Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 1992, **2(2)**, 47–48
Mendeleev Communications

Transformation of Androsta-4,9-diene-3,17-dione into 16α,17α-Epoxycorticosterone

Alevtina M. Turuta,* Aleksei V. Kamernitsky, Tat'yana M. Fadeeva and Luu Duc Huy

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation. Fax: + 7 095 135 5328

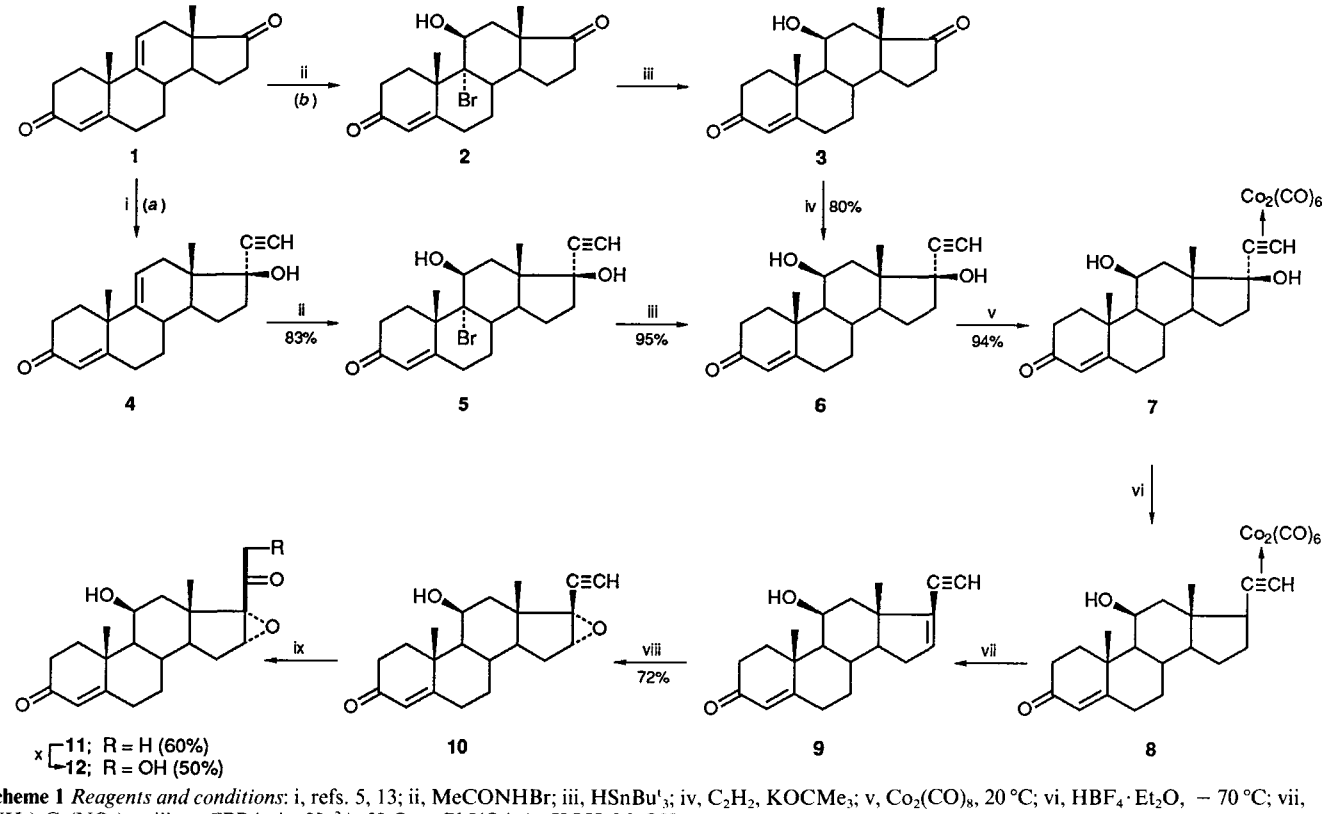
An effective synthesis of 16α,17α-epoxycorticosterone from androsta-4,9-diene-3,17-dione via 17α-ethynylandrost-4-ene-11β,17β-diol-3-one has been developed.

Microbial degradation of naturally occurring sterols provides an inexpensive source of 17-ketosteroids such as androst-4-ene-3,17-dione, androsta-1,4-diene-3,17-dione and 9α-hydroxyandrost-4-ene-3,17-dione.[1,2] The latter[3] and its Δ^9-analogue **1**[4,5] are considered at present to be the most attractive intermediates for conversion into the commercially important corticosteroids.[6–9] We now describe the conversion of androsta-4,9-diene-3,17-dione **1**[4,5] into 16α,17α-epoxycorticosterone,[10–12] which is a valuable starting material for the synthesis of corticosterone and artificial corticoids, especially dexamethasone, triamcinolone *etc*. Recently we described an alternative path for the synthesis of 16α,17α-epoxycorticosterone starting from 16α,17α-epoxypregn-5-en-3β-ol-20-one.[10]

The methods employed in this conversion are summarized in Scheme 1. The first step in the present sequence is the addition of a two-carbon acetylene fragment to either (*a*) the 17-oxo function of **1**[5,13] or (*b*) 11β-hydroxyandrost-4-ene-3,17-dione **3**, obtained by known methods[14,15] from bromohydrin **2**. According to path (*a*), 17α-ethynylalcohol **4**,[5] obtained by known methods is transformed into bromohydrin **5**,[16]† which is then

† ^{1}H NMR *Spectroscopic data* (250 MHz, standard $SiMe_3$, $CDCl_3$) for **5**: 1.16 (s, H^{18}), 1.77 (d, H^{19}, J = 0.5 Hz), 2.67 (s, H^{21}), 4.68 (H^{11}, J = 5.75, 3.5 Hz), 5.76 (d, H^4, J = 2.25 Hz). For **7**: 1.32 (s, H^{19}), 4.44 (m, H^{11}, $\Delta w_{1/2}$ = 9 Hz), 5.68 (d, H^4, J = 1.25 Hz), 6.08 (s, H^{21}). For **8**: 1.23 (s, H^{18}), 1.51 (s, H^{19}), 4.46 (m, H^{11}, $\Delta w_{1/2}$ = 10.5 Hz), 5.7 (d, H^4, J = 1.6 Hz), 6.15 (m, H^{16}), 6.17 (s, H^{21}). For **9**: 1.18 (s, H^{18}), 1.48 (s, H^{19}), 3.09 (s, H^{21}), 4.44 (m, H^{11}, $\Delta w_{1/2}$ = 9.5 Hz), 5.67 (m, H^4), 6.09 (m, H^{16}, $\Delta w_{1/2}$ = 6.75 Hz). For **10**: 1.22 (s, H^{18}), 1.45 (s, H^{19}), 2.42 (s, H^{21}), 3.64 (s, H^{16}), 4.46 (m, H^{11}, $\Delta w_{1/2}$ = 10 Hz), 5.67 (m, H^4). For **12**: 1.41 (s, H^{18}), 1.46 (s, H^{19}), 3.72 (s, H^{16}), 4.03 and 4.35 (dd, H^{21}, J = 19 Hz), 4.42 (m, H^{11}, $\Delta w_{1/2}$ = 10 Hz), 5.68 (m, H^4).

Melting points /°C for **5**: 184–187 (MeOH–$CHCl_3$); for **9**: 183–188 (Me_2CO–C_6H_{14}); for **10**: 277–282 (MeOH); for **12**: 176–181 (Me_2CO–C_6H_{14}).



Scheme 1 *Reagents and conditions*: i, refs. 5, 13; ii, MeCONHBr; iii, $HSnBu^t_3$; iv, C_2H_2, $KOCMe_3$; v, $Co_2(CO)_8$, 20 °C; vi, $HBF_4 \cdot Et_2O$, − 70 °C; vii, $(NH_4)_2Ce(NO_3)_6$; viii, *m*-CPBA; ix, Hg^{2+}, H_2O; x, $PhI(OAc)_2$–KOH–MeOH

debrominated by $HSnBu^t_3$,[16] giving rise to ethynylalcohol **6**, in 80% yield over the two steps.† The second route (*b*) for the transformation of **1** into **6** follows literature methods, involving bromohydroxylation of **1**,[14,18] followed by debromination of the obtained bromohydrin **2**[14,15] and 17α-ethynylation of **3**.[15,19] However, this sequence is limited by a low yield (30%) in the final step, which also requires protection of the Δ^4-3-oxo group. We found that acetylene condensation of **3** gives 80% yield of **6** without protection of the Δ^4-3-oxo group (overall yield of **6** from **1** 68%). Selective dehydration of the 17β-hydroxy group in ethynylalcohol **6**[15,19,20] was successfully achieved using the Nicholas reaction.[21] Ethynylalcohol **6** was transformed in quantitative yield into cobalt complex **7**, followed by dehydration with $HBF_4 \cdot Et_2O$ into **8** and then decomplexation by the usual methods.[13,16,21]† Enyne **9**, obtained by this route in 70% yield, was transformed into epoxide **10** by treatment with *m*-chloroperbenzoic acid, followed by Hg^{2+} catalysed hydration. As a result, the epoxyketone **11**[22] was prepared in good yield and its conversion into 21-hydroxyepoxide **12**[10] was accomplished according to Moriarty's method,[23,24] using the oxidative system $PhI(OAc)_2$–KOH–MeOH.†

The newly available 17α-ethynylalcohols with Δ^9-, 9α-hydroxy- and 11β-hydroxy-groups in the *C*-ring are envisaged as prospective intermediates in corticoid synthesis. The scheme proposed here for the synthesis of 11β-hydroxy-16α,17α-epoxypregnanes **11** and **12** compares favourably with the known procedures, which are less effective.[11,12,22]

Received: Moscow, 23rd October 1991
Cambridge, 18th December 1991; Com. 1/05547J

References

1 M. Nagasawa, H. Hashiba, N. Watababe, M. Bae, G. Tamura and K. Arima, *Agric. Biol. Chem.*, 1970, **34**, 801.
2 C. J. Sih, F. L. Wesenborn, *US. Pat.*, 3065146, 1962; *Chem. Abstr.*, 1963, **58**, 11668g.
3 M. G. Woicha, F. J. Antosz, J. C. Knight, L. A. Kominek and T. R. Pyke, *Biochim. Biophys. Acta*, 1978, **531**, 308.
4 J. M. Beaton, A. G. Padilla, J. E. Huber and M. E. Breuer, *Ger. Offen.* 2.814.747, 1978; *Chem. Abstr.*, 1979, **91**, 74781f.
5 V. Van Rheeneh and K. P. Shephand, *J. Org. Chem.*, 1979, **44**, 1582.
6 J. C. Kapur, A. F. Marx and J. Verweij, *Steroids*, 1989, **52**, 181.
7 J. N. M. Batist, A. F. M. Slobbe and A. F. Marx, *Steroids*, 1989, **54**, 321.
8 J. N. M. Batist, M. C. M. E. Barendse and A. F. Marx, *Steroids*, 1990, **55**, 109.
9 I. Nitta, S. Fujimori and H. Ueno, *Bull. Chem. Soc., Jpn.*, 1985, **58**, 978.
10 A. M. Turuta, A. V. Kamernitzky, N. E. Voishvillo, N. V. Jlantiashvili, A. P. Krymov and N. V. Domrachev, *Mendeleev Commun.*, 1991, 113.
11 E. J. Agnello, B. M. Bloom and G. D. Laubach, *US. Pat.*, 2.835.274, 1958; *Chem. Abstr.*, 1958, **52**, 16424g.
12 E. J. Agnello, B. M. Bloom and G. D. Laubach, *US. Pat.*, 2.976.283, 1961; *Chem. Abstr.*, 1961, **55**, 16603f.
13 A. M. Turuta, T. M. Fadeeva, A. V. Kamernitzky, A. A. Korobov, E. D. Cherepanova and Luu Duc Huy, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 675 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, 595).
14 J. B. Heather and D. R. White, *US. Pat.*, 4.304.727, 1981; *Chem. Abstr.*, 1982, **96**, 163049u.
15 C. W. Marshall, J. W. Ralls, F. J. Saunders and B. Riegel, *J. Biol. Chem.*, 1957, **228**, 339.
16 A. M. Turuta, T. M. Fadeeva, A. V. Kamernitzky and Luu Duc Huy, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 724.
17 H. Parnes and J. Pease, *J. Org. Chem.*, 1979, **44**, 151.
18 R. H. Lenhard and S. Bernstein, *J. Am. Chem. Soc.*, 1955, **77**, 6665.
19 D. H. Gould, H. L. Herzog and E. B. Hershberg, *US. Pat.*, 2.816.121, 1957; *Chem. Abstr.*, 1958, **52**, 6422a.
20 G. Muller, R. Jeguier and C. Plotka, *J. Am. Chem. Soc.*, 1958, **80**, 2026.
21 K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207.
22 A. M. Turuta, A. V. Kamernitzky, A. A. Korobov, V. S. Bogdanov, T. G. Baklashova, T. V. Komarova and K. A. Kosheenko, *Khim. Farm. Zh.*, 1990, 652.
23 R. M. Moriarty, H. Hu and S. C. Gupta, *Tetrahedron Lett.*, 1981, **22**, 1283.
24 A. V. Kamernitzky, A. M. Turuta, T. M. Fadeeva and Z. I. Istomina, *Synthesis*, 1985, 326.