Tetrahedron Vol. 44, No. 22, pp. 6881 to 6888, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + .00

REACTION OF DIANIONS DERIVED FROM β-KETOESTERS WITH EPOXIDES- UTILITY IN THE PREPARATION OF SYNTHETICALLY USEFUL TETRAHYDROFURANS.

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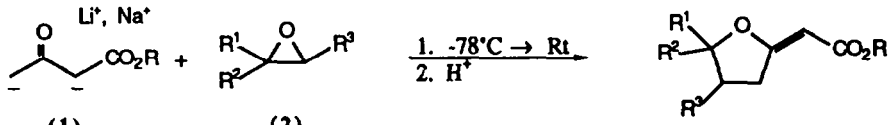
(*Received in UK* 16 *August* 1988)

Summary: Presented here are several examples which demonstrate that ether substituents α- or β- to an epoxide ring can be tolerated in the ring-opening reaction with β-keto ester dianions. Subsequent acid-promoted cyclisation of the γ-hydroxy β-ketoesters then leads to synthetically useful tetrahydrofurans, as demonstrated by application of this approach to the preparation of (±)-methyl nonactate and (±)-methyl 8-*epi*-nonactate.

The ring opening of an epoxide ring with functionalised carbon nucleophiles is a process of great synthetic importance[1], especially since there are now a range of methods for the preparation of substituted epoxides in optically-active form[1,2]. One such reaction, namely that between a dianion derived from a β-keto ester (1) and an epoxide (2), leads on subsequent treatment with acid, to substituted tetrahydrofurans (3) (scheme 1)[3]. This offers a potentially useful route to a range of biologically interesting tetrahydrofurans such as those found in the macrotetrolide nactins and many polyether antibiotics[4]. Previous studies on this reaction had indicated that a range



(1) (2) (3)

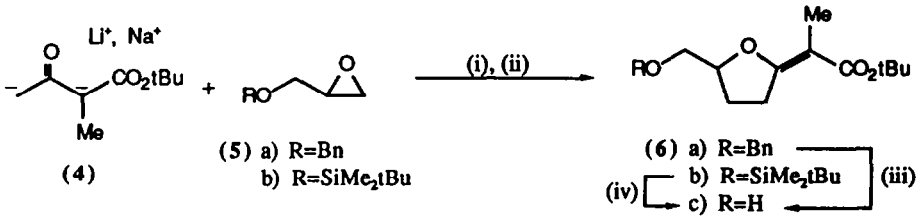
a) R^1=Me, R^2=R^3=H, 62% (ref. 3)
b) R^1=$CH_2CH(Me)OSi(Me)_2tBu$, R^2=R^3=H, 0% (ref. 6)

Scheme 1.

of alkyl substituents in the epoxide moiety could be tolerated, although Lewis acid activation of the epoxide was necessary in the more hindered cases[5]. It has also been noted that the acid-promoted cyclisation leads to the thermodynamically favoured *E*-olefin isomer with high selectivity. However very few epoxides previously investigated contained further oxygenation[5,6], and an attempt to apply this approach to the nonactic acid series (2b) had proved unsuccessful[7]. This failure suggested a serious limitation, since many naturally-occurring

tetrahydrofurans contain highly functionalised substituents, and their synthesis by this approach would almost certainly require the presence of functionality in the epoxide moiety, to enable subsequent elaboration. Indeed application of this reaction in the preparation of natural products has so far been limited[6,8]. Here we report some examples from our work in this area in which ether substitution α- or β- to the epoxide ring has been present, leading to the preparation of synthetically useful tetrahydrofurans[9].

The first two examples involve the reaction between simple glycidol derivatives (5) and the dianion derived from *tert*-butyl(2-methyl, 3-oxo)butanoate (4) (scheme 2).



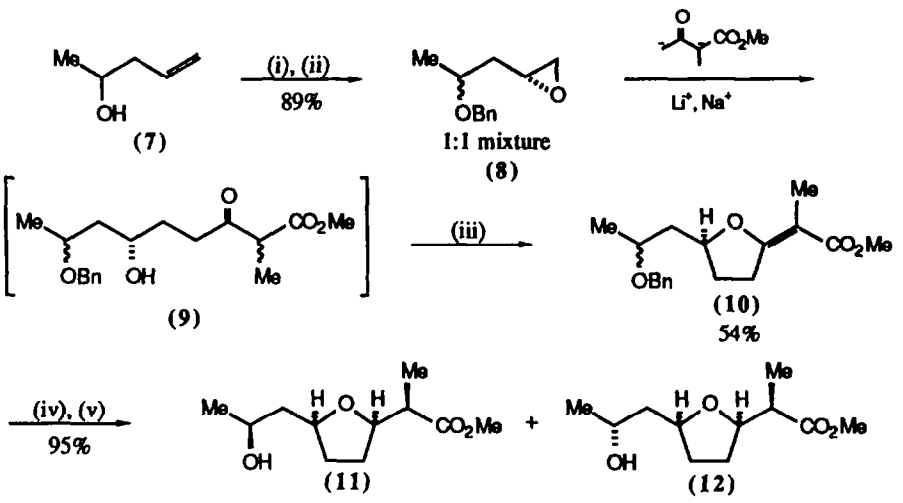
Scheme 2.

Reagents: (i) RT, 24h; (ii) Oxalic acid; (iii) H_2, Pd/C, 1atm.; (iv) nBu_4NF.

It was found that the benzyl-protected glycidol (5a) gave tetrahydrofuran (6a) in 32% overall yield, while the *tert*-butyldimethylsilyl-protected glycidol (5b) gave the corresponding tetrahydrofuran (6b) in only 14% overall yield. Examination of the reaction products suggests that the lower yield obtained with epoxide (5b) is probably not a consequence of acid-promoted cleavage of the silyl group during cyclisation. This observation is consistent with the suggestion that the steric bulk of the *tert*-butyldimethylsilyl unit is detrimental to the dianion opening reaction[7]. Deprotection of compounds (6a) and (6b) under standard conditions lead to the known alcohol (6c), a precursor to the natural product nonactin[10].

While the product tetrahydrofurans were obtained in only modest yields, this does constitute a rapid and general entry into such systems. In addition these results suggest that more distant ether substituents in the epoxide can be tolerated, since a group α- to the epoxide will generally be expected to have a greater steric and electronic effect on the ring-opening reaction than one more remote.

With the benzylated glycidol giving significantly better yields than the corresponding *tert*-butyldimethylsilyl protected species, we decided to examine whether the benzylated analogue of epoxide (2b) could be employed in the synthesis of nonactic acid derivatives. To this end, the epoxide (8) (1:1 mixture of diastereoisomers) was prepared by standard methods from 4-penten-1-ol (7), and then treated with the dianion derived from methyl(2-methyl, 3-oxo)butanoate (scheme 3). Reaction proceeded smoothly to give the γ-hydroxy β-ketoester intermediates (9). These materials proved difficult to purify without substantial decomposition, and so were cyclised directly with oxalic acid giving the tetrahydrofurans (10) as single double bond isomers, in 52% overall yield. The higher overall yield obtained in this case reflects the more remote nature of the ether substituent compared with the glycidol series.

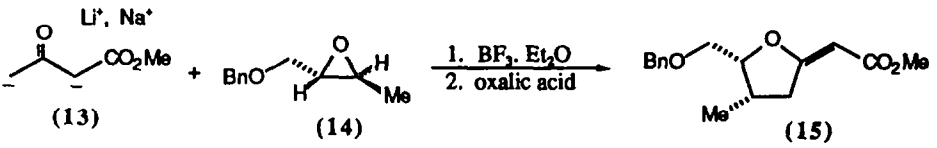


Scheme 3.

Reagents: (i) NaH; BnBr; (ii) mCPBA; (iii) $(CO_2H)_2$; (iv) 10% Pd/C, H_2, 1atm; (v) 5% Rh/Al_2O_3, H_2, 65psi.

Synthesis of the nonactic acid system was then completed *via* debenzylation of the tetrahydrofuran (10) followed by stereoselective hydrogenation of the double bond[11]. This gave a mixture of (±)-methyl nonactate (11) and (±)-methyl 8-*epi*-nonactate (12) which could be separated by chromatography. Both these isomers have previously been employed in syntheses of the antibiotic macrotetrolide nonactin[12]. Although not stereoselective at C-8, this constitutes a very short approach to the nonactic acid system and gives the final products in 40% overall yield, demonstrating the utility of this approach in natural product synthesis.

The final example in this study concerns reactions of the more highly substituted epoxide (14), prepared in the usual way from crotyl alcohol. To our disappointment, no reaction was observed on treatment of this epoxide with the dianion derived from methyl acetoacetate (13). Presumably the increased steric hindrance at the site of reaction being sufficient to prevent the dianion addition. It was found however, by analogy with reported additions to other highly substituted systems, that reaction could be effected using boron trifluoride activation of the epoxide ring. Thus after cyclisation of the initial product, the tetrahydrofuran (15) was obtained in 20% yield (scheme 4).

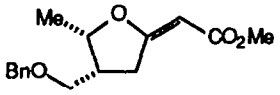


Scheme 4.

None of the tetrahydrofuran (16) derived from opening the epoxide at C-2 rather than at C-3 could be isolated from the reaction mixture, suggesting that the ring opening probably proceeded with good regioselectivity[13].

Failure of the reaction with epoxide (14) in the absence of Lewis acid activation is further evidence to

support the idea that ring opening is sensitive to steric hindrance around the epoxide group, although it should be noted that epoxide (17) has been reported to react with β-ketoester dianions in the absence of boron trifluoride etherate giving the corresponding tetrahydrofuran in 64% yield[5].



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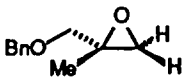

(17)

The results presented here suggest that the β-ketoester dianion-epoxide reaction will tolerate oxygenation in the epoxide substituents, however more highly substituted systems will require Lewis acid activation, and the use of bulky silicon groups in close proximity to the epoxide ring is not recommended. We are presently investigating the application of this approach to more complex natural product synthesis.

Acknowledgements. We thank SERC for a studentship (N.O'Connor), SERC Mass Spectroscopy Service, Swansea for spectra, and Dr. A.H. Davidson for providing spectra of his synthetic intermediates.

EXPERIMENTAL

^{1}H nmr spectra were obtained at 300MHz on a Bruker AC-300 spectrometer and at 60MHz on a Varian EM360 spectrometer in deuteriochloroform solutions, δ-values are quoted relative to tetramethylsilane. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer as liquid films on NaCl plates. Low resolution mass spectra were obtained on a VG 12-253 quadrupole instrument and high resolution spectra on a VG ZAB-E instrument. Column chromatography was performed on MN-silica gel 60 230-400 mesh, under pressure. Petroleum ether refers to the fraction boiling 40°-60°C. Solvents were purified and dried by standard methods.

General Procedure for the Preparation of Benzyloxyalkyl-Substituted Epoxides. Alcohol (10mmol) was added dropwise to a suspension of sodium hydride (0.53g of a 50% dispersion in oil, washed twice with dry petroleum ether, 1.1eq) in dry tetrahydrofuran (25ml) at 0°C under argon. After stirring at room temperature for 1h, benzyl bromide (1eq) was added dropwise, and the resulting mixture left overnight. Saturated aqueous sodium chloride (15ml) was added, and the mixture extracted with diethyl ether (3x25ml). The organic extracts were dried over magnesium sulphate, and the solvent removed under reduced pressure, to give the crude benzyl ether.

Crude benzyl ether (10mmol) was dissolved in dichloromethane (20ml) and the solution cooled to 0°C. Sodium hydrogen carbonate (1.5g) was added, followed by 80% *m*-chloroperoxybenzoic acid (3.2g, 15mmol, added in batches). The mixture was stirred at 0°C for 1h, and then at room temperature overnight. Solid sodium thiosulphate (1g) was added, the mixture stirred for 15min, filtered, and concentrated under reduced pressure. The resulting solid was dissolved in water (15ml) and extracted with diethyl ether (3x25ml). The organic extracts were dried over magnesium sulphate, and the solvent removed under reduced pressure, to give the crude epoxide. Chromatography on silica gel gave the pure epoxide.

Preparation of (±)-1-(benzyloxy)prop-2-ene oxide (5a). Allyl alcohol (5.8g, 100mmol) was benzylated according to the above procedure to give crude 1-benzyloxy prop-2-ene (14.1g, 95mmol, 95%), **^{1}H nmr** (60MHz, $CDCl_3$) δ 7.3(5H, s, Ar*H*), 6.2-5.6(1H, m, C*H*=CH_2), 5.5-4.9(2H, m, CH=CH_2), 4.5(2H, br.s, CH_2Ph), and 4.2-3.8(2H, m, CH_2OBn). This material (11.9g, 80mmol) was epoxidised according to the above procedure to give, after chromatography on silica gel (15% ethyl acetate - 85% petroleum ether), (±)-1-(benzyloxy)prop-2-ene oxide (5a) (11.4g, 70mmol, 87%) as a colourless oil, **^{1}H nmr** (300MHz, $CDCl_3$) δ 7.34-7.25(5H, m, Ar*H*), 4.59(1H, d, J=12Hz, CH_aH_bPh), 4.53(1H, d, J=12Hz, CH_aH_bPh), 3.75(1H, dd, J=3 and

11.5Hz, C$H_a$$H_b$OBn), 3.41(1H, dd, J=6 and 11.5Hz, CH$_a$$H_b$OBn), 3.19-3.14(1H, m, C$H$ΩCH$_2$), 2.77(1H, dd J=4.5 and 5Hz, CHΩCH_aH$_b$), and 2.59(1H, dd, J=2.5 and 5Hz, CHΩCH$_a$$H_b$); **vmax** (neat) 2850 and 1070cm^{-1}; **m/z** (NH_3, CI) 182 ($M+NH_4^+$). Found $M+NH_4^+$ 182.1180 $C_{10}H_{16}NO_2$ requires 182.1182.

Preparation of (±)-2-(benzyloxy)pent-4-ene oxide (8). 4-Penten-2-ol (7) (2g, 23.2mmol) was benzylated according to the above procedure to give 2-benzyloxy pent-4-ene (4g, 22.7mmol, 98%) as a colourless oil, **^{1}H nmr** (300MHz, $CDCl_3$) δ 7.35-7.21(5H, m, ArH), 5.82(1H, tdd, J=7, 10, and 17Hz, CH=CH$_2$), 5.10-5.02(2H, m, CH=CH_2), 4.54(1H, d, J=12Hz, CH_aH$_b$Ph), 4.48(1H, d, J=12Hz, CH$_a$$H_b$Ph), 3.56(1H, sextet, J=6Hz, CH(Me)OBn), 2.41-2.17(2H, m, CH_2), and 1.18(3H, d, J=6Hz, CH_3). This material (1.9g, 10.8mmol) was epoxidised according to the above procedure to give, after chromatography on silica gel (10% diethyl ether - 80% petroleum ether), (±)-2-(benzyloxy)pent-4-ene oxide.(8) (1.85g, 9.6mmol, 89%) as a colourless oil. The product appeared to be a 1:1 mixture of diastereoisomers; **^{1}H nmr** (300MHz, $CDCl_3$) δ 7.40-7.22(5H, m, ArH), 4.61(0.5H, d, J=8.5Hz, CH_aH$_b$Ph), 4.57(0.5H, d, J=8.5Hz, CH$_a$$H_b$Ph), 4.48(0.5H, d, J=7Hz, CH_aH$_b$Ph), 4.44(0.5H, d, J=7Hz, CH$_a$$H_b$Ph), 3.81-3.65(1H, m, C$H$OBn), 3.10-3.00(1H, m, C$H$ΩCH$_2$), 2.79-2.71(1H, m, CHΩC$H_aH_b$), 2.49-2.44(1H, m, CHΩCH$_a$CH_b), 1.90-1.46(2H, m, CH_2), 1.27(1.5H, d, J=6Hz, CH_3), and 1.24(1.5H, d, J=6Hz, CH_3); **vmax** (neat).2900 and 1090cm^{-1}; **m/z**.(NH_3, CI) 193($M+H^+$). Found $M+H^+$ 193.1231 $C_{12}H_{17}O_2$ requires 193.1230.

Preparation of (±)-*trans*-1-(benzyloxy)but-2-ene oxide (14). Crotyl alcohol (2.0g, 27.7mmol) was benzylated according to the above procedure to give crude 1-(benzyloxy)but-2-ene (3.95g, 24.4mmol, 88%), **^{1}H nmr** (300MHz, $CDCl_3$) δ 7.39-7.22(5H, m, ArH), 5.77-5.54(2H, m, CH=CH), 4.46(2H, s, PhCH_2), 3.93(2H, dd, J=1 and 6Hz, BnOCH_2), and 1.71(3H, dd, J=1 and 6.5Hz). This material (3.7g, 22.8mmol) was epoxidised according to the above procedure to give, after chromatography on silica gel (15% ethyl acetate - 85% petroleum ether), (±)-1-(benzyloxy)but-2-ene oxide (14) (2.31g, 13.0mmol, 57%) as a colourless oil, **^{1}H nmr** (300MHz, $CDCl_3$) δ 7.30-7.21(5H, m, ArH), 4.54(1H, d, J=11.9Hz, CH_aH$_b$Ph), 4.47(1H, d, J=11.9Hz, CH$_a$$H_b$Ph), 3.64(1H, dd, J=2.9 and 11.3Hz, BnOCH_aH$_b$), 3.40(1H, dd, J=5.3 and 11.3Hz, BnOCH$_a$$H_b$), 2.86-2.83(2H, m, C$H$ΩC$H$), and 1.26(3H, d, J=4.8Hz, CHCH_3); **vmax** (neat) 2850 and 1090cm^{-1}; **m/z**.(NH_3, CI) 196 ($M+NH_4^+$). Found $M+NH_4^+$ 196.1339 $C_{11}H_{18}NO_2$ requires 196.1338.

Preparation of (±)-1-(*tert*-butyldimethylsilyloxy)prop-2-ene oxide (5b). Allyl alcohol (2.0g, 34mmol) was added dropwise to a stirred solution of *tert*-butyldimethylsilylchloride (7.6g, 50mmol) and imidazole (6.7g, 100mmol) in dry N,N'-dimethyl formamide (50ml) under argon. After stirring at room temperature for 16h, petroleum ether (100ml) was added, and the mixture washed with water (3x50ml). The petroleum solution was dried over magnesium sulphate and the solvent removed under reduced pressure to give the crude silyl ether. This product (5.7g, *ca.* 33mmol) was dissolved in dichloromethane (150ml) and the solution cooled to 0°C. Sodium hydrogen carbonate (4.2g) was added, followed by 80% *m*-chloroperoxybenzoic acid (8.6g, 43mmol, added in batches). The mixture was stirred at 0°C for 1h, and then at room temperature overnight. Solid sodium thiosulphate (5g) was added, the mixture stirred for 15min, filtered, and concentrated under reduced pressure. The resulting solid was dissolved in water (100ml) and extracted with diethyl ether (3x50ml). The organic extracts were dried over magnesium sulphate, and the solvent removed under reduced pressure, to give the crude epoxide. Chromatography on silica gel (20% ethyl acetate - 80% petroleum ether) gave, (±)-1-(*tert*-butyldimethyl silyloxy) prop-2-ene oxide (5b) (4.7g, 25mmol, 73%) as a colourless oil; **^{1}H nmr** (60MHz, $CDCl_3$) δ 3.9-3.3(2H, m, CH_2OSiMe$_2$tBu), 3.2-2.8(1H, m, CHΩCH$_2$), 2.8-2.5(2H, m, CHΩCH_2), 0.83(9H, s, SiMe$_2$C[CH_3]$_3$), and 0.00(6H, s, Si[CH_3]$_2$tBu); **vmax** (neat) 2940, 1260, and 1100cm^{-1}; **m/z** .(NH_3, CI) 206($M+NH_4^+$). Found $M+NH_4^+$ 206.1575 $C_9H_{24}NO_2Si$ requires 206.1578.

General Procedure for the non-Lewis Acid Mediated Condensation of β-Ketoesters with Epoxides. β-Ketoester (10mmol) was added dropwise to a stirred suspension of sodium hydride (0.53g of a 50% dispersion in oil, washed twice with dry petroleum ether, 1.1eq) in dry tetrahydrofuran (100ml) under argon at 0°C. The mixture was then stirred at room temperature for 30min, usually giving a thick white precipitate. After cooling to -10°C, n-butyl lithium (8.1ml of a 1.38M solution in hexanes, 1.1eq) was added, and the mixture stirred for a further 15min giving a clear solution. Epoxide (1.1eq) in dry tetrahydrofuran (3ml) was added and the mixture allowed to warm

to room temperature over 3h. After stirring at room temperature for 24h, 1M hydrochloric acid (50ml) was added cautiously, and the resulting mixture extracted with diethyl ether (3x75ml). The organic extracts were dried, and the solvent removed under reduced pressure to give the crude adduct as a pale yellow oil. This material was immediately dissolved in dichloromethane (40ml), and solid oxalic acid (3g) added. The mixture was stirred at reflux under argon for 2-3h, cooled to room temperature, and filtered through a pad of silica. Evaporation of the dichloromethane gave the crude product.

Preparation of (±)-2[S]-[1-(benzyloxy)methyl]-5-(E)-[1-(*tert*-butyloxycarbonyl)ethylidene] tetrahydrofuran (6a). The dianion derived from *tert*-butyl(2-methyl,3-oxo)butanoate (3.9g, 23mmol) was reacted with 1-(benzyloxy)prop-2-ene oxide.(5a) (4.1g, 25mmol) according to the general procedure outlined above. After cyclisation with oxalic acid, the crude product was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give (±)-2[S]-[1-(benzyloxy)methyl]-5-(E)-[1-(*tert*-butyloxycarbonyl)ethylidene] tetrahydrofuran (6a) (2.3g, 7.2mmol, 32%) as a colourless oil, ^{1}H nmr (300MHz, $CDCl_3$) δ 7.37-7.18(5H, m, Ar*H*), 4.53(2H, s, CH_2Ph), 4.53-4.45(1H, m, C*H*OR), 3.54(1H, dd, J=4 and 11Hz, CH_aH_bOBn), 3.49(1H, dd, J=5 and 11Hz, CH_aH_bOBn), 3.16-3.05(1H, m, CH_aH_bC=C), 2.88(1H, qtd, J=1.5, 9.5, and 18Hz, CH_aH_bC=C), 2.11-2.00(1H, m), 1.88-1.76(1H, m), 1.75(3H, t, J=1.5Hz, CH_3), and 1.43(9H, s, OC[CH_3]$_3$); νmax (neat) 1685 and 1640cm^{-1}; m/z (CI, NH_3) 319(M+H^+). Found M+H^+ 319.1909 $C_{19}H_{27}O_4$ requires 319.1911.

Preparation of (±)-[1-(*tert*-butyldimethylsilyloxy)methyl]-5-(E)-[1-(*tert*-butyloxy carbonyl) ethylidene] tetrahydrofuran (6b). The dianion derived from *tert*-butyl(2-methyl,3-oxo)butanoate (2.0g, 12mmol) was reacted with 1-(*tert*-butyldimethylsilyloxy)prop-2-ene oxide (5b) (2.4g, 13mmol) according to the general procedure outlined above. After cyclisation with oxalic acid, the crude product was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give, (±)-1-[(tert-butyldimethylsilyloxy)methyl]-5-(E)-[1-(*tert*-butyloxycarbonyl) ethylidene] tetrahydrofuran (6b) (2.3g, 1.6mmol, 14%) as a colourless oil, ^{1}H nmr (300MHz, $CDCl_3$) δ 4.42-4.34(1H, m, C*H*OR), 3.69(1H, dd, J=4 and 11Hz, CH_aH_bOSiMe$_2$tBu), 3.61(1H, dd, J=4 and 11Hz, CH_aH_bOSiMe$_2$tBu), 3.12-2.82(2H, m, CH_2C=C), 2.07-1.81(2H, m), 1.71(3H, t, J=1.5Hz, CH_3), 1.41(9H, s, OC[CH_3]$_3$), 0.82(9H, s, SiMe$_2$C[CH_3]$_3$), 0.00(3H, s, $SiCH_3$MetBu), and -0.02(3H, s, $SiCH_3$MetBu); νmax (neat) 1685 and 1645cm^{-1}; m/z (CI, NH_3) 343(M+H$^+$), 287, 269, and 229. Found M+H^+ 343.2313 $C_{18}H_{35}O_4Si$ requires 343.2307.

Preparation of (±)-2[S]-[2(S/R)-(benzyloxy)propyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (10). The dianion derived from methyl(2-methyl,3-oxo)butanoate (0.95g, 7.3mmol) was reacted with 2-(benzyloxy)pent-4-ene oxide (8) (1.4g, 7.3mmol) according to the general procedure outlined above. After cyclisation with oxalic acid, the crude product was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give (±)-2(S)-[2(S/R)-(benzyloxy)propyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (10) (1.2g, 3.9mmol, 54%) as a colourless oil. This material was obtained as a 1:1 mixture of diastereoisomers; ^{1}H nmr (300MHz, $CDCl_3$) δ 7.34-7.20(5H, m, Ar*H*), 4.62-4.37(3H, m, C*H*OR and CH_2Ph), 3.82-3.63(1H, m, C*H*OBn), 3.67(3H, s, CO_2CH_3), 3.27-3.11(1H, m, CH_aH_bC=C), 2.96-2.76(1H, m, CH_aH_bC=C), 2.20-1.52(4H, m), 1.77(3H, t, J=1.5Hz, C=CCH_3), 1.26(1.5H, d, J=6Hz, CHCH_3 one isomer), and 1.20(1.5H, d, J=6Hz, CHCH_3 one isomer); νmax (neat) 1690 and 1645cm^{-1}; m/z (EI) 304(M^+), 105, 91, and 77. Found M^+ 304.1666 $C_{18}H_{24}O_4$ requires 304.1676.

Preparation of (±)-2[R]-[1-(benzyloxy)methyl]-5-(E)-[1-(*tert*-butyloxycarbonyl)methylidene]-3[S]-methyl tetrahydrofuran (15). Methyl acetoacetate (2.16ml, 20mmol) was added dropwise to a stirred suspension of sodium hydride (0.96g of a 50% dispersion in oil, washed twice with dry petroleum ether, 20mmol) in dry tetrahydrofuran (75ml) under argon at 0°C. The mixture was then stirred at room temperature for 30min. After cooling to -10°C, n-butyl lithium (13.3ml of a 1.5M solution in hexanes, 20mmol) was added, and the mixture stirred for a further 15min giving a yellow solution. Epoxide (14) (1.78g, 10mmol) in dry tetrahydrofuran (5ml) was added, followed by boron trifluoride etherate (4ml, 32mmol) and the mixture allowed to warm to room temperature over 3h. Saturated aqueous sodium bicarbonate (40ml) was added, and the resulting mixture extracted with diethyl ether (3x75ml). The organic extracts were dried, and the solvent removed under reduced pressure to give the crude adduct as a

pale yellow oil. This material was immediately dissolved in dichloromethane (20ml), and solid oxalic acid (3g) added. The mixture was stirred at reflux under argon for 2.5h, cooled to room temperature, and filtered through a pad of silica. Evaporation of the dichloromethane gave the crude product which was purified by silica gel chromatography (15% ethyl acetate - 85% petroleum ether) to give (±)-2[R]-[1-(benzyloxy)methyl]-5-(E)-[1-(*tert*-butyloxycarbonyl)methylidene]-3[S]-methyl tetrahydrofuran (15) (0.55g, 2.0mmol, 20%) as a colourless oil, **^{1}H nmr** (300MHz, $CDCl_3$) δ 7.31-7.20(5H, m, Ar*H*), 5.30(1H, t, J=1.7Hz, C=C*H*), 4.54-4.39(3H, m, CH_2Ph and C*H*OR), 3.62-3.51(2H, m, BnOCH_2), 3.61(3H, s, OCH_3), 3.13(1H, ddd, J=1.7, 8.0, and 17.8Hz, CH_aH$_b$C=C), 2.89(1H, ddd, J=1.7, 6.1, and 17.8Hz, CH$_a$$H_b$C=C), 2.53-2.44(1H, m, C*H*CH$_3$), and 0.94(3H, d, J=7.1Hz, CHCH_3); **νmax** (neat) 1707 and 1642cm^{-1}; **m/z** (CI, NH_3) 294(M+NH_4^+). Found M+NH_4^+294.1708, $C_{16}H_{24}NO_4$ requires 294.1707.

General Procedure for Debenzylation. Benzyl ether (5mmol) was dissolved in methanol (25ml) containing 10% palladium-on-carbon (0.1g), the mixture was degassed, then placed under an atmosphere of hydrogen (ca. 1 atm.) maintained *via* a hydrogen-filled balloon. After stirring for 2-6h, the mixture was filtered through a pad of celite and the solvent removed under reduced pressure to give the crude alcohol. The product was usually sufficiently pure for use in subsequent reactions.

Debenzylation of (±)-2[S]-[1-(benzyloxy)methyl]-5-(E)-[1-(*tert*-butyloxycarbonyl)ethylidene] tetrahydrofuran (6a). 2[S]-[1-(benzyloxy)methyl]-5-(E)-[1-(tert-butyloxycarbonyl)ethylidene] tetrahydrofuran (6a) (2.2g, 7mmol) was debenzylated according to the general procedure to give (±)-2(S)-(hydroxymethyl)-5-(E)-[1-(methoxycarbonyl)ethylidene]tetrahydrofuran (6c) (1.0g, 4.5mmol, 64%) as a colourless oil, **^{1}H nmr** (300MHz, $CDCl_3$) δ 4.46-4.39(1H, m, C*H*OR), 3.78(1H, dd, J=3 and 12Hz, CH_aH$_b$OH), 3.58(1H, dd, J=6 and 12Hz, CH$_a$$H_b$OH), 3.19-3.08(1H, m, C$H_aH_b$C=C), 2.90(1H, qtd, J=1.5, 8.5, and 18Hz, CH$_a$$H_b$C=C), 2.11-1.81(3H, m), 1.73(3H, t, J=1.5Hz, CH_3), and 1.43(9H, s, C[CH_3]$_3$); **νmax** (neat) 3415, 1680, and 1640cm^{-1}; **m/z** (EI) 228(M^+), 172, 155, 154, 98, and 57. Found M^+ 228.1361 $C_{12}H_{20}O_4$ requires 228.1363.

Debenzylation of (±)-2(S)-[2(S/R)-(benzyloxypropyl)]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (10). 2(S)-[2(S/R)-(benzyloxy)propyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (10) (0.5g, 1.6mmol) was debenzylated according to the general procedure to give crude 2(S)-2[S(R)]-(hydroxypropyl)-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (354mg, 100%) as a colourless oil (1:1 mixture of diastereoisomers), **^{1}H nmr** (300MHz, $CDCl_3$) δ 4.56-4.40(1H, m, C*H*OR), 4.00-3.92(1H, m, C*H*OH), 3.60(3H, s, CO_2CH_3), 3.19-3.10(1H, m, CH_aH$_b$C=C), 2.88-2.75(1H, m, CH$_a$$H_b$C=C), 2.74(0.5H, br.s, O*H* one isomer), 2.52(0.5H, br.s, O*H* one isomer), 2.21-2.07(1H, m), 1.80-1.52(3H, m), 1.70(3H, t, J=1.5Hz, C=CCH_3), and 1.60(3H, d, J=6Hz, CHCH_3); **νmax** (neat) 3440, 1700, and 1635cm^{-1}; **m/z** (EI) 214(M^+), 183, 124, 115, 98, 83, 67, and 55. Found M^+ 214.1199 $C_{11}H_{18}O_4$ requires 214.1206.

Desilylation of (±)-2(S)-[1-(*tert*-butyldimethylsilyloxy)methyl]-5-(E)-[1-(*tert*-butyloxy carbonyl) ethylidene] tetrahydrofuran (6b). Tetra-*n*-butylammonium fluoride (1.5ml, 1M solution in tetrahydrofuran, 1.5mmol) was added dropwise to a solution of 2(S)-[1-(tert-butyldimethylsilyloxy)methyl]-5-(E)-[1-(tert-butyloxy carbonyl) ethylidene] tetrahydrofuran (6b) (250mg, 0.73mmol) in tetrahydrofuran (10ml) at room temperature. The mixture was stirred at room temperature for 3h, then the solvent removed under reduced pressure. Chromatography of the residue on silica gel (20% ethylacetate - 80% petroleum ether) gave (±)-2(S)-(hydroxymethyl)-5-(E)-[1-(methoxycarbonyl)ethylidene]tetrahydrofuran (6c) (140mg, 0.63mmol, 86%) as a colourless oil, identical with the previously prepared material.

Hydrogenation of (±)-2(S)-[2(S/R)-hydroxypropyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran over Rhodium-on-Alumina. Crude 2(S)-[2(S/R)-hydroxypropyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (*ca.* 1.6mmol) was dissolved in methanol (25ml), the solution placed in a glass bomb, and the mixture degassed. Fresh 5% rhodium-on-alumina (0.3g) was added to the solution, and the system placed under an atmosphere of hydrogen pressurised at 70psi. This mixture was then ultrasonicated for 20min in a cleaning bath, then stirred at room temperature for 90h. The pressure was released and the mixture filtered through a pad of silica to remove the catalyst. Evaporation of the solvent under reduced pressure, followed by chromatography

of the residue on silica gel (diethyl ether) gave; (±)-methyl 8-*epi* nonactate (12) (166mg, 0.77mmol, 48%) as a colourless oil, ^{1}H nmr (300MHz, $CDCl_3$) δ 4.06-3.86(3H, m, C*H*OR), 3.63(3H, s, OCH_3), 2.48(1H, qd, J=7 and 8.5Hz, C*H*[Me]CO_2Me), 2.08-1.84(2H, m), 1.67-1.39(4H, m), 1.10(3H, d, J=6.5Hz, CH_3), and 1.05(3H, d, J=7Hz, CH_3), vmax (neat) 3550 and 1740cm^{-1}; m/z (EI) 217($M+H^+$), 157, 129, 85, 71, 67, and 55, found M+H$^+$ 217.1437 $C_{11}H_{21}O_4$ requires 217.1441, and methyl nonactate (11) (163mg, 0.75mmol, 47%) as a colourless oil, ^{1}H nmr (300MHz, $CDCl_3$) δ 4.17-3.89(3H, m, C*H*OR), 3.62(3H, s, OCH_3), 2.92(1H, br.s, O*H*), 2.50(1H, qd, J=7 and 8.5Hz, C*H*[Me]CO_2Me), 2.08-1.50(6H, m), 1.17(3H, d, J=6.5Hz, CH_3), and 1.09(3H, d, J=7Hz, CH_3), vmax (neat) 3540 and 1740cm^{-1}; m/z (EI) 217($M+H^+$), 157, 129, 125, 85, 71, 67, and 55. Found $M+H^+$ 217.1436 $C_{11}H_{21}O_4$ requires 217.1441.

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13. The main by-products in this reaction tend to be the two starting materials, although the epoxide is decomposed on prolonged reaction times.