The allylic oxidation of unsaturated steroids by *tert*-butyl hydroperoxide using surface functionalised silica supported metal catalysts

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Metal complexes based on Co(II), Cu(II), Mn(II) and V(II) immobilised on mesoporous silica, efficiently catalyse the selective allylic oxidation of unsaturated steroids and valencene, and can be easily recovered and reused.

Introduction

Allylic oxidation is a fundamental organic reaction of significant interest to organic chemists with applications in areas ranging from agricultural products to pharmaceuticals.[1,2] The allylic oxidation of steroids is a particularly important subject and has attracted interest over many years. The Δ^5-steroids can be oxidised to 5-en-7-ones, which are known as inhibitors of sterol biosynthesis and have some use in cancer chemotherapy.[3]

The allylic oxidation of unsaturated steroids such as Δ^5-steroids, has traditionally been performed with chromium reagents such as CrO_3–pyridine complex,[4] CrO_3 and 3,5-dimethylpyrazole,[5] pyridinium chlorochromate, (PCC),[6,7] pyridinium dichromate (PDC),[7] sodium chromate,[8] sodium dichromate in acetic acid,[9] pyridinium fluorochromate,[10] and 3,5-dimethylpirazolium fluorochromate(VI).[11] However, the great excess of ecologically and physiologically undesirable chromium reagent and the large volume of solvent required in these procedures, in combination with the difficult work-up and the production of environmentally hazardous chromium residues, causes such procedures to be inconvenient on a commercial scale.

Of greater preparative interest has been the use of hydroperoxides combined with different types of catalyst.[12–19] Despite the good yields reported with CrO_3,[12] hexacarbonylchromium $Cr(CO)_6$,[13,14] pyridinium dichromate,[15] and $RuCl_3$[16] to prepare allylic oxidation products from Δ^5-steroids, the toxicity of the chromium compounds and the high cost of the ruthenium catalyst hinders commercialisation of the procedures.

More environmentally acceptable methods based on the use of copper salts and copper metal have been reported[19] but a difficult separation step is needed to remove the catalyst which cannot easily be recovered and reused.

Hence there is need for a simple, efficient, safe and cost effective procedure for selectivity effecting the allylic oxidation of steroids and especially where the separation stages of the reaction are simple and enable catalyst recycling.

The heterogenisation of inorganic reagents and catalysts useful in organic reactions is a very important area[20] and led us to recently report the use of $Co(OAc)_2{\cdot}4H_2O$ as catalyst in heterogeneous forms for this type of allylic oxidation reaction.[21]Here we report the use of other steroids and non-steroids compounds as substrates and cobalt, copper, manganese and vanadium catalysts in heterogeneous forms (prepared as reported previously,[22,23] Fig. 1) for this type of reaction.

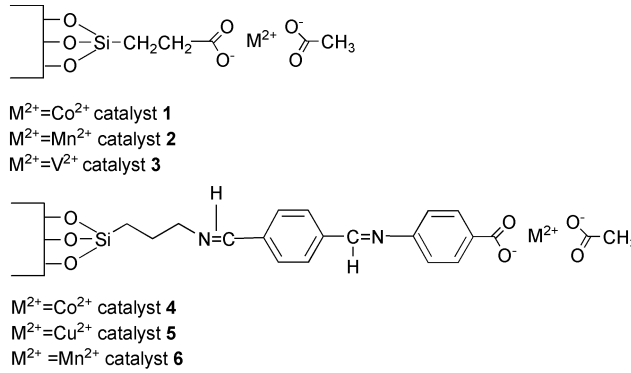

Fig. 1

Results and discussion

Recently we reported the use of $Co(OAc)_2{\cdot}4H_2O$ as catalyst in heterogeneous forms (catalyst **1**, $Co(OAc)_2/SiO_2$, catalyst **2** and **5**) for this type of allylic oxidation reaction.[21] In order to ascertain the efficacy of the oxidative system (*t*-BuOOH/catalyst **2**) a more polar substrate, the steroid **8** was used as substrate leading to the formation of the allylic oxidation product **9** in a very high yield and very high selectivity, (Scheme 1, Table 1).

Similar oxidation can be performed on valencene **10**. Using the catalyst **2**, the sesquiterpenoid nootkatone **11**, a major contributor to the aroma of grapefruit present in commercial flavourings was the major product (75%), although the catalyst **5** gave the nootkatone in 70% yield, (Table 1).

Green Context

The oxidation of naturally occurring alkenes such as steroids and terpenoid compounds can lead to a range of very useful products. Usaing traditional oxidants is wasteful and alternatives are required. Here, the use of various transition metal salts attached to silica as catalysts in such oxidations is described, with *tert*-butyl hydroperoxide as primary oxidant. Products are formed in good to excellent yields. This paper demonstrates that the promising results with these catalysts using model compounds can be transferred to bulkier substrates. ***DJM***

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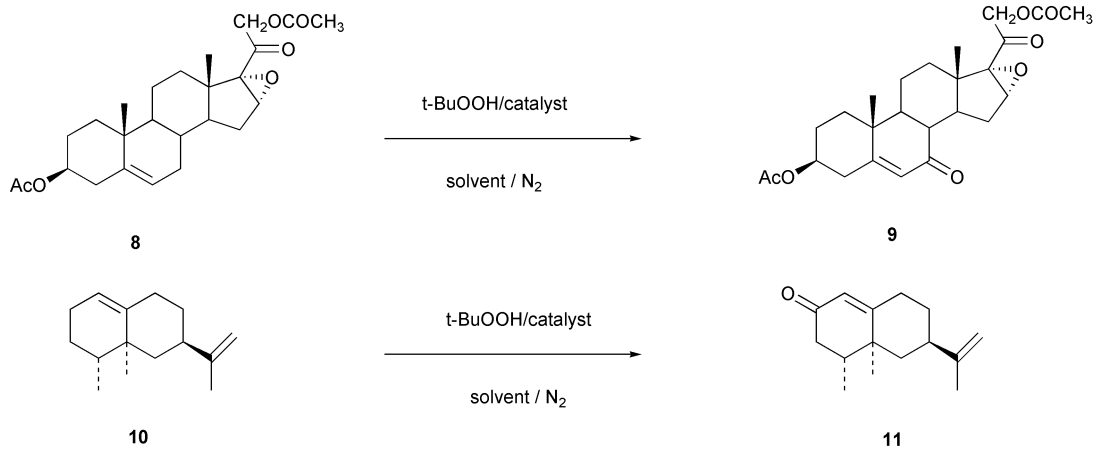


Scheme 1

Table 1 Allylic oxidation with cobalt catalyst

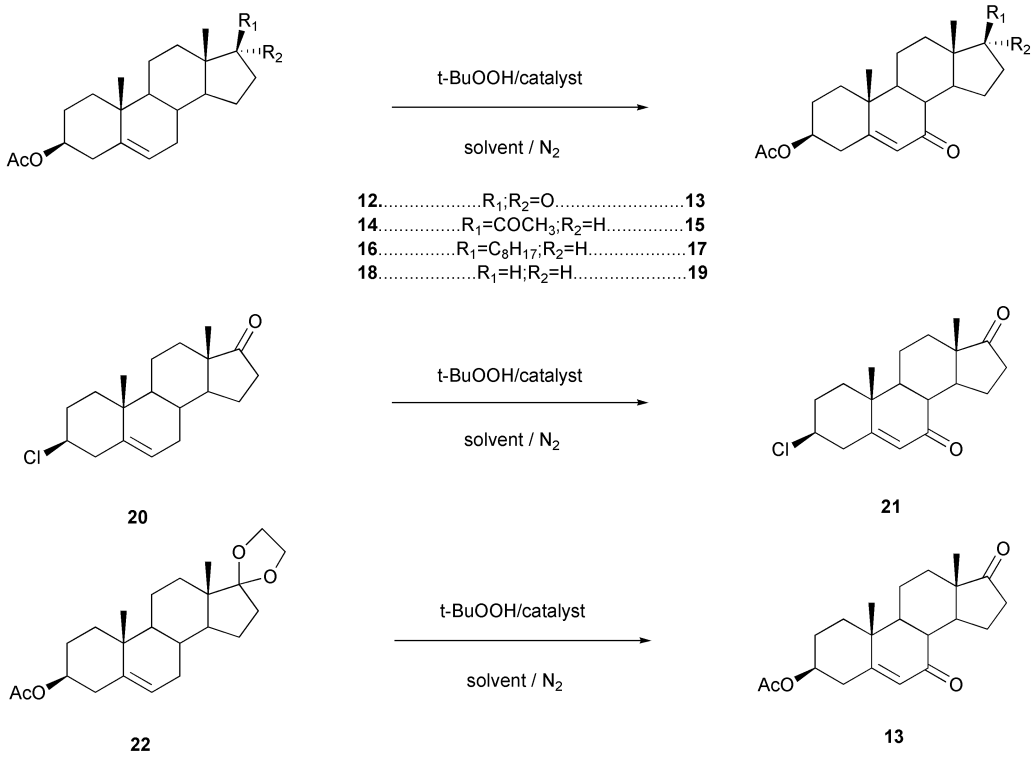
Substrate/mmol	*t*-BuOOH[a]/ml	Catalyst/cobalt mmol	Solvent	Time/h	Temp./°C	Product	Isolated yield (%)
8/0.16	0.2	**1**/0.002	CH_3CN	20	50	**9**	84[b]
10/2.45	2.4	**1**/0.018	CH_3CN	24	55	**11**	75[c]
10/2.45	2.4	**4**/0.025	CH_3CN	24	55	**11**	70[c]

[a] 5.0–6.0 M solution in decane (Aldrich). [b] Traces of starting material and a by product are visible in TLC plates but not detectable in ^{1}H NMR spectrum (300 MHz) of the crude product. [c] Recovered by flash chromatography (ethyl acetate–light petroleum (bp 40–60 °C).

Despite the good yields with the copper catalyst in homogeneous conditions reported in a previous communication[19] the catalyst cannot be easily recovered and reused which encouraged us to use heterogeneous forms of a copper catalyst **5** for this type of allylic oxidation reaction.Using Δ^5-steroids **8**, **12**–**22** and valencene **10** as substrates (Schemes 1 and 2) allylic oxidation products **9**, **13**–**21** and **11** were obtained in very high isolated yields, 72–86% (Table 2).The reactions were generally performed in acetonitrile except for the substrate **16** which required benzene as solvent.

These reactions are very selective compared to those carried out using $Fe(acac)_3$ as catalyst reported by Kimura and Muto.[17] $Mo(CO)_6$ has also been described as a catalyst for this reaction but this led to epoxidation of the cholesteryl acetate under similar oxidative conditions.[18] On the contrary, using manganese catalysts **2** and **6** and vanadium catalyst **3**, the allylic oxidation occurs in very good yields (Table 3).

While the product yields of the allylic oxidations are very similar under homogeneous[19] and heterogeneous conditions the easier recovery of the catalyst in heterogeneous conditions,



Scheme 2

Table 2 Allylic oxidation with copper catalyst

Substrate/mmol	*t*-BuOOH[a]/ml	Catalyst/copper mmol	Solvent	Time/h	Temp./°C	Product	Isolated yield (%)
8/0.16	0.2	**5**/0.0004	CH_3CN	18	50	**9**	85
10/2.45	2.4	**5**/0.008	CH_3CN	24	50	**11**	75[c]
12/2	2.4	**5**/0.006	CH_3CN	18	55	**13**	86
12/2	2.4	**5**/recycled	CH_3CN	24	55	**13**	84
14/2	2.4	**5**/0.006	CH_3CN	20	55	**15**	81[b]
14/2	2.4	**5**/recycled	CH_3CN	20	55	**15**	79[b]
16/1	1.2	**5**/0.06	Benzene	48	70	**17**	72[c]
18/2	2.4	**5**/0.006	CH_3CN	24	55	**19**	74[c]
20/1	1.2	**5**/0.01	CH_3CN	24	55	**21**	78[c]
22/1	1.2	**5**/0.003	CH_3CN	24	55	**13**	80
23/0.53	0.6	**5**/0.002	CH_3CN	10	55	**24**	72[c]
25/1	1.2	**5**/0.01	CH_3CN	24	55	**26**	75[c]

[a] 5.0–6.0 M solution in decane (Aldrich). [b] Traces of starting material and a by product are visible in TLC plates but not detectable in ^{1}H NMR spectrum (300 MHz) of the crude product. [c] Recovered by flash chromatography (ethyl acetate–light petroleum (bp 40–60 °C).

Table 3 Allylic oxidation with manganese and vanadium catalysts

Substrate/mmol	*t*-BuOOH[a]/ml	Catalyst/metal mmol	Solvent	Time/h	Temp./°C	Product	Isolated yield (%)
12/2	2.4	**2**/0.06	CH_3CN	24	55	**13**	82[b]
12/2	2.4	**3**/0.06	CH_3CN	24	55	**13**	73[c]
12/2	2.4	**6**/0.082	CH_3CN	24	55	**13**	81[b]
12/2	2.4	**6**/recycle	CH_3CN	24	55	**13**	77[b]

[a] 5.0–6.0 M solution in decane (Aldrich). [b] Traces of starting material and a by product are visible in TLC plates but not detectable in ^{1}H NMR spectrum (300 MHz) of the crude product. [c] Recovered by flash chromatography (ethyl acetate–light petroleum (bp 40–60 °C).

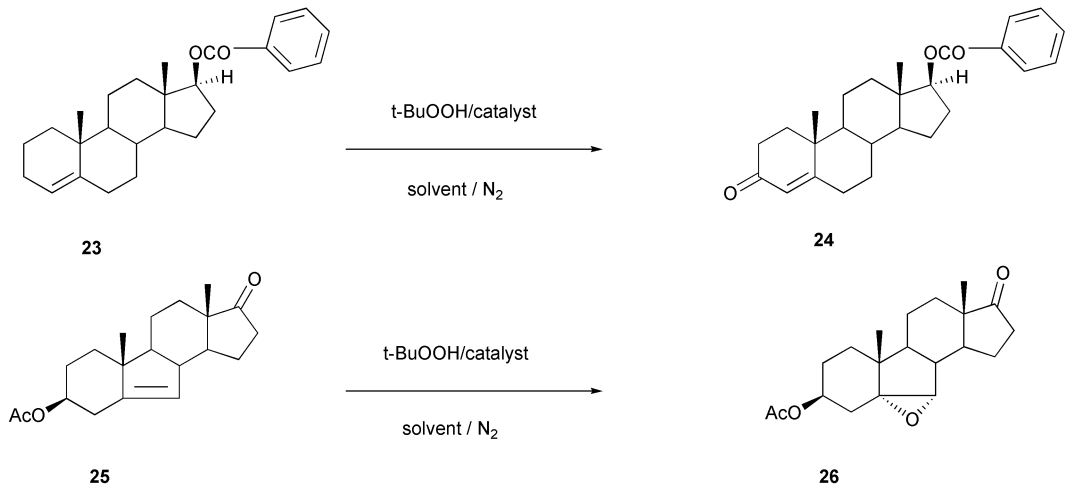
make these more environmentally friendly processes. Furthermore, using the heterogeneous catalysts **5** and **6**, it was possible to reuse the catalyst with only a small reduction in the products yields, under similar experimental conditions (79% for recycled catalyst **5**, Table 2, and 77% for recycled catalyst **6**, Table 3).

No significant reaction occurs in the absence of catalyst or in the presence of the catalyst support only. The dioxolane group present in the steroid **22** was removed in the presence of the copper catalyst **5** corroborating the previous findings.[24] The catalytic process is also effective for other unsaturated steroids. The substrate **23** gives testosterone benzoate **24** in a yield of 72% (Scheme 3).

The use of 3β-acetoxy-7-nor-androst-5-en-17-one **25** as substrate prepared according to the method of Knof[25] led us to obtain the 5α,6α-epoxide **26** as the major product. The absence of C-7 and the fact that the axial hydrogen at C-4 lies on the more hindered β-face of the molecule reduces the tendency of β-nor-5-enes to undergo allylic oxidative reactions involving bulky reagents that may initially coordinate to the double bond. Thus the axial attack on the π-system of 3β-acetoxy-7-nor-androst-5-en-17-one **25** will be favoured from the less-hindered α-face leading to the formation of the 5α,6α-epoxide **26**.

Conclusions

In conclusion, we have discovered an efficient and relatively environmentally friendly method for allylic oxidation of unsaturated steroids and valencene in very good yields and high selectivity.The reaction requires *t*-BuOOH as oxidant and a supported and easily recoverable and reusable catalyst such as Co(II), Cu(II), Mn(II), and V(II).



Scheme 3

Experimental

The steroids used as substrates were commercially available from Sigma and Aldrich. Reaction solvents were distilled before use according to standard procedures. Kieselgel 60 HF_{254}/Kieselgel 60G was used for TLC analysis. Melting points were determined with a Reichert microscope apparatus and were uncorrected. IR spectra were performed in a JASCO FT/IR-420 spectrophotomer. ^1H and ^{13}C NMR were recorded on a Bruker AMX 300 in $CDCl_3$ solution with Me_4Si as internal standard.

Allylic oxidation catalized by cobalt catalyst (general procedure)

In a typical reaction, to a solution of valencene **10** (0.54 ml/2.45 mmol) in acetonitrile (15 ml) under nitrogen, catalyst **4** (0.06 g/0.025 mmol) and *tert*-butyl hydroperoxide (*ca*. 2.4 ml/12 mmol) were added. After 24 h under magnetic stirring at 55 °C, the catalyst was removed by filtration and the solution was poured into sodium sulfite solution (10% aq.) and extracted with diethyl ether. The extract was washed with an aq. saturated solution of $NaHCO_3$, water, dried and evaporated to dryness. The residue after flash chromatography (light petroleum (bp 40–60 °C)–ethyl acetate) gave nootkatone **11** (0.40 g, yield 75%). Mp 30–32 °C, lit.,[26] 33–35 °C; IR: 1617, 1662, 2967, 3024, 3078 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.93 (d, J = 6.8 Hz, 3H, 15-H_3), 1.07 (s, 3H, 14-H_3), 1.69 (s, 3H, 13-H_3), 4.69 (m, 2H, 12-H_2), 5.72 (s, 1H, 1-H_1); ^{13}C NMR ($CDCl_3$,75 MHz): δ 109.12 (C^{12}), 124.44 (C^1), 148.87 (C^{11}), 170.82 (C^{10}), 199.79 (C^2).

Allylic oxidation catalized by copper catalyst (general procedure)

In a typical reaction, to a solution of 20-oxopregn-5-en-3β-yl acetate **14** (0.72 g/2 mmol) in acetonitrile (12 ml) under nitrogen, catalyst **5** (0.015 g/0.006 mmol) and *tert*-butyl hydroperoxide (*ca*. 2.4 ml/12 mmol) were added. After 20 h under magnetic stirring at 55 °C, the catalyst was removed by filtration and the solution was poured into sodium sulfite solution (10% aq.) and extracted with diethyl ether. The extract was washed with an aq. saturated solution of $NaHCO_3$, water, dried and evaporated to dryness to give 7,20-dioxopregn-5-en-3-β-yl acetate **15** (0.60 g, yield 81%), mp 151–152 °C (MeOH), lit.,[27]153–153.5 °C; IR: 1243, 1630, 1670, 1704, 1726, 2945, 3012 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.65 (s, 3H, 18-H_3), 1.21 (s, 3H, 19-H_3), 2.05 (s, 3H, CH_3CO), 2.13 (s, 3H, 21-H_3), 4.72 (m, 1H, 3α-H), 5.72 (m, 1H, 6-H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 72.00 (C^3) 126.41 (C^6), 164.13 (C^5), 170.23 (CH_3CO), 201.11 (C^7), 209.64 (C^{20}).

9. Mp 175–177 °C (ethyl acetate–*n*-hexane); IR: 1230, 1671, 1721, 1731, 1752, 2945 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.12 (s, 3H, 18-H_3), 1.22 (s, 3H, 19-H_3), 2.05 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3COO at C^{21}), 3.82 (s, 1H, 16β-H), 4.65 (q_{AB}, δ_A = 4.71, δ_B = 4.61, J_{AB} = 17.4 Hz, 2H, 21-H_2), 4.72 (m, 1H, 3α-H), 5.72 (m, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 61.98 (C^{16}), 65.84 (C^{21}), 69.53 (C^{17}), 71.90 (C^3), 126.25 (C^6), 164.93 (C^5), 170.24, 170.30 (2 × CH_3CO), 199.37 (C^{20}), 200.57 (C^7).

13. Mp 181–183 °C (MeOH); lit.,[28] 184 °C; IR: 1231, 1627, 1671, 1723, 1739, 2951, 3008 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.9 (s, 3H, 18-H_3), 1.24 (s, 3H, 19-H_3), 2.05 (s, 3H, CH_3CO), 4.73 (m, 1H, 3α-H), 5.76 (m, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 71.90 (C^3), 126.43 (C^6), 164.79 (C^5), 170.19 (CH_3CO), 200.66 (C^7), 220.14 (C^{17}).

17. Mp 156–158 °C (MeOH); lit.,[4] 157–158 °C; IR: 1237, 1629, 1669, 1730, 2938, 3028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.68 (s, 3H, 18-H_3), 1.21 (s, 3H, 19-H_3), 0.86 (d, J = 6.6 Hz, 6H, 26-H_3, 27-H_3), 0.92 (d, J = 6.6 Hz, 3H, 21-H_3), 2.05 (s, 3H, CH_3CO), 4.69 (m, 1H, 3α-H), 5.70 (m, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 72.17 (C^3), 126.64 (C^6), 163.82 (C^5), 170.22 (CH_3CO), 201.87 (C^7).

19. Mp 177–179 °C (EtOH–H_2O); lit.,[29] 178–180 °C; IR: 1234, 1667, 1725, 2940 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.72 (s, 3H, 18-H_3), 1.21 (s, 3H, 19-H_3), 2.06 (s, 3H, CH_3CO), 4.72 (m, 1H, 3d-H), 5.72 (m, 1H, 6-H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 72.84 (C^3), 127.28 (C^6), 164.84 (C^5), 171.00 (CH_3CO), 202.58 (C^7).

21. Mp 189–191 °C (MeOH); lit.,[30] 189–191 °C; IR 1457, 1652, 1730, 2943, 3030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.90 (s, 3H, 18-H_3), 1.25 (s, 3H, 19-H_3), 3.84 (m, 1H, 3α-H), 5.74 (m, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 57.92 (C^3), 125.90 (C^6), 164.82 (C^5), 200.81 (C^7), 220.22 (C^{17}).

24. Mp 193–194 °C (acetone–light petroleum (bp 60–80 °C)), lit.,[31] 191–193 °C; IR: 1269, 1451, 1578, 1596, 1614, 1668, 1703, 2974, 3028, 3060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.94 (s, 3H, 18-H_3), 1.16 (s, 3H, 19-H_3), 4.81 (t, J = 8.2 Hz, 1H, 17α-H), 5.69 (s, 1H, 4-H), 7.40 (t, J = 7.3 Hz, 2H, 3′-H and 5′-H), 7.52 (t, J = 7.2 Hz, 1H, 4′-H), 8.00 (d, J = 7.0 Hz, 2H, 2′-H and 6′-H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 82.85 (C^{17}), 123.86 (C^4), 128.24 ($C^{3'}$ and $C^{5'}$), 129.40 ($C^{2'}$ and $C^{6'}$), 130.49 ($C^{1'}$), 132.74 ($C^{4'}$), 166.34 (C^5), 170.84 (C_6H_5COO), 199.35 (C^3).

26:. Mp 167–169 °C (ethyl acetate–hexane), lit.,[32] 170–172 °C; IR: 1245, 1723, 1738, 2970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.81 (s, 3H, 18-H_3), 0.88 (s, 3H, 19-H_3), 1.98 (s, 3H, CH_3CO), 3.33 (s, 1H, 6β-H), 4.91 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 58.94 (C^6), 68.45 (C^5), 71.93 (C^3), 170.07 (CH_3CO), 219.68 (C^{17}).

Allylic oxidation catalyzed by manganese and vanadium catalysts (general procedure)

In a typical reaction, to a solution of 17-oxoandrost-5-en-3β-yl acetate **12** (0.66 g/2 mmol) in acetonitrile (12 ml) under nitrogen, catalyst **2** (0.2 g/0.06 mmol) and *tert*-butyl hydroperoxide (*ca*. 2.4 ml/12 mmol) were added. After 24 h under magnetic stirring at 55 °C, the catalyst was removed by filtration and the solution was poured into sodium sulfite solution (10% aq.) and extracted with diethyl ether. The extract was washed with an aq. saturated solution of $NaHCO_3$, water, dried and evaporated to dryness to give 7,17-dioxoandrost-5-en-3β-yl acetate **13** (0.57 g, yield 82%).

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References

1 J. Muzart, *Bull. Soc. Chim. Fr.*, 1986, **65**, 2.
2 P. C. Bulman Page and T. J. Mccarthy, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford–New York–Seoul–Tokyo, 1991, vol. 7, p. 83.
3 Y. Sato, Y. Sonoda, M. Morisaki and N. Ikekawa, *Chem. Pharm. Bull.*, 1984, **32**, 3305; K. P. Cheng, H. Nagana, L. Bang and G. Ourisson, *J. Chem. Res. (S)*, 1997, 217; H. Nagana, J. P. Poyser, K. P.

Cheng, L. Bang and G. Ourisson, *J. Chem. Res. (S)*, 1997, 218; V. Kumar, A. Alain, G. Ourisson and B. Luu, *Synth. Commun.*, 1987, **17**, 1279.
4 G. W. Dauben, M. Lorber and D. S. Fullerton, *J. Org. Chem.*, 1969, **34**, 3587; D. S. Fullerton and C. M. Chen, *Synth. Commun.*, 1976, **6**, 217.
5 W. G. Salmond, M. A. Barta and J. L. Havens, *J. Org. Chem.*, 1978, **43**, 2057.
6 E. J. Parish, S. Chitrakorn and T.-Y. Wei, *Synth. Commun.*, 1986, **16**, 1371.
7 E. J. Parish and T.-Y. Wei, *Synth. Commun.*, 1987, **17**, 1227.
8 C. W. Marshall, R. E. Ray, I. Laos and B. Reigel, *J. Am. Chem. Soc.*, 1957, **79**, 6308.
9 A. Amann, G. Ourisson and B. Luu, *Synthesis*, 1987, 1002.
10 E. J. Parish, H. Sun and S. A. Kizito, *J.Chem. Res. (S)*, 1996, 544.
11 U. Bora, M. K. Chaudhuri, D. Dey, D. Kalita, W. Kharmawphlang and G. C. Mandal, *Tetrahedron*, 2001, **57**, 2445.
12 J. Muzart, *Tetrahedron Lett.*, 1987, **28**, 4665.
13 A. J. Pearson, Y. S. Chen, Y. S. Hsu and T. Ray, *Tetrahedron Lett.*, 1984, **25**, 1235.
14 A . J. Pearson, Y. S. Chen, G. R. Hang, S. Y. Hsu and T. Ray, *J.Chem .Soc., Perkin Trans. 1*, 1985, 267.
15 N. Chidambaran and S. Chandrasekaran, *J. Org. Chem.*, 1987, **52**, 5048.
16 R. A. Miller, W. Li and G. R. Humprey, *Tetrahedron Lett.*, 1996, **37**, 3429.
17 M. Kimura and T. Muto, *Chem. Pharm. Bull.*, 1979, **27**, 109.
18 M. Kimura and T. Muto, *Chem. Pharm. Bull.*, 1980, **28**, 1836.
19 J. A. R. Salvador, M. L . Sáe Melo and A. S. Campos Neves, *Tetrahedron Lett.*, 1997, **38**, 119.
20 J. H. Clark, *Catalysis of Organic Reactions using Supported Inorganic Reagents*, VCH, New York, 1994; *Chemistry of Waste Minimisation*, ed. J. H. Clark, Chapman and Hall, London, 1995.
21 J. A. R. Salvador and J. H. Clark, *Chem. Commun.*, 2001, 33.
22 A. J. Butterworth, J. H. Clark, P. H. Walton and S. J. Barlow, *Chem. Commun.*, 1996, 1859.
23 J. Chisen, I. C. Chisen, J. S. Rafelt, D. J. Macquarrie and J. H. Clark, *Chem. Commun.*, 1997, 2203.
24 J. Wang, C. Zhang, Z. Qu, Y. Hou, B. Chen and P. Wu, *J. Chem. Res. (S)*, 1999, 294.
25 L. Knof, *Justus Liebigs Ann. Chem.*, 1962, **657**, 171; R. M. Scribner in *Organic Reactions in Steroid Chemistry*, ed. J. Fried and J. A. Edwards, van Nostrand Reinhold, New York, 1972, vol. 2, p. 434.
26 S. F. Arantes, A. Farooq and J. R. Hanson, *J. Chem. Res. (M)*, 1999, 801.
27 C. W. Marshall, R. E. Ray, I. Laos and B. Riegel, *J. Am. Chem. Soc.*, 1957, **79**, 6308.
28 J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, 1948, **31**, 629.
29 V. E. M. Chambers, W. A. Denny, J. M. Evans, E. R. H. Jones, A. Kasal, G. D. Meakins and J. Pragnell, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1500.
30 H. A. Lardy and P. Marwah, *World Pat.*, WO 9947485, 1999.
31 M. Havel, J. Velek, J. Pospisek and M. Soucek, *Collect. Czech. Chem. Commun.*, 1979, **44**, 2443.
32 J. Joska, J. Fajkos and F. Sorm, *Collect. Czech. Commun.*, 1963, **28**, 82.