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An Easy Deoxygenation of Conjugated Epoxides

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Abstract—An easy and high yielding transformation of epoxyketones and phenyl substituted epoxides to *trans* olefins in a convergent diastereoselective process is reported. The method was applied to the selective C-25 hydroxy-functionalisation of 3-keto-Δ^4-cholestan-3-one, a key intermediate for the synthesis of C-25 hydroxy vitamin D_3.

Introduction

The deoxygenation of epoxides to olefins is an important transformation in organic synthesis since it allows the use of the oxirane ring as a protective group for double bonds and to control the geometry of the olefins. In fact a number of reagents are known to deoxygenate epoxides with retention or inversion of configuration, by multi-step or one-step procedures.[1]

Of the yet reported efficient methods, some were described to work in only few cases, whilst others use harsh reaction conditions or complicated reagents.

During our previous studies on the selective direct hydroxylation at the side-chain C-25 of cholestane derivatives to provide a useful approach to 25-hydroxy-vitamin D_3,[2] we attempted the protection of the double bond by some of the methods already reported (i.e. the bromination/debromination procedure), which however gave low yields of desired products. These results prompted us to study an alternative method for similar transformations.

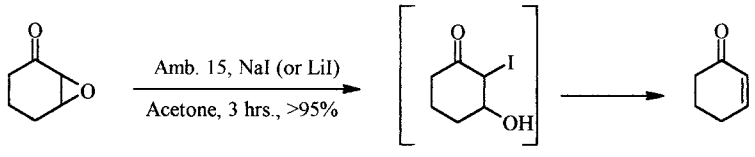
Since we have developed, in the last few years, new efficient methodologies to open regio and stereo selectively the oxirane ring by metal halides,[3] we decided to explore the possibility to perform a 'one pot' opening–elimination sequence to restore the double bond.

Results and Discussion

In this paper, we describe a simple and general procedure for deoxygenation of epoxides conjugated with sp^2 systems, which makes possible the use of the oxirane ring as protecting group for conjugated double bonds (Scheme 1). The α,β-epoxy ketone, dissolved in acetone, is treated with NaI or LiI and Amberlyst 15 for 3–6 h at rt to give the corresponding conjugated olefin in high yields.

Moreover, *cis*-epoxides isomerised during the elimination step to give *trans*-olefins. Considering that the epoxidation was carried out by dimethyldioxirane solution in acetone and water and that the ring opening–elimination step was compatible with this solvent mixture, the method is also a useful route for the isomerisation of *cis*-olefins by a simple 'one pot' procedure in an almost quantitative yield.

As reported in Table 1, every epoxide carrying a carbonyl or phenyl group in the α position gave an excellent yield of deoxygenated product. In the case of epoxyketones, the



Scheme 1.

Keywords: oxiranes; deoxygenation; isomerisation.

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Table 1. Deoxygenation of epoxides by metal halides/Amberlyst 15

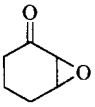
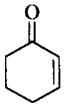
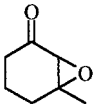
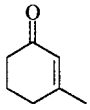
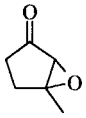
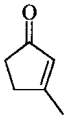
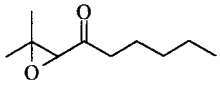
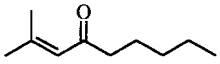
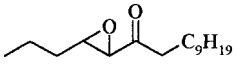
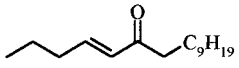
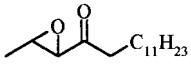
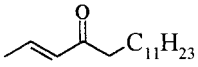
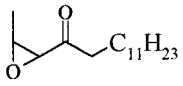
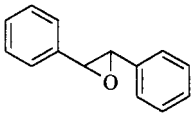
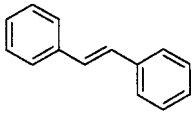
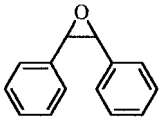
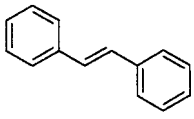
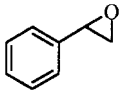
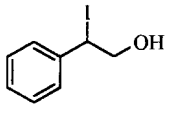
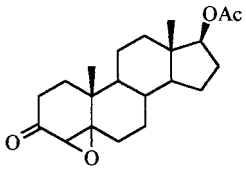
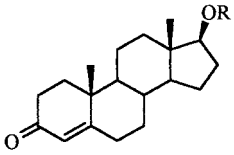
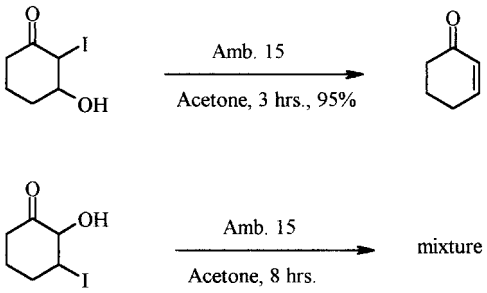
Entry	Starting material	Method	Time (h)	Product	Yield (%)[a]
1	 **1**	LiI	3	 **2**	95
2		NaI	3		98
3	 **3**	LiI	3	 **4**	93
4		NaI	3		96
5	 **5**	LiI	3	 **6**	94
6		NaI	3		98
7	 **7**	Lil	3	 **8**	92
8		NaI	3		97
9	 **9**	LiI	6	 **10**	94
10		NaI	6		98
11	 **11**	LiI	6	 **12**	95
12		NaI	6		98
13	 **13**	Lil	6	 **14**	95
14		NaI	6		97
16	 **15**	NaI	6		92
17	 **16**	LiI	3	 **17**	93
18		NaI	3		95
19	 **18**	LiI	8	 **17**	93
20		NaI	8		92
21	 **19**	LiI	3	 **20**	85

Table 1 (*continued*)

Entry	Starting material	Method	Time (h)	Product	Yield (%)[a]
23			24		95
22		NaI	3		95
	21 R=Ac **23** R=H			**22** R=Ac **24** R=H	

[a] Yields are those of isolated products



Scheme 2.

reaction worked well for both β-substituted and unsubstituted compounds.

Mechanistically, there should be an intermediate iodohydrin which rapidly loses HOI. In fact, in the case of *cis*-epoxystilbene, it was possible to isolate the iodohydrin which, stirred in acetone and Amberlyst 15, gave the expected *trans*-stilbene.

Moreover, we prepared the two regioisomeric iodohydrins by reacting 2,3-epoxy-cyclohexane-3-one with MgI_2; only 2-iodo-3-hydroxy-cyclohexanone gave 2-cyclohexenone when treated with Amberlyst 15 in acetone. Under the same conditions, 3-iodo-2-hydroxy-cyclohexanone lead instead to a complex mixture of products (Scheme 2).

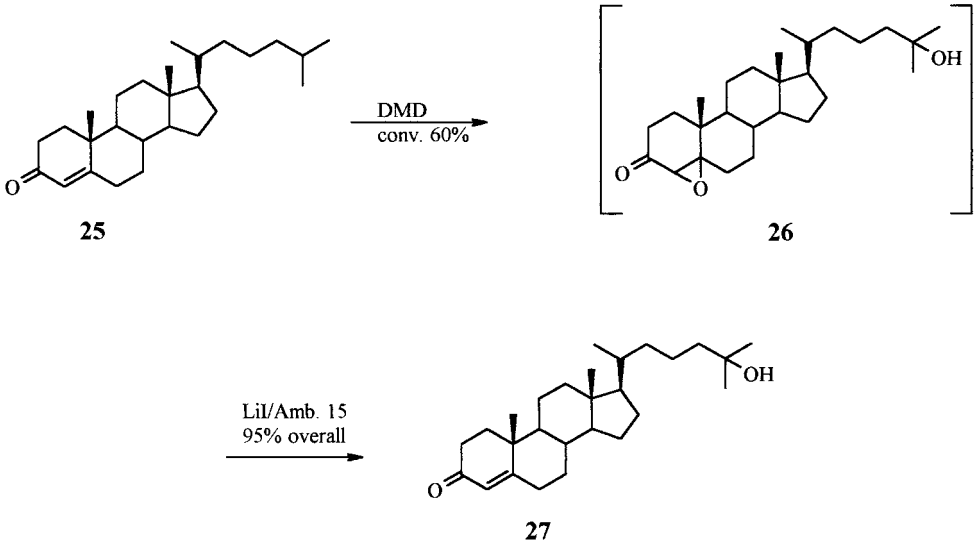
All these observations are in accordance with: (1) the first step is a regioselective nucleophilic attack of the halide to the oxirane ring at C-2,[4] and (2) the second step is the elimination of HOI in a non-concerted process.[5]

These results allowed us to perform the direct one pot transformation of cholestanone into its 25-hydroxy derivative. 25-Hydroxy vitamin D_3 is a metabolite of vitamin D_3 and is the true biologically active compound responsible for the regulation of calcium and phosphate ion concentration in cells.[6] 25-Hydroxy-Δ^4-cholest-3-one can be then considered as a key intermediate for the synthesis of 25-hydroxy vitamin D_3.

The oxyfunctionalisation by DMD of C-25 centre of cholestanes is a reaction already optimised in our group; however, in the presence of the enone moiety, the double bond must be protected to prevent its oxidation.[2]

The reaction of **25** (Scheme 3) with DMD led to excellent yields of 25-hydroxy-4,5-epoxy-cholestan-3-one (with a conversion of 60%). Addition of LiI and Amberlyst 15 to the reaction mixture afforded almost quantitatively the desired 25-hydroxycholestenone, in a one-pot procedure and very mild conditions.

In conclusion the reaction reported represents a very mild and high yield method for both the protection and



25 **26** **27**

Scheme 3. C-25 hydroxyfunctionalisation of 25-hydroxy-Δ^4-cholest-3-one.

the *cis-trans* isomerisation of conjugated double bonds.[7] As demonstrated in Scheme 3 it can be very useful to resolve some synthetic problems; currently under investigation are other straightforward synthetic applications.

Experimental

General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL 300 and Varian Gemini 200 spectrometers in $CDCl_3$ as the solvent, if not specified. All chemical shifts are reported in parts per million against internal tetramethylsilane. Coupling constants *J* were measured in Hz. All reactions were monitored by TLC (Merck F254) or GC. GC analyses were performed on a HP 5880A chromatograph equipped with a OV 101 capillary column and a flame ionisation detector. GC-MS analyses were performed on a HP 5890 chromatograph and HP 5971 as mass detector. Silica gel Merck (200–400 mesh) was used for flash chromatography. DMD solutions were prepared as reported by Adam[7] and co-workers using Oxone available from the Fluka company. IR spectra were recorded in $CHCl_3$ solution.

Starting materials

Olefins **2**, **4**, **6**, **8**, **17**, **25**, *cis*-stilbene and styrene are commercially available. 17-Acetyl-testosterone **22**[8] was prepared by reacting testosterone **24** with a 1:1 mixture of pyridine and acetic anhydride. All other olefins were prepared as following reported.

General procedures

As a general procedure an enone was epoxidised by treatment with 1.5 equiv. of a 0.9 M solution of DMD in acetone previously prepared (see Ref. [2]), in the dark at rt for 8 h. After evaporation of acetone under reduced pressure, the crude was treated with $Na_2S_2O_3$ sat. sol., extracted with ethyl acetate, dried with anhydrous Na_2SO_4 and the solvent evaporated.

The double bond was restored by reacting 1 mmol of an epoxide solution in 4 ml of acetone with NaI or LiI (4 equiv.) and Amberlyst 15 (860 mg) for the required time (see Table 1). The crude was concentrated, extracted with diethyl ether, washed with brine, dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo.

The two reactions can be performed in a 'one pot' procedure, when desired, such as for the transformation of **25** into **27** (see Experimental).

Products

Physical data for compounds **1**,[9] **3**,[10] **5**,[11] **7**,[12] **10**,[13] **16**,[14] **18**,[15] **19**,[16] **20**,[17] **21**, **22**, **23**, and **24**[18] are in agreement with that reported in literature. All others were fully characterised.

2-Methyl-2,3-oxynonan-4-one (9). Colourless oil. ^{1}H NMR δ (ppm): 0.85 (3H, t, *J*=6 Hz), 1.2 (3H, s), 1.4 (3H, s), 1.35–1.45 (4H, m), 1.55 (2H, m), 1.5–1.65 (2H, m), 2.48 (2H, t, *J*=7 Hz), 3.37 (1H, s). ^{13}C NMR δ (ppm): 13.78, 18.24, 22.28, 22.82, 24.60, 31.24, 40.83, 60.95, 65.25, 206.62. IR ν_{max} 1707, 1235 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_2$: C 70.55, H 10.66. Found: C 70.3, H 10.8.

***Trans*-4,5-oxyhexadecan-6-one (11).** Colourless oil. ^{1}H NMR δ (ppm): 0.85 (3H, t, *J*=6.7 Hz), 0.95 (3H, t, *J*=7.3 Hz), 1.54–2.25 (20H, m), 2–2.25 (2H, m), 3.02 (1H, m), 3.18 (1H, d, *J*=2 Hz). ^{13}C NMR δ (ppm): 13.73, 14.05, 19.10, 22.62, 23.07, 29.10, 29.25, 29.30, 29.39, 24.49, 31.83, 33.78, 37.14, 58.12, 59.54, 207.93. IR ν_{max} 1705, 1250 cm^1. Anal. Calcd for $C_{16}H_{30}O_2$: C 75.54, H 11.89. Found: C 75.3, H 11.9.

***Trans*-4-hexadecen-6-one (12).** Colourless oil. ^{1}H NMR δ (ppm): 0.89 (3H, t, *J*=8.0 Hz), 0.92 (3H, t, *J*=8.0 Hz), 1.2–1.35 (12H, broad s), 1.4–1.6 (4H, m), 2.2 (2H, dq, *J*=1.5, 7.5 Hz), 2.53 (2H, t, *J*=8 Hz), 6.09 (1H, dt, *J*=1.5, 13.8 Hz), 6.81 (1H, dt, *J*=6.9, 13.8 Hz). ^{13}C NMR δ (ppm): 13.67, 14.09, 21.35, 22.65, 24.33, 29.29, 29.41, 29.46, 29.54, 31.86, 34.42, 40.09, 130.45, 147.03, 201.05. IR ν_{max} 1670, 1700 cm^1. Anal. Calcd for $C_{16}H_{30}O$: C 80.61, H 12.68. Found: C 80.4, H 12.4.

***Trans*-2,3-oxyhexadecan-4-one (13).** Colourless oil. 0.8–1.7 (26H, m), 2.34 (2H, m), 3.10 (1H, m), 3.17 (1H, d, *J*=2.0 Hz). ^{13}C NMR δ (ppm): 14.05, 17.49, 22.62, 23.01, 29.09, 29.28, 29.38, 29.52, 29.57, 31.65, 37.09, 54.25, 60.51, 207.87. IR ν_{max} 1255, 1708 cm^1. Anal. Calcd for $C_{16}H_{30}O_2$: C 75.54, H11.89. Found: C 75.,7 H 11.6.

***Trans*-2-hexadecen-4-one (14).** Colourless oil. ^{1}H NMR δ (ppm): 0.96 (3H, t, *J*=7.5 Hz), 1.2–1.35 (16H, broad s), 1.6 (4H, m), 1.9 (3H, dd, *J*=1.5, 7.0 Hz), 2.54 (2H, t, *J*=7.0 Hz), 6.15 (1H, dq, *J*=1.5, 15.8 Hz), 6.85 (1H, dq, *J*=7.0, 15.8 Hz). ^{13}C NMR δ (ppm): 14013, 18.24, 22.69, 24.32, 29.34, 29.49, 29.62, 31.91, 40.06, 131.95, 142.32, 200.66. IR ν_{max} 1665, 1698 cm^1. Anal. Calcd for $C_{16}H_{30}O$: C 80.61, H 12.68. Found: C 80.5, H 12.8.

***Cis*-2,3-oxyhexadecan-4-one (15).** Colourless oil. 0.7–0.9 (6H, m), 1.15–1.3 (18H, broad s), 1.5–1.65 (2H, m), 2.48 (2H, t, *J*=7.2 Hz), 3.29 (1H, quint, *J*=5.0 Hz), 3.55 (1H, d, *J*=5.0 Hz). ^{13}C NMR δ (ppm): 12.91, 14.00, 22.59, 23.10, 29.12, 29.26, 29.35, 29.54, 31.82, 41.04, 54.06, 58.41, 206.12. IR ν_{max} 1260, 1710 cm^1. Anal. Calcd for $C_{16}H_{30}O_2$: C 75.54, H11.89. Found: C 75.5, H 11.7.

25-Hydroxy-4-cholesten-3-one (27). Prepared by the one pot procedure: To 24 ml of a 0.08 M solution of DMD in acetone 1 mmol of 4-cholesten-3-one **25** was added. After 24 h the mixture was concentrated and other 24 ml of DMD solution were added. The mixture was left at rt for an additional 24 h, then 536 mg (4 mmols) of LiI and 860 mg of Amberlyst 15 were added. After 5 h of stirring at rt the analysis on TLC revealed the presence of the starting material and of a polar product. Chromatography on silica gel gave 50% yield of **25** (starting cholestanone) and 47% of **27** (94% overall yield calculated on the converted compound). **27**. White solid, mp 146–149 (from MeOH) (lit. 146–150[19]); $[\alpha]_D^{20}=+79°$ (*c*=0.2, $CHCl_3$) (lit.,[19] +76°, *c*=0.037, +96°, *c*=0.6). ^{1}H NMR δ (ppm): 0.7 (3H, s), 0.9 (3H, d, *J*=6.5 Hz), 1.17 (3H, s), 1.2 (6H,

broad s), 5.72 (1H, s). ^{13}C NMR δ (ppm): 11.93, 17.35, 18.58, 20.73, 20.99, 24.14, 28.16, 29.19, 29.32, 32.00, 32.91, 33.95, 35.57, 35.67, 36.34, 38.57, 39.58, 42.37, 44.34, 55.76, 55.83, 55.99, 71.06, 1213.71, 171.71, 199.68. IR ν_{max} 1660, 1710, 1610, 1210, 3400 cm^{1}. Anal. Calcd for $C_{27}H_{44}O_2$: C 80.94, H 11.07. Found: C 81.1, H 11.1

References

1. See for example: Rajan Babu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408–6409. Gable, K. P.; Zhuravlev, F. A.; Yokochi, A. F. T. *J. Chem. Soc., Chem Commun.* **1998**, 799–800. Wong, H. N. C.; Fok, C. C. M.; Wong, T. *Heterocycles* **1987**, *26*, 1345–1382. Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *24*, 251–254. Mandal, A. K.; Mahajan, S. W. *Tetrahedron* **1988**, *44*, 2293–2300.

2. Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 5052–5054 and references therein..

3. For a review see: Bonini, C.; Righi, G. *Synthesis* **1994**, 225–238. Bonini, C.; Righi, G.; Rumboldt, G. *Tetrahedron* **1995**, *51*, 13 401–13 404.

4. Bherens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696–5701. Bordwell, F. G., Brannen Jr., W. T. *J. Am. Chem. Soc.* **1964**, *64*, 4645–4650.

5. The same selectivity was found with other halogens during a process in which 2-haloenones were prepared from α,β unsaturated ketones: Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron. Lett.* **1999**, *40*, 5889. Use of NaI or LiI lead to similar results meaning an absence of counter ion effects.

6. Wilson, S. R.; Davey, A. E.; Guazzaroni, M. E. *J. Org. Chem.* **1992**, *57*, 2007.2012 Kutner, A.; Perlman, K. L.; Lago, A.; Sicinski, R. R.; Schnoes, H. K.; De Luca, H. F. *J. Org. Chem.* **1988**, *53*, 3450–3457.

7. Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

8. Characterised comparing **22** with an authentic sample from Sigma company.

9. Jung, M. E.; Starkey, L. S., *Tetrahedron* **1997**, *53*, 8815–8824. Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1997**, *61*, 1830–1841.

10. Brault, M.; Pollack, R. M.; Bevins, C. L. *J. Org. Chem.* **1976**, *41*, 346–350.

11. Balenkova; Gorokhova *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 1501–1503.

12. Yadav, V. K.; Kapoor, K. K. *Tetrahedron* **1996**, *52*, 3659–3668.

13. Bates, F. X.; Donnelly, J. A.; Keegan, J. R. *Tetrahedron* **1991**, *47*, 4991–5000.

14. Coates, R. M.; Williams, J. W. *J. Org. Chem.* **1974**, *39* (20), 3054–3056.

15. Milstein, O.; Buchman, J.; Blum, O. *J. Org. Chem.* **1977**, *42*, 2299–2301.

16. Ogata, Y.; Sawaki, Y.; Shimizu, H. *J. Org. Chem.* **1978**, 1760–1763.

17. Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709–2722.

18. Bovicelli, P.; Lupattelli, P.; Mincione, E.; Principe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 2182–2184.

19. Barton, H. R. D.; Boivin, J.; Lelandais, P. *J. Chem. Soc. Perkin Trans. I* **1989**, 463–468. Fieser, L. F.; Huang, W. Y.; Battacharya, B. K. *J. Org. Chem.* **1957**, *22*, 1380.