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CONVERSION OF 8-LANOSTEN-24-ONE INTO 8-LANOSTEN-23-ONE. 1,2-CARBONYL TRANSPOSITION ON THE LANOSTANE SIDE CHAIN

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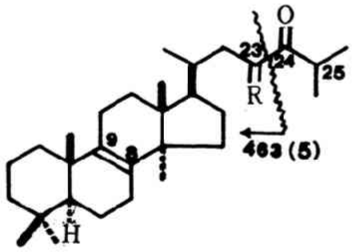
8-Lanosten-24-one was converted into 8-lanosten-23-one by carbonyl transposition _via_ 23,23-dimethoxy-8-lanosten-24-one without degradation and reconstruction of the side chain. By the same procedure 29-nor-9(11)-lanosten-24-one was transformed into the corresponding 23-one.

Functionalization of steroidal and tetracyclic triterpene side chain has been the subject of a number of studies in connection with biological activity, this functionalization being carried out by degradation and reconstruction of the side chain or by transformation of the functional groups originally present in the side chain.[1)] However, degradation of the side chain is not always facile, giving often the product in an unsatisfactory yield. Although a number of 1,2-carbonyl transposition reactions have been described,[2)] most of them were applied to cyclic carbonyl compounds and no application to a carbonyl group on the side chain of steroids and triterpenes has yet been reported to our knowledge. Recently the isolation[3)] and the synthesis[4)] of steroids and triterpenes with a side chain oxygenated at C-23 have been described. We wish to report a transformation of 8-lanosten-24-one (**1**)[5)] into 8-lanosten-23-one (**2**) _via_ 23,23-dimethoxy-8-lanosten-24-one (**3**).

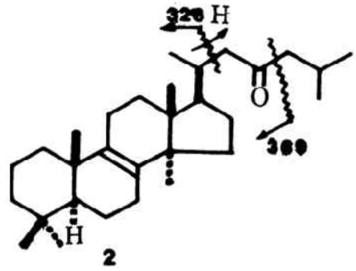
It was necessary to employ strictly kinetically controlled reaction for selective functionalization of the C-23 carbon α to the carbonyl at C-24, because the enolization towards C-25 rather than C-23 position is thermodynamically favored for the C-24 carbonyl derivative. Application of some known 1,2-carbonyl transposition procedures[2a,2d,6)] to the conversion of 24-one into the corresponding 23-one was unsuccessful as shown below. This would be due to the unexpected large steric effect caused by the presence of lanostane (steroidal) cyclic skeleton.

According to the procedure recently reported by Nakai _et al._,[2a)] the dianion of a tosylhydrazone derived from 8-lanosten-24-one (**1**) was treated successively with a sulfenylating agent (MeSSMe, PhSSPh, PhSCl, or MeSCl) and alkyllithium. The product was a mixture of unsaturated hydrocarbons;[7,8)] the desired enol thioether (such as **4**) was not obtained.

The route for 1,2-carbonyl transposition developed by Trost _et al._[2d)] was then examined. Regioselective sulfenylation at C-23 of the 24-one (**1**) was carried out by addition of the anion produced from **1** under kinetically controlled



	R
1	H_2
3	OCH_3, OCH_3
5a,b	SPh , H
8	SPh , OAc



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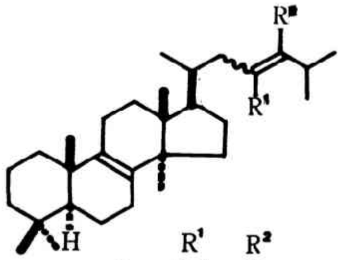
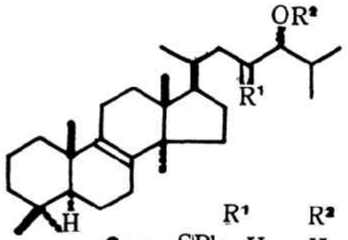
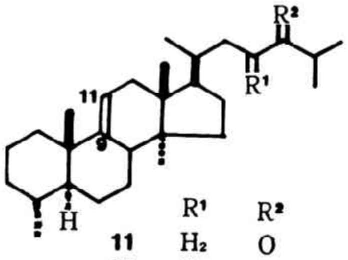


	R¹	R²
4	SPh	H
7	H	SPh



	R¹	R²
6a,b	SPh ,H	H
9	O	H
10	O	Ac



	R¹	R²
11	H_2	O
12	O	H_2

condition [lithium diisopropylamide / THF / hexamethylphosphoric triamide (HMPA) / -78 °C]2d) into a solution of diphenyl disulfide in THF and HMPA to give a mixture (ca. 1:1) of 23-phenylthio-8-lanosten-24-ones (**5**) in 67% yield, which was separated by preparative TLC affording each diastereomer (**5a** and **5b**).9,10) The carbonyl group of **5a** was reduced with lithium aluminium hydride (LAH) in ether to give a 23-phenylthio 24-ol (**6a**) as a main product, its stereoisomer (**6b**) being formed as a major product from **5b** by the same treatment. However, no desired enol thioether (**4**) was obtained when the alcohols (**6a** and **6b**) were subjected to dehydration under various conditions.2d,11) The alcohol (**6b**) was mesylated and treated with potassium t-butoxide in dimethyl sulfoxide2d) to give 24-phenylthio-8,23-lanostadiene (**7**).12) Hydrolysis of **7** resulted in a formation of the starting ketone (**1**). A 1,2-shift of the phenylthio group had occurred during the conversion to give **7**; this would be caused by a non-bonded interaction between the phenylthio group and the cyclic skeleton.13)

Finally, a transformation of the 23-phenylthio 24-one (**5**) into the 23-one (**2**) was accomplished via 23,23-dimethoxy 24-one (**3**). According to the procedure reported by Trost et al. for the preparation of 1,2-diketone and its dimethyl acetal,14) **5a** (or **5b**) was heated under reflux with lead(IV) acetate in a mixture of acetic acid and benzene to give 23-acetoxy-23-phenylthio-8-lanosten-24-one (**8**)15) in 56% yield. On refluxing in methanol containing iodine, **8** gave **3** in 73 % yield. The dimethyl acetal (**3**) was then reduced with LAH in ether and hydrolyzed with hydrochloric acid, affording 24-hydroxy-8-lanosten-23-one (**9**) in 80% yield. On acetylation **9** gave an acetate (**10**) in a quantitative yield, which was reduced with calcium in liquid ammonia16) to afford the 23-one (**2**) in 98% yield. Thus **2** was obtained from the 24-one (**1**) in an overall yield of 21%.

29-Nor-9(11)-lanosten-24-one (**11**)17) was converted into the corresponding 23-one (**12**) in 16% yield without affecting the 9(11)-double bond by the same procedure as described above.

Characterization of **1-3**, **5-11**, and **12** is as follows; these compounds showed the IR and ^{1}H n.m.r. spectra[18)] compatible with their structures; **1**: mp 88-89 °C, $C_{30}H_{50}O$ (MW 426.3816), IR 1715 cm^{-1}; ^{1}H n.m.r. δ 2.39 (1H, dd, J=10 and 6 Hz; $C_{(23)}$-H), 2.45 (1H, dd, J=9 and 6 Hz; $C_{(23)}$-H), and 2.61 (1H, septet, J=7 Hz; $C_{(25)}$-H); **2**: mp 82-83.5 °C, $C_{30}H_{50}O$ (MW 426.3883), 1710 cm^{-1}; δ 2.14 (1H, d, J=15 Hz; $C_{(22)}$-H), 2.27 (1H, s; $C_{(24)}$-H), 2.28 (1H, d, J=7 Hz; $C_{(24)}$-H), and 2.45 (1H, dd, J=15 and 2 Hz; $C_{(22)}$-H); MS m/e 326 (due to McLafferty rearrangement) and 369; **3**: mp 140.5-142 °C, 1720 cm^{-1}; δ *ca.* 3.1 (1H, m; $C_{(25)}$-H), 3.17 and 3.20 (each 3H, s; OCH_3); MS m/e 454.3814 ($C_{31}H_{50}O_2$; M - CH_3OH); **5a**: mp 135-136 °C, $C_{36}H_{54}OS$ (MW 534.3878), 1698 and 1580 cm^{-1}; δ 2.92 (1H, septet, J=7 Hz; $C_{(25)}$-H), 3.88 (1H, dd, J=12 and 3 Hz; $C_{(23)}$-H), and 7.3 (5H, m; SPh); MS m/e 463; **5b**: amorphous solid, $C_{36}H_{54}OS$ (MW 534.3844); IR (neat) 1708 and 1582 cm^{-1}; δ 2.97 (1H, septet, J=7 Hz; $C_{(25)}$-H), 3.80 (1H, dd, J=11 and 3 Hz; $C_{(23)}$-H), and 7.3 (5H, m; SPh); MS m/e 463; **6a**: mp 114-116 °C, $C_{36}H_{56}OS$ (MW 536.4065); 3500 and 1580 cm^{-1}; δ 3.35 (2H, m; $C_{(23)}$-H and $C_{(24)}$-H) and 7.3 (5H, m; SPh); **6b**: mp 118-119 °C; 3530 and 1590 cm^{-1}; δ 3.2 (2H, m; $C_{(23)}$-H and $C_{(24)}$-H) and 7.3 (5H, m; SPh); MS m/e 536; **7**: mp 107-109 °C, $C_{36}H_{54}S$ (MW 518.3981), 1580 cm^{-1}; δ 6.0 (1H, dd, J=8 and 6 Hz; $C_{(23)}$-H) and 7.2 (5H, m; SPh); **8** (a mixture of diastereomers at C-23): mp 170-172 °C, 1750 and 1720 cm^{-1}; δ 2.08 (3H, s; OAc), 3.03 (1H, septet, J=6 Hz; $C_{(25)}$-H), and 7.35 (5H, m; SPh); MS m/e 532.3747 ($C_{36}H_{52}OS$; M - AcOH); **9** (a mixture of diastereomers at C-24): amorphous solid; δ 3.98 and 4.06 [*ca.* 1:2, total 1H; each dd, J=6 and 3 Hz; $C_{(24)}$-H; each changed into a doublet (J=3 Hz) on addition of D_2O]; MS m/e 442.3778 ($C_{30}H_{50}O_2$); **10**: (a mixture of diastereomers at C-24): amorphous solid; δ 2.14 (3H, s; OAc), 4.84 and 4.87 (*ca.* 1:2, total 1H; each d, J=4 Hz; $C_{(24)}$-H); MS m/e 484.3882 ($C_{32}H_{52}O_3$); **11**: mp 84-85 °C, $C_{29}H_{48}O$ (MW 412.3695); 1712 and 1630 cm^{-1}; δ 2.52 (1H, septet, J=7 Hz; $C_{(25)}$-H) and 5.27 (1H, m; $C_{(11)}$-H); **12**: mp 88-89 °C, $C_{29}H_{48}O$ (MW 412.3705), 1715 and 1630 cm^{-1}; δ 2.12 (1H, d, J=15.5 Hz; $C_{(22)}$-H), 2.24 (1H, s; $C_{(24)}$-H), 2.26 (1H, d, J=7 Hz; $C_{(24)}$-H), 2.44 (1H, dd, J=15.5 and 2 Hz; $C_{(22)}$-H), and 5.28 (1H, m; $C_{(11)}$-H).

References and notes

1) D. M. Piatak and J. Wicha, Chemical Reviews, **78**, 199 (1978).

2) a) T. Nakai and T. Mimura, Tetrahedron Lett., **1979**, 531. And references cited therein; b) Review on carbonyl transposition: T. Nakai and T. Mimura, Yuki Gosei Kagaku Kyokai Shi (J. Synth. Org. Chem., Jpn.), **35**, 964 (1977); c) J. E. Bridgeman, C. E. Butchers, E. R. H. Jones, A. Kasal, G. D. Meakins, and P. D. Woodgate, J. Chem. Soc. (C), **1970**, 244; d) B. M. Trost, K. Hiroi, and S. Kurozumi, J. Am. Chem. Soc., **97**, 438 (1975); *cf.* B. M. Trost, T. N. Salzmann, and K. Hiroi, *ibid.*, **98**, 4887 (1976).

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Ramundo, Tetrahedron Lett., **1978**, 2609; S. Ikegami, K. Okano, and H. Muragaki, ibid., **1979**, 1769.

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5) **1** could easily be prepared from 8,24-lanostadiene by hydroboration and successive oxidation with the Jones reagent.

6) cf. Ref. 2c. No 23-benzylidene derivative was obtained when **1** was treated with benzaldehyde under the usual conditions(KOH, EtOH, reflux).

7) Their structures remained undetermined.

8) cf. R. H. Shapiro and M. J. Heath, J. Am. Chem. Soc., **89**, 5734 (1967); R. H. Shapiro, M. F. Lipton, K. J. Kolonko, R. L. Buswell, and L. A. Capuano, Tetrahedron Lett., **1975**, 1811; R. H. Shapiro, Org. React., **23**, 405 (1976).

9) Treatment of the anion with methanesulfenyl chloride gave a mixture of 23-methylthio-8-lanosten-24-ones.

10) No tosylhydrazone was formed, when each of the 23-methylthio 24-ketones (ref. 9), **5a**, or **5b** was treated with tosylhydrazine under various conditions.

11) e.g. On treatment of **6a** in refluxing benzene in the presence of p-toluenesulfonic acid, a product suggested to be 24-phenylthio-8,22-lanostadiene was formed.

12) When 23-methylthio-8-lanosten-24-ol derived from the corresponding 24-one was treated with mesyl chloride in pyridine and then potassium t-butoxide in dimethyl sulfoxide, a mixture of enol thioethers was formed. Hydrolysis of this mixture afforded a ca. 3:1 mixture (examined by GLC) of 24-one (**1**) and 23-one (**2**).

13) e.g. An influence of the C-17 and C-20 chiral centers on the stereoselectivity of the epoxidation and the subsequent reduction was described for steroidal 23-enes: J. J. Partrige, V. Toome, and M. R. Uskoković, J. Am. Chem. Soc., **98**, 3739 (1976).

14) B. M. Trost and G. S. Massiot, J. Am. Chem. Soc., **99**, 4405 (1977).

15) The product (**8**) is a mixture of diastereomers at C-23, because the reaction proceeds via an enol intermediate. The same **8** was obtained from **5a** and **5b**.

16) J. A. Marshall and H. Roebke, J. Org. Chem., **34**, 4188 (1969).

17) **11** was prepared from lanosterol via 24-acetoxy-29-nor-8-lanosten-3-one.

18) IR spectra were measured in Nujol mull unless otherwise cited. ^{1}H n.m.r. spectra were taken in $CDCl_3$ at 270 MHz for **1**, **2**, and **12** and at 90 MHz for the other compounds.

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