Inversion of Configuration of Secondary Alcohols, in Particular in the Steroid and Prostaglandin Series[1]

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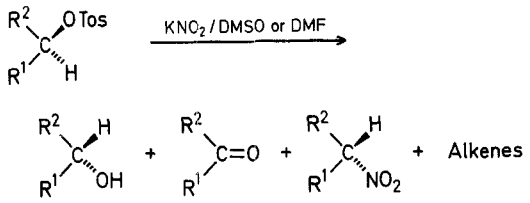
Of the methods available for the inversion of hydroxy functions[2-6], the procedure of Latrell and Lohaus[7] has not yet found further application. Latrell and Lohaus treated the sulfonate of a secondary alcohol with potassium nitrite in dimethyl sulfoxide and obtained (without isolation of the intermediate nitrous ester) directly the alcohol having the inverted configuration. We used this principle to invert the configuration of a series of secondary alcohols and found that it is in certain cases superior to the other methods in terms of yield and ease of performance.

The reaction of the tosylate of a secondary alcohol with potassium nitrite in dimethyl sulfoxide or dimethylformamide affords the inverted alcohol as the main product; the corresponding nitroalkane, ketone, and alkene may be formed in addition.



The utility of the method is shown by the examples listed in Table 1 which were mainly selected from the steroid and prostaglandin fields.

In the following cases, the present method was compared with the established methods (cf. Table 1).

Entry 1: Reaction of **1**[8] with sodium benzoate in dimethyl sulfoxide (in analogy to a published procedure[2]) gave a 60:40 mixture of **10**-benzoate and Δ^{10}-olefin (prostaglandin numbering) which was difficult to separate. In a further attempt, compound **1** was treated with potassium superoxide[4] to give, after relactonization (tetrahydrofuran/1 normal hydrochloric acid, 25 °C), 32% of **10** and 51% of the Δ^{10}-olefin.

Entry 3: Starting with **3**[9], the application of the potassium superoxide procedure[4] yielded, after reesterification with diazomethane, 50% of **12** and 12% of the Δ^{9}-olefin. Starting with **13** and using the method of Mitsunobu[3] (diethyl diazenedicarboxylate/triphenylphosphine/benzoic acid) we obtained, upon transesterification (sodium methoxide/methanol), 60% of **12** and 27% of an olefin mixture.

Entry 9: (*S*)-2-Octanol (**17**) was obtained in 49% yield from **9** using potassium nitrite whereas the potassium superoxide procedure has been reported to afford 75% of (*R*)-**17** from (*S*)-**9**[10].

Entries 7 and 8: Only poor conversion to **16** was obtained starting from the steroidal 17-tosylate **7** whereas the analogous conversion of the 17-(pyridine-3-sulfonate) **8** which possesses the better leaving group[11] gave **16** in 41% yield.

Entries 1, 3, and 9: The method of Phillips[19] (substitution of tosylate by acetate or benzoate) applied to compounds **1**[8], **3**, and **9**[19] gives lower yields of the inverted alcohols **10**, **12**, and **17**, respectively.

It appears that the formation of nitro compounds as side products is observed when the approach of the nitrite ion to

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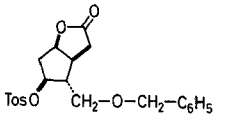
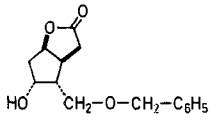
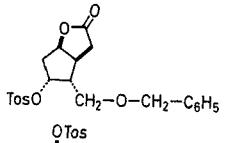
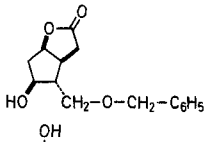
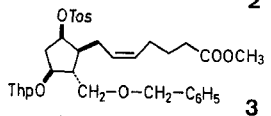
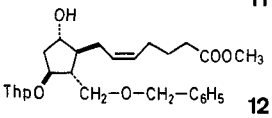
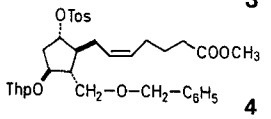
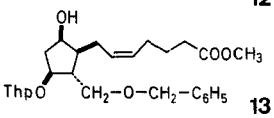
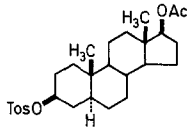
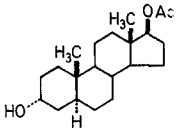
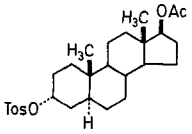
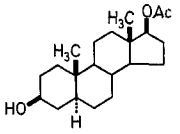
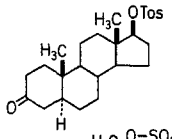
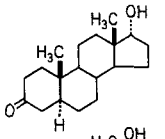
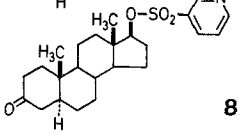
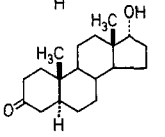
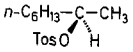
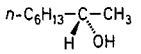
Table 1. Inverted Alcohols (**10–17**) from *O*-Derivatives of Alcohols (**1–9**)

Entry	Substrate	Inverted Alcohol	Reaction conditions	Yields[a] [%]			
				Inverted Alcohol	Inverted Nitroalkane	Ketone	Olefin
1	 **1**	 **10**	DMF, 85 °C, 18 h	75	n.d.	n.d.	3
2	 **2**	 **11**	DMF, 55 °C, 4 h	64	10	n.d.	not determined
3	 **3**	 **12**	DMSO, 65 °C, 3 h	63	5	20	7
4	 **4**	 **13**	DMSO, 85 °C, 2.5 h	61	n.d.	11	4
5	 **5**	 **14**	DMSO, 90 °C, 2 h	67	n.d.	10	3
6	 **6**	 **15**	DMSO, 90 °C, 1 h	71	n.d.	9	12
7	 **7**	 **16**	DMF, 130 °C, 24 h	25[b]	n.d.	n.d.	15
8	 **8**	 **16**	DMSO, 90 °C, 16 h	41	n.d.	11	13
9	 **9**	 **17**	DMSO, 65 °C, 3.5 h	49[c]	n.d.	36	11

[a] Yields of pure products isolated by chrmatography and characterized by comparison with authentic samples. n.d. = not detected.

[b] In addition, 5% of the 17α-formate and 15% of the starting tosylate were isolated.

[c] No racemization exceeding the limits of experimental error was observed. (*R*)-2-Octanol which was used for the preparation of **9** had $[\alpha]_D^{20}$: −7.89°.

the sulfonate group is *trans* with respect to vicinal substituents as in **2** and **3**. A possible explanation for the formation of ketones is the joint reaction of intermediate nitro compounds with potassium nitrite and nitrite esters[12] or the thermal disproportionation of nitrite esters[13]. The ketones are apparently *not* formed by reaction of sulfonates with dimethyl sulfoxide (which is a common procedure for the preparation of aldehydes from primary tosylates[14]), since the tosylates on heating (60–90 °C) in dimethyl sulfoxide or dimethylformamide are only slowly oxidized to the corresponding ketones, as compared to the inversion rates. The free alcohols are inert towards solvent and solvent/potassium nitrite mixtures.

Best results are obtained using dimethyl sulfoxide or dimethylformamide as solvent and a 10- to 20-fold molar excess of potassium nitrite.

(3a*S*, 4*S*, 5*R*, 6a*R*)-4-Benzyloxymethyl-5-hydroxy-2-oxohexahydrocyclopenta[*b*]furan (10); Typical Procedure:

A mixture of (3a*S*, 4*S*, 5*S*,6a*R*)-4-benzyloxymethyl-2-oxo-5-tosyloxyhexahydrocyclopenta[*b*]furan[8] (**1**; 1.50 g, 3.60 mmol) and potassium nitrite (4.60 g, 54 mmol) is stirred in dimethylformamide (80 ml) for 18 h under nitrogen at 85 °C. Most of the solvent is removed in vacuo, the residue is diluted with saturated aqueous sodium chloride (150 ml), and the solution extracted with dichloromethane (4 × 50 ml). The combined extracts are dried with magnesium sulfate and evaporated in vacuo. The residue is purified by

Table 2. Data of Compounds **1**–**17**

Compound	Physical Data found		Physical Data reported (or Molecular Formula)[a]		^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
	m.p. [°C] (solvent)	$[\alpha]_D^{22}$[b]	m.p. [°C]	$[\alpha]_D^{22}$	
1			—[8]	—[8]	—
2	70–71 (diisopropyl ether)	−4.8°	$C_{22}H_{24}O_6S$ (416.5)		—
3	viscous oil	—	$C_{33}H_{44}O_8S$ (600.8)	—	7.81 (dd, 2H, J=8, 1.5 Hz); 7.21–7.38 (m, 7H); 5.20–5.38 (m, 2H); 4.83–5.06 (m, 1H); 4.45–4.58 (m, 1H); 4.47 (s, 2H); 3.90–4.25 (m, 1H); 3.68 (s, 3H); 3.30–3.65 (m, 2H); 2.44 (s, 3H); 2.26 (t, 2H, J=7 Hz)
4	viscous oil	—	$C_{33}H_{44}O_8S$ (600.8)	—	7.75 (dd, 2H, J=8, 1.5 Hz); 7.2–7.4 (m, 7H); 5.15–5.40 (m, 2H); 4.50–4.74 (m, 2H); 4.46 (s, 2H); 3.95–4.21 (m, 1H); 3.67 (s, 3H); 3.30–3.56 (m, 2H); 2.43 (s, 3H); 2.28 (t, 2H, J=7 Hz)
5	127–128 (diisopropyl ether)	—	$C_{28}H_{40}O_5S$ (488.7)	—	—
6	148–150 (diisopropyl ether)	—	$C_{28}H_{40}O_5S$ (488.7)	—	—
7	—	—	—[17]	—[17]	—
8	166–168 (hexane/C_2H_5OAc)	—	$C_{24}H_{33}NO_4S$ (431.6)	—	—
9	—	—	—[18]	—	—
10	79–80 (diisopropyl ether)	−22.3°	78–79[8]	−21.5°[8]	7.31 (s, 5H); 5.05 (m, 1H); 4.52 (s, 2H); 4.48 (m, 1H); 3.71 (d, 2H, J=5.5 Hz); 3.03–1.80 (m, 7H)
11	viscous oil	+5.5°	—	+7.0°[8]	7.30 (s, 5H); 4.89 (m, 1H); 4.50 (s, 2H); 4.12 (m, 1H); 3.4 (d, 2H, J=5.5 Hz); 2.90–1.80 (m, 7H)
12	viscous oil	—	$C_{26}H_{38}O_6$ (446.6)	—	7.32 (s, 5H); 5.55–5.30 (m, 2H); 4.58 (m, 1H); 4.52 (s, 2H); 4.35–3.75 (m, 2H); 3.68 (s, 3H); 2.22 (t, 2H, J=7 Hz)
13	viscous oil	—	—[9]	—	7.31 (s, 5H); 5.63–5.10 (m, 2H); 4.69 (m, 1H); 4.50 (s, 2H); 4.35–3.75 (m, 2H); 3.65 (s, 3H); 2.28 (t, 2H, J=7 Hz)
14	190–193 (diisopropyl ether)	+4.3°	191–192[16]	—	—
15	148–150 (diisopropyl ether)	+5.0°	150–151[16]	+5.0°[16]	4.60 (m, 1H); 3.85–3.30 (m, 1H); 2.05 (s, 3H); 0.88 (s, 3H); 0.80 (s, 3H)
16	177–179 (cyclohexane/dichloromethane)	+11.5°, +12.0°	179–180[15]	+12.8°[15]	3.75 (d, 1H, J=5.5 Hz); 1.04 (s, 3H); 0.70 (s, 3H)
17	liquid	+7.85°[c]	—[10,18]	+8°[10,18]	—

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.23; H, ±0.30; O, ±0.23; S, ±0.25; **8**: N, −0.17.
[b] In chloroform.
[c] See footnote c of Table 1.

column chromatography on silica gel using hexane/ethyl acetate (10/1–1/1) as eluent; yield: 708 mg (75%); m.p. 79–80 °C (Ref.[8], m.p. 78–79 °C); $[\alpha]_D^{20}$: −22.3° (*c* 1, chloroform) (Ref.[8], $[\alpha]_D^{20}$: −21.5°).

I.R. ($CHCl_3$): ν=3480; 2865; 1768; 1170; 1082; 903 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ=7.31 (s, 5H); 5.05 (m, 1H); 4.52 (s, 2H); 4.48 (m, 1H); 3.71 (d, 2H, J=5.5 Hz); 3.03–1.80 ppm (m, 7H).

17α-Hydroxy-5α-androstan-3-one (16); Typical Procedure:
A mixture of sulfonate **8** (1.0 g, 2.39 mmol); potassium nitrite (3.05 g, 35.85 mmol), and dimethyl sulfoxide (50 ml) is stirred for 16 h at 90 °C, then diluted with water (400 ml), and extracted with ether (4×50 ml). The combined extracts are washed with saturated aqueous sodium chloride, dried with magnesium sulfate, and evaporated in vacuo. The oily residue (677 mg) is adsorbed on silica gel. Elution with hexane/ethyl acetate (10/1–1/1) affords **16**; yield: 285 mg (41%); m.p. 176–178 °C; upon recrystallization from cyclohexane/dichloromethane, m.p. 177–179 °C (Ref.[15], m.p. 179–180 °C); $[\alpha]_D^{20}$: +12.0° (*c* 0.95, chloroform) (Ref.[15], $[\alpha]_D^{20}$: +12.8°).

I.R. ($CHCl_3$): ν=1720 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ=3.75 (d, 1H, J=5.5 Hz); 1.04 (s, 3H); 0.70 ppm (s, 3H).

(*S*)-(+)-2-Octanol (17):
To a solution of the tosylate of (*R*)-(−)-2-octanol (**9**; 12.4 g, 43.6 mmol) in dimethyl sulfoxide (400 ml) is added potassium nitrite (37.1 g, 436 mmol). The solution is stirred for 3.5 h at 65 °C, then diluted with saturated aqueous sodium chloride (1500 ml), and extracted with ether/pentane (1/1; 4×250 ml). The combined extracts are washed with saturated aqueous sodium chloride (50 ml), dried with magnesium sulfate, and evaporated under normal pressure. The liquid residue (9.5 g) is adsorbed on silica gel (200 g) and the column eluted with pentane/ether with an increasing ether gradient. The first fraction is a mixture of olefins (0.54 g, 11%). The second fraction is 2-octanone (2.01 g, 36%; I.R.: ν=1710 cm^{-1}). The third fraction is product **17**, a colorless liquid; yield: 2.78 g (49%). Traces of solvents are removed by Kugelrohr distillation at 140 °C/100 torr; $[\alpha]_D^{20}$: +7.85° (*c* 12, chloroform); purity according to G.L.C. analysis (10% SE 30): 99.7%. (The G.L.C. retention time was identical with that of a commercial sample.)

I.R. ($CHCl_3$): ν=3620; 2960; 2930; 2862; 1460; 1382 cm^{-1}.

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[1] Initial results concerning this procedure were reported at the "Symposium on the Chemistry and Biochemistry of Prostanoids" in Salford, U.K., July 1978.
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