Selective Cleavage of Ditertiary Glycols under Mild Conditions, with Bisacetylacetonato-oxovanadium

Michael Zviely,* Alexander Goldman, Isaac Kirson, and Erwin Glotter
Faculty of Agriculture, The Hebrew University of Jerusalem, Rehovot 76-100, Israel

Bisacetylacetonato-oxovanadium [$VO(acac)_2$] is a selective reagent for the quantitative cleavage of ditertiary glycols, under mild conditions. The reaction takes place also with catalytic amounts of the reagent, in the presence of t-butyl hydroperoxide or *m*-chloroperbenzoic acid.

The dioxovanadium cation VO_2^+ was recognized in the late fifties as a useful oxidizing agent for cleavage of ditertiary and secondary tertiary glycols.[1] The reactions were performed in aqueous acidic solutions (H_2SO_4 or $HClO_4$). It is well known that periodic acid, which is widely used for glycol cleavage, is ineffective with ditertiary members of this group of compounds.[2]

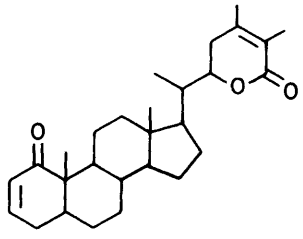
We now report that bisacetylacetonato-oxovanadium [$VO(acac)_2$] in aprotic solvents (CH_2Cl_2, C_6H_6, or mixtures thereof) is a selective reagent for smooth cleavage of ditertiary glycols which can form intermediate complexes with the reagent. The reactions take place at room or higher temperatures (up to 70 °C), according to the substrate, and can be performed with stoicheiometric or catalytic amounts of the reagent; the latter option requires the presence of an oxidizing agent, such as t-butyl hydroperoxide (Sharpless reagent[3] for the selective epoxidation of allylic alcohols) or an organic peracid (*e.g. m*-chloroperbenzoic acid). It is noteworthy that the turnover of both catalytic reactions (at least 140) is the same as in the Sharpless method of epoxidation.

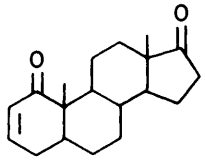
Thus, pinacol was converted into acetone and benzpinacol into benzophenone in good to excellent yields. The reactions were carried out in benzene solution, at 40 °C and 70 °C, respectively. No attempts were made to optimize the experimental conditions. The behaviour of these ditertiary glycols is in sharp contrast with that of butane-2,3-diol which remained essentially unchanged even after 48 h at 70 °C. Attempted cleavage of cyclohexane-1,2-diol (*cis–trans* mixture), under similar conditions, resulted in only a 1% conversion into the corresponding acyclic dialdehyde, whose formation was inferred from the n.m.r. spectrum of the crude mixture.

The 17,20-ditertiary glycol system in withanolide E (**1a**),[4] a naturally occurring steroidal lactone with an α-oriented side chain, is quantitatively cleaved with stoicheiometric or catalytic amounts of the reagent to the corresponding androstan-17-one derivative (**2a**) and the unsaturated lactone (**3**).[5] The reactions were carried out at 25—30 °C for not more than 1 h.

The reaction with the stereoisomeric isowithanolide E (**1b**)[6] (β-oriented side chain) required 24 h at 70 °C in order to bring about the quantitative cleavage of the 17,20-glycol. This was performed in benzene–dichloromethane solution with a catalytic amount of [$VO(acac)_2$], in the presence of t-butyl hydroperoxide as the oxidant.

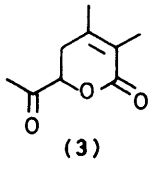
The different behaviour of compounds (**1a**) and (**1b**) can easily be rationalized by taking into account the preferred conformations of the corresponding molecules along the C(17)–C(20) bond. In (**1a**) (see A) the two hydroxy groups are in a *gauche* relationship and can easily form a cyclic complex with the reagent (after a slight rotation in order to achieve a *syn* relationship). In (**1b**) (see B), these groups are in an *anti* relationship and rotation to the *syn* position, although possible, requires more energy due to steric interference between the 18-methyl group and the lactone ring.



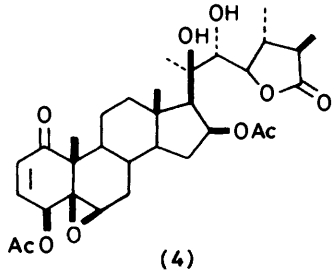


(**1**) **1a**; 14α,17β,20-trihydroxy-5β,6β-epoxy.
b; 14α,17α,20-trihydroxy-5β,6β-epoxy.
c; 6β,14α,17β,20-tetrahydroxy-5α-methoxy.
d; 14α,17β,20-trihydroxy-5α,6α-epoxy.
e; Δ^{14}, 17β-20-dihydroxy-5α,6α-epoxy.
f; 4β-acetoxy-14α,17β,20-trihydroxy-5β,6β-epoxy.
g; 4β,14α,17β,20-tetrahydroxy-5β,6β-epoxy.

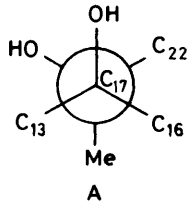
(**2**) **a**; 14α-hydroxy-5β,6β-epoxy.
c; 6β,14α-dihydroxy-5α-methoxy.
d; 14α-hydroxy-5α,6α-epoxy.
e; Δ^{14}, 5α,6α-epoxy.
f; 4β-acetoxy-14α-hydroxy-5β,6β-epoxy.
g; 4β, 14α-dihydroxy-5β,6β-epoxy.
h; 14α-hydroxy-4-oxo-5β,6β-epoxy.



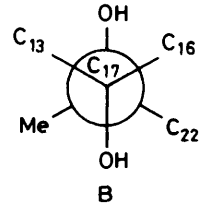
(**3**)



(**4**)



A



B

Similarly, withanolide S 5-methyl ether (**1c**), α-epoxywithanolide E (**1d**), 14-deoxy-α-epoxywithanolide E (**1e**),[7] and 4β-acetoxywithanolide E (**1f**),[8] afforded the androstane derivatives (**2c—f**), respectively. Complications may arise with

Table. N.m.r. data *

Compound.	2-H	3-H	4-H	6-H	18-H	19-H	Other signals
(**2a**)†	6.04dd (9.7, 2.6)	6.90ddd (9.7, 6.2, 2.6)	3.01dt (19.1, 2.7) 2.05dt (19.1, 3.3)	3.26d (2.5)	1.01s	1.29s	
(**2c**)‡	5.88dt (10, 2.5)	6.88ddd (10.5, 2.5)		4.20m ($W_{\frac{1}{2}}$ *ca.* 4)	0.97s	1.30s	3.07s, 5α-OMe
(**2c**)-acetate	5.85dt (10, 2.5)	6.49ddd (10.5 2.5)		5.17m ($W_{\frac{1}{2}}$ *ca.* 4)	1.05s	1.30s	3.07s, 5α-OMe 2.16s, 6β-OCOMe
(**2f**)	6.25d (6)	7.02dd (10, 6)	4.68d (6)	3.35m ($W_{\frac{1}{2}}$ *ca.* 3)	1.00s	1.42s	2.06s, 4β-OCOMe
(**2g**)	6.16d (6)	6.92dd (10, 6)	3.76d (6)	3.32m ($W_{\frac{1}{2}}$ *ca.* 2)	1.15s	1.42s	
(**2h**)	6.85s			3.52m ($W_{\frac{1}{2}}$ *ca.* 4)	1.03s	1.40s	

* Recorded in $CDCl_3$ at 80 MHz, unless stated otherwise. Signals recorded as δ values; coupling constants or signal widths ($W_{\frac{1}{2}}$, Hz) are in parentheses. † Recorded at 360 MHz. ‡ CD_3COCD_3 solution.

substrates possessing an allylic hydroxy group in addition to the ditertiary glycol system, when the reactions are performed with catalytic amounts of $[VO(acac)_2]$ in the presence of t-butyl hydroperoxide. Such a case is exemplified by 4β-hydroxywithanolide E (**1g**)[8] which afforded a mixture of 4β,14α-dihydroxy-5β,6β-epoxyandrost-2-ene-1,17-dione (**2g**) and the corresponding 1,4,17-trione derivative (**2h**). The cleavage of the 17,20-gycol is, however, significantly faster than the oxidation of the above 4β-OH. Whereas compound (**2g**) is the major product (along with unchanged material) when the reaction is limited to 1 h at room temperature, a *ca.* 3:2 mixture of (**2g**) and (**2h**) was obtained when the reaction was allowed to proceed overnight at 40 °C.

Attempted cleavage of the three steroidal secondary-tertiary glycols 3β,5α,6β-trihydroxycholestane (*trans*-diaxial configuration of the glycol system), 3β,5β,6β-trihydroxycholestane (*cis*-glycol system), and ixocarpalactone A 4,16-diacetate (**4**)[9] (20*R*,22*R* glycol) was unsuccessful.

Experimental

M.p.s were taken with a Fisher-Johns apparatus. Optical rotations were measured with an automatic Perkin-Elmer 141 polarimeter. ^1H N.m.r. spectra were determined at 80 MHz on a Varian FT-80A instrument. T.l.c. was carried out on plates of silica gel 60 F_{254} (Merck); preparative chromatoplates (1 mm thick) were prepared with silica gel PF_{254} (Merck). Commercial t-butyl hydroperoxide was purified as indicated.[3] Analyses were performed in the microanalytical laboratory of the Hebrew University, under the direction of Mrs S. Blum.

Cleavage of the C(17)–C(20) *Bond in Withanolide E* (**1a**).—*Procedure A.* To a solution of (**1a**) (0.1 mmol) in dry benzene (10 ml), a solution of $[VO(acac)_2]$* (0.1 mmol) in the same solvent (5 ml) was added. The starting material (**1a**) completely disappeared after 1 h at room temperature (*ca.* 25 °C, t.l.c. evidence). The solution was filtered through Florisil (100—200 mesh; 3 g) and elution was completed with dichloromethane–ethyl acetate (7:3). The n.m.r. spectrum of the crude mixture pointed to the total disappearance of the 22-H signal (multiplet, δ 4.88) in the starting material and the appearance of a triplet, δ 4.67 (*J* 7 Hz), due to the above proton in lactone (**3**). This signal had the same intensity as that of the vinylic 2-H and 3-H. The integration was done on expanded spectra (20 Hz cm^{-1}) recorded at 300 MHz. The crude product (two spots on t.l.c.) gave, after separation on a preparative chromatoplate, (**2a**) (26 mg) and (**3**) (15 mg).

Procedure B. To a solution of (**1a**) (0.1 mmol) in dry benzene (10 ml), a solution of $[VO(acac)_2]$ (7.5×10^{-4} mmol) in dry benzene (0.2 ml), followed by a 2.7M-solution of t-butyl hydroperoxide (0.12 mmol) in the same solvent, was added. Further treatment was carried out as described above and resulted in (**2a**) (28 mg) and (**3**) (15 mg).

Procedure C. A solution of *m*-chloroperbenzoic acid (0.12 mmol) in dry benzene (5 ml) was dropwise added to a mixture of (**1a**) (0.1 mmol) in dry benzene (10 ml) and $[VO(acac)_2]$ (7.5×10^{-4} mmol) in dry benzene (0.2 ml). Further treatment was carried out as indicated in procedure A and resulted in (**2a**) (25 mg) and (**3**) (13 mg). 14α-Hydroxy-5β,6β-epoxyandrost-2-ene-1,17-dione (**2a**) had m.p. 159—161 °C (from benzene); $[\alpha]_D$ +51° (*c* 0.1, chloroform); $\nu_{max.}$ 1 670 and 1 740 cm^{-1} (chloroform solution) (Found: C, 72.0; H, 7.8. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.65%). Compound (**3**) was identified by direct comparison with an authentic sample.[5]

17-*Isowithanolide E* (**1b**).[6]—According to procedure B; the compound was suspended with stirring in a 1:1 mixture of benzene and dichloromethane (10 ml) and dissolution occurred after 3 h. The total disappearance of (**1b**) required 24 h at 70 °C. After separation on a preparative chromatoplate, compounds (**2a**) (25 mg) and (**3**) (15 mg) were obtained.

Withanolide S 5-Methyl Ether (**1c**).[7]—According to procedure B; the compound was dissolved in a 1:1 mixture of benzene and dichloromethane (10 ml). Although the starting material almost disappeared (t.l.c. evidence) after 2 h at 40 °C, the reaction was allowed to proceed overnight at the same temperature. After separation on a preparative chromatoplate, compounds (**2c**) (30 mg) and (**3**) (15 mg) were obtained. 6β,14α-*Dihydroxy*-5α-*methoxyandrost*-2-*ene*-1,17-*dione* (**2c**) had m.p. 232—234 °C (from chloroform). Acetylation with acetic anhydride–pyridine overnight at room temperature afforded the 6-acetate, m.p. 217—219 °C (from methanol), $[\alpha]_D$ +65.2° (*c* 0.1, ethanol) (Found: C, 67.8; H, 7.7. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.75%).

α-*Epoxywithanolide E* (**1d**).[7]—According to procedure B; the compound was suspended with stirring in a 1:1 mixture of benzene and dichloromethane (10 ml). The starting material almost disappeared after 2 h at 40 °C; the reaction was allowed, however, to proceed overnight. 14α-Hydroxy-5α,6α-epoxyandrost-2-ene-1,17-dione (**2d**) and the lactone (**3**) were

* acac = MeCOCHCOMe.

identified by n.m.r. as the only components of the crude mixture [total disappearance of the 22-H signal in the starting compound (**1d**) and appearance of a triplet δ 4.67 (*J* 7 Hz) due to the above proton in lactone (**3**)]. Compound (**2d**) could not be purified by preparative t.l.c. because of extensive decomposition.

14-*Deoxy-α-epoxywithanolide E* (**1e**).[7]—According to procedure B; the reaction was performed as described for compound (**1d**). 5α,6α-Epoxyandrosta-2,14-diene-1,17-dione (**2e**) and the lactone (**3**) were the only components of the crude product (t.l.c. and n.m.r. evidence). The compound (**2e**) could not be purified by preparative t.l.c.

4β-*Acetoxywithanolide E* (**1f**).[8]—According to procedure B; the compound (**1f**) (0.1 mmol) was dissolved in dichloromethane. The reaction was allowed to proceed overnight at 40 °C. The crude mixture of (**2f**) and (**3**) was separated on a preparative chromatoplate. 4β-Acetoxy-14α-hydroxy-5β,6β-epoxyandrost-2-ene-1,17-dione (**2f**) (40 mg) could not be induced to crystallize, $[\alpha]_D$ +148° (*c* 0.1, chloroform). Chemical ionization mass spectrometry: MH^+ absent; 356.8 ($MH^+ - H_2O$, 14.6%), 296.9 ($MH^+ - H_2O$ – AcOH, 100). 14α-Hydroxy steroids with a β-oriented side chain are known to undergo facile dehydration under the conditions employed in mass spectrometric determinations. Therefore, the molecular ions are rarely obtained.[6] The androstane derivatives (**2f**) and (**2g**) behaved in a similar manner (Found: C, 67.2; H, 7.1. $C_{21}H_{26}O_6$ requires C, 67.4; H, 7.0%).

4β-*Hydroxywithanolide E* (**1g**).[8]—According to procedure B; compound (**1g**) (50 mg) was dissolved in dichloromethane (10 ml). The reaction was discontinued after 1 h at room temperature and the crude mixture was separated on a preparative chromatoplate to give unchanged material (**1g**) (23 mg), compound (**2g**) (13 mg), and the lactone (**3**) (5 mg). The reaction was repeated with 100 mg of (**1g**) and the corresponding amounts of reagents, overnight at 40 °C. After separation on a chromatoplate, compounds (**2g**) (36 mg), (**2h**) (24 mg), and (**3**) (17 mg) were obtained. 4β,14α-Dihydroxy-5β,6β-epoxyandrost-2-ene-1,17-dione (**2g**) could not be induced to crystallize, *m/z* (c.i.) MH^+, absent; 314.8 ($MH^+ - H_2O$, 31%); 296.8 ($MH^+ - 2H_2O$, 100). 14α-Hydroxy-5β,6β-epoxyandrost-2-ene-1,4,17-trione (**2h**) could not be induced to crystallize; its n.m.r. spectrum was identical with that described in the literature.[5a]

Pinacol (2,3-*Dimethylbutane*-2,3-*diol*).—According to procedure B; the reaction was performed overnight, at 40 °C with a benzene solution (10 ml) of pinacol (2 mmol), [$VO(acac)_2$] (3×10^{-2} mmol), and t-butyl hydroperoxide (2.5 mmol). The crude product contained acetone (79%) and unchanged pinacol (21%) by integration of the n.m.r. spectrum.

Benzpinacol (*Tetraphenylethane*-1,2-*diol*).—According to procedure B; the reaction was performed as described for pinacol. The crude product contained benzophenone (25%) and unchanged benzpinacol (75%). Alternatively, the reaction was allowed to proceed at 70 °C for 40 h. According to the n.m.r. spectrum of the crude product, the conversion was practically complete.

Acknowledgements

This work was supported by grant I-142-80 from the U.S.–Israel Binational Agricultural Research and Development Fund (BARD). We are grateful to Dr. Miriam Cojocaru (Bar Ylan University) and Mrs. Zina Kustanovich (Weizmann Institute) for the mass spectra.

References

1 J. S. Littler, A. I. Mallet, and W. A. Waters, *J. Chem. Soc.*, 1960, 276.
2 C. A. Bunton, in 'Oxidation in Organic Chemistry,' ed. K. B. Wibert, part A, ch. VI, Academic Press, New York, London, 1965.
3 K. Barry Sharpless and T. R. Verhoeven, *Aldrichimica Acta*, 1979, **12**, 63 and references cited therein.
4 E. Glotter, A. Abraham, G. Gunzberg, and I. Kirson, *J. Chem. Soc., Perkin Trans. 1*, 1977, 341.
5 (*a*) K. Sakurai, H. Ishii, S. Kobayashi, and T. Iwao, *Chem. Pharm. Bull.*, 1976, **24**, 1403; (*b*) F. Frolow, A B. Ray, M. Sahai, E. Glotter, H. E. Gottlieb, and I. Kirson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1029.
6 I. Kirson and H. E. Gottlieb, *J. Chem. Res.* (*S*), 1980, 339; (*M*), 4275.
7 E. Glotter, A. Goldman, M. Sahai, and I. Kirson, unpublished results.
8 I. Kirson, A. Abraham, P. D. Sethi, S. S. Subramanian, and E. Glotter, *Phytochemistry*, 1976, **15**, 340.
9 I. Kirson, A. Cohen, M. Greenberg, H. E. Gottlieb, E. Glotter, P. Varenne, and A. Abraham, *J. Chem. Res.* (*S*), 1979, 103; (*M*), 1178.

Received 9*th April* 1985; *Paper* 5/584