z* 399 [$(M-I)^+$, 0.2%] and 271 (100); ^{1}H NMR δ 0.87 (3H, s, 18-H), 1.06 (3H, s, 19-H), 3.14 (3H, s, SO_2Me), 3.19 (1H, m, 3β-H), 3.27 (1H, d, *J*=10.63 Hz, 12-H), 3.32 (1H, d, *J*=10.63 Hz, 12-H), 3.35 (3H, s, OMe), 4.87 (1H, d, *J*=10.99 Hz, 9α-H).

19) MS *m/z* 336 (M^+, 33%); ^{1}H NMR δ 0.84 (3H, s, 18-H), 1.11 (3H, s, 19-H), 2.35 (1H, d, *J*=12.46 Hz, 12-H), 2.47 (1H, d, *J*=5.49 Hz, 9β-H), 2.60 (1H, d, *J*=12.46 Hz, 12-H), 3.40 (1H, m, 3β-H), 3.49 (1H, s, OMe).

20) Mp 178-180 °C; IR (Nujol) 3340, 1292, and 953 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, s, 18-H), 1.04 (3H, s, 19-H), 2.37 (1H, d, *J*=12.5 Hz, 12-H), 2.49 (1H, d, *J*=5.5 Hz, 9β-H), 2.62 (1H, d, *J*=12.5 Hz, 12-H), 4.05 (1H, m, 3β-H); MS *m/z* 322 (M^+, 88%), 304 (100). Found: M^+, 322.2313. Calcd for $C_{20}H_{34}OS$: M, 322.2320.

21) Satisfactory analytical and spectral (Mass, ^{1}H NMR, IR) results were obtained for all the compounds described in this paper.

(Received January 21, 1987)