Tetrahedron Vol. 44, No. 22, pp. 6889 to 6896, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + .00
© 1988 Pergamon Press plc

STEREOSELECTIVE SYNTHESIS OF (±)-METHYL HOMONONACTATE AND (±)-METHYL 8-*EPI*-HOMONONACTATE.

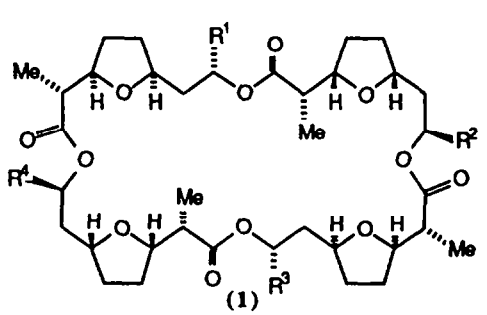
BARRY LYGO

Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT, U.K.

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

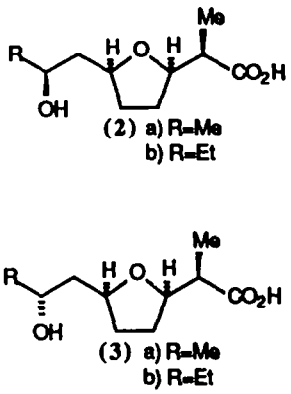
Summary: A stereoselective route to (±)-methyl homononactate (4b) and (±)-methyl 8-*epi*-homononactate (5b), synthetic precursors to the antibiotic tetranactin, is presented. Key steps involve employing the regioselective ring opening of 1-(benzyloxy)but-3-ene oxide (8) with the dianion derived from methyl(2-methyl, 3-oxo)butanoate (9), and the stereoselective addition of dialkyl zinc species to a β-alkoxyaldehyde precursor (6). Conditions have been developed to enable the diethyl zinc addition to give either isomer with reasonable selectivity.

The nactins are a class of macrotetrolide antibiotics isolated from a variety of Streptomyces cultures, and include nonactin (1a), monactin (1b), dinactin (1c), trinactin (1d), and tetranactin (1e)[1]. Structurally the nactins are composed of four subunits, the most common being nonactic acid (2a) and homononactic acid (2b)[2]. Interestingly, both enantiomers of the subunits are found in the tetramers. Several synthetic routes to the nactins have been reported, all involving the coupling together of the monomer units *via* lactonisation procedures Approaches to nonactin (1a) have involved the non-selective coupling of racemic nonactic acid (2a)[3], as well as the stereoselective "reverse coupe du roi" coupling of optically-pure nonactic acid (2a) and 8-*epi*-nonactic acid (3a) derivatives[4,5]. Tetranactin has also been synthesised stereoselectively *via* the coupling of optically-pure homononactic acid (2b) and 8-*epi*-homononactic acid (3b) derivatives[6].



(1)

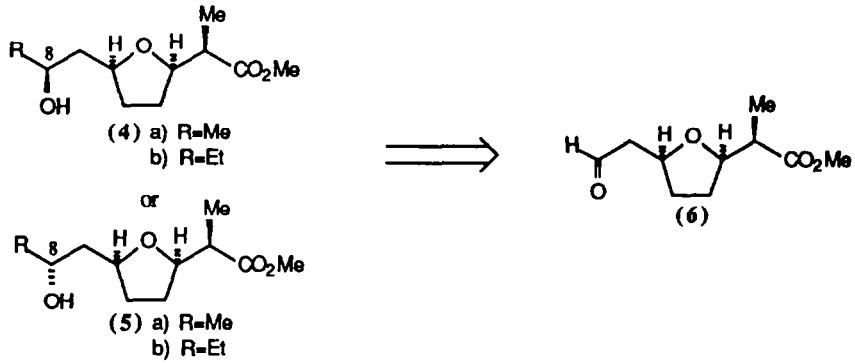
a) $R^1=R^2=R^3=R^4=Me$
b) $R^1=Et$, $R^2=R^3=R^4=Me$
c) $R^1=R^3=Et$, $R^2=R^4=Me$
d) $R^1=R^2=R^3=Et$, $R^4=Me$
e) $R^1=R^2=R^3=R^4=Et$



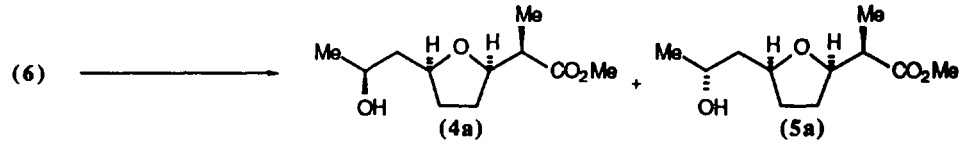
(2) a) R=Me
b) R=Et

(3) a) R=Me
b) R=Et

There have been many reported syntheses of nonactic acid derivatives in both optically active and racemic form[4,5,7], however few of these approaches have been extended to the preparation of homononactate derivatives[6]. Here we report full details of a stereoselective approach that allows preparation of methyl nonactate (4a), methyl homononactate (4b), and their C-8 epimers (5a,b)[7q].



In order to develop a general approach to monomer units suitable for the construction of the nactins, we considered preparation of the aldehyde (6)[7f,p]. With such an aldehyde available, it seemed reasonable that the stereocontrolled addition of a group R should then allow access to a range of substituted tetrahydrofurans of the type incorporated in the macrocyclic nactins. In addition, it should be possible to produce either stereoisomer at C-8 *via* this approach. Indeed, while this work was in progress the stereocontrolled addition of a methyl group to aldehyde (6) was reported and conditions selective for either isomer found, providing a route to both methyl nonactate (4a) and methyl 8-*epi*-nonactate (5a) (scheme 1)[7p].

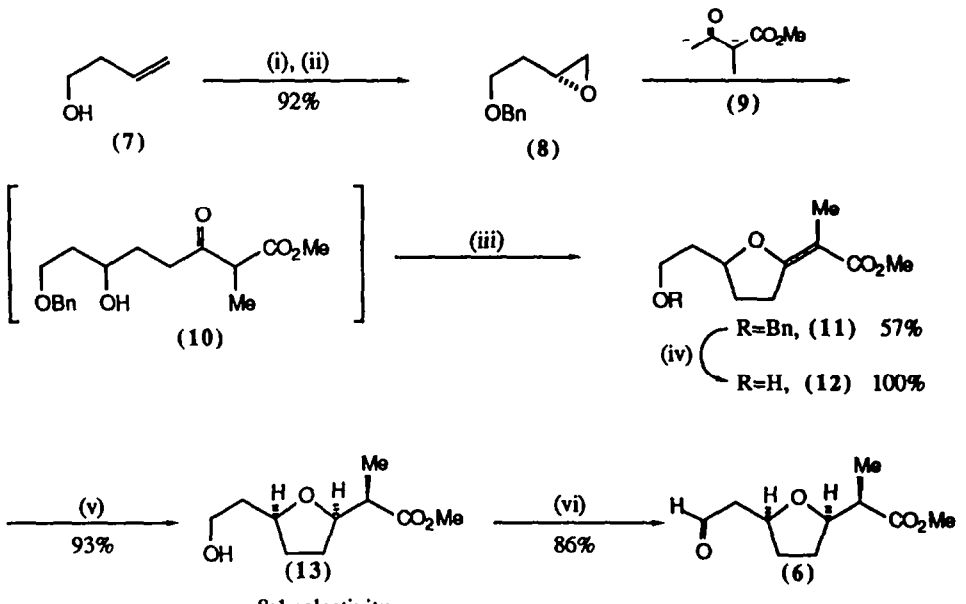


$TiCl_4$, Me_2Zn , CH_2Cl_2	24	:	1	85%
Me_2CuLi , Et_2O	1	:	4.5	78%

Scheme 1.

Our approach to the key aldehyde (6) centered around the reaction between the dianion (9) and epoxide (8), to give after acid cyclisation the tetrahydrofuran (11)[8] (scheme 2). The dianion was readily generated from methyl(2-methyl, 3-oxo)butanoate by sequential treatment with sodium hydride and n-butyl lithium, whilst the epoxide (8) was prepared by standard methods from 3-buten-1-ol (7). Purification of the intermediate hydroxy β-keto ester (10) was not attempted since such materials are not very stable. The cyclised product (11) appeared to be only one olefin isomer by high field ^1H nmr, and this was assumed to be the more stable *E*-isomer by analogy with similar reactions. Debenzylation, followed by stereoselective hydrogenation of the olefinic bond with Rh/Al_2O_3 catalyst gave the known tetrahydrofuran (13) in 49% overall yield. In general the reduction gave *ca.* 8:1 selectivity for the desired isomer (13) over other possible diastereoisomers, the hydrogen being delivered predominantly to the less sterically hindered face of the double bond, however some batches of the rhoduim catalyst would not effect the reduction[9]. It was found that new batches of the catalyst generally gave the best results. The reduction selectivity and variability of the catalyst is consistent with observations made on very similar systems[5]. Oxidation of the

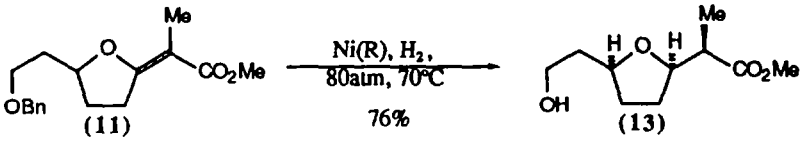
hydroxyl group lead to the required aldehyde (6) in 86% yield[10].



Scheme 2.

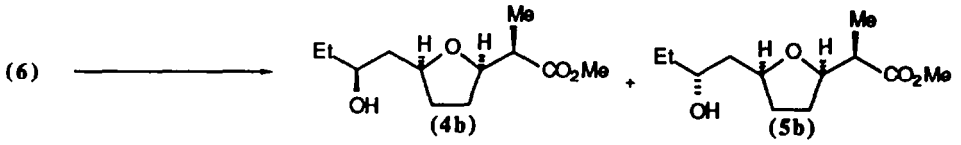
Reagents: (i) NaH; BnBr; (ii) mCPBA; (iii) Oxalic acid; (iv) H_2, 1atm., Pd/C; (v) H_2, 70psi, Rh/Al_2O_3; (vi) Py-SO_3, DMSO, Et_3N.

Because of the variability and expense of the rhodium catalyst, other reduction systems were investigated and it was found that hydrogenation using a Raney nickel catalyst[11] consistently gave reasonable (*ca.* 4:1) selectivity for the required diastereoisomer (13). These conditions had the added advantage that the benzyl protecting group was removed during the reaction, avoiding a separate step[12] (scheme 3).



Scheme 3.

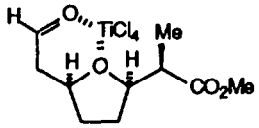
Since the aldehyde (6) had already been converted stereoselectivly into methyl nonactate (4a) and methyl 8-*epi*-nonactate (5a)[7b], we then turned our attention to the problem of preparing the homononactate system. This required developing conditions for the stereoselective nucleophilic addition of an ethyl group to aldehyde (6). By analogy with the previous work it was found that the "chelation control" addition could be achieved using diethyl zinc as the nucleophile in the presence of titanium tetrachloride (scheme 4). This resulted in a mixture of stereoisomers favouring the natural stereochemistry (4b) by about 4:1, confirming the generality of this approach to such systems. This reaction presumably proceeds *via* the chelated intermediate (14) followed by addition of the nucleophile to the less hindered face of the aldehyde.



Et_2Zn, $TiCl_4$, CH_2Cl_2	4	:	1	85%
Et_2Zn, $BF_3.Et_2O$, CH_2Cl_2	1	:	10	80%

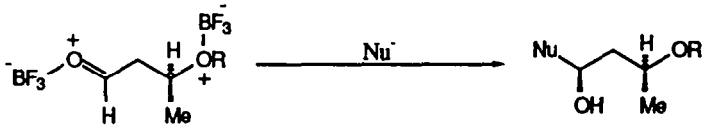
Scheme 4.

Stereoselective addition of an ethyl group to aldehyde (6) to give the unnatural C-8 isomer (5b) was however less straightforward. Direct extrapolation of the conditions required for the corresponding methyl addition (ie Et_2CuLi) did not lead to good selectivity. This result is perhaps not surprising since there may well be significant differences between the two cuprate species concerned. After investigation of a range of nucleophilic systems it was



(14)

found that good selectivity for the isomer (5b) could be obtained using diethyl zinc and boron trifluoride etherate (scheme 4). The stereoselectivity observed in this case is opposite to that normally obtained with simple β-alkoxy aldehydes under similar conditions. In the latter case addition of the nucleophile to a chelated intermediate (15) is proposed to explain the stereoselectivity[13]. The precise reasons for a reversal of stereoselectivity with aldehyde (6) are not clear, and this will be the subject of future studies[14].



(15)

In conclusion, we have developed a short and efficient route to substituted tetrahydrofurans of the type incorporated in the nactins. This approach has resulted in the first stereoselective route to methyl homononactate (4b) and its C-8 epimer (5b). Work is now underway to develop new methods for the construction of the naturally-occurring tetrameric units of these materials.

Acknowledgements. We thank the Nuffield Foundation for financial support, SERC Mass Spectroscopy Service, Swansea for spectra, and Prof. U. Schmidt for providing data on authentic samples of methyl homononactate and methyl 8-*epi*-homononactate.

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.

Preparation of (±)-1-(benzyloxy)but-3-ene oxide (8). 3-Buten-1-ol (7) (1g, 13.9mmol) was added dropwise to a suspension of sodium hydride (0.74g of a 50% dispersion in oil, washed twice with dry petroleum ether, 15.4mmol) in dry tetrahydrofuran (30ml) at 0°C under argon. After stirring at room temperature for 1h, benzyl bromide (1.8ml, 15.2mmol) 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 crude 1-benzyloxy but-3-ene (2.18g, 13.5mmol, 97%) as a colourless oil, **^{1}H nmr** (300MHz, $CDCl_3$) δ 7.41-7.15(5H, m, Ar*H*), 5.82(1H, tdd, J=7,10, and 17Hz, C*H*=CH_2), 5.12-5.00(2H, m, C*H*$_2$=CH), 4.52(2H, ~d, J=12Hz, CH_2Ph), 3.51(2H, t, J=7Hz, CH_2OBn), and 2.36(2H, tq, J=3 and 7Hz, CH_2).

Crude benzyl ether (2.18g, *ca.* 13.5mmol) 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 (4.4g, 21mmol, 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 (20% diethyl ether - 80% petroleum ether), gave (±)-1-(benzyloxy)but-3-ene oxide (8) (2.09g, 11.7mmol, 95%) as a colourless oil, **^{1}H nmr** (300MHz, $CDCl_3$) δ 7.46-7.18(5H, m, Ar*H*), 4.52(2H, s, CH_2Ph), 3.68-3.52(2H, m, CH_2OBn), 3.04 (1H, m, C*H*$^{\Omega}$$CH_2$), 2.76(1H, t, J=4.5Hz, CH$^{\Omega}$CH_aH$_b$), 2.50(1H, dd, J=2.5 and 4.5Hz, CH$^{\Omega}$CH$_a$CH_b), and 1.95-1.70(2H, m, CH_2); **νmax** (neat).2870 and 1090cm^{-1}; **m/z** (NH_3, CI) 196(*M*+NH_4^+). Found *M*+NH_4^+ 196.1335 $C_{11}H_{18}NO_2$ requires 196.1338.

Preparation of (±)-[2-(benzyloxy)ethyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (11). Methyl(2-methyl, 3-oxo)butanoate (1g, 7.7mmol) was added dropwise to a stirred suspension of sodium hydride (0.41g of a 50% dispersion in oil, washed twice with dry petroleum ether, 8.5mmol) 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 (6.2ml of a 1.38M solution in hexanes, 8.5mmol) was added, and the mixture stirred for a further 15min giving a clear solution. Epoxide (8) (1.5g, 8.5mmol) in dry tetrahydrofuran (3ml) was added and the mixture allowed to warm to room temperature over 3h. After stirring at room temperature for 30h, 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 which was purified by chromatography on silica gel (20% diethyl ether - 80% petroleum ether) to give, (±)-[2-(benzyloxy)ethyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (11)

(1.3g, 4.5mmol, 57%) as a colourless oil, ^{1}H nmr (300MHz, $CDCl_3$) δ 7.35-7.22(5H, m, Ar*H*), 4.56-4.46(3H, m, CH_2Ph and C*H*OR), 3.72-3.53(2H, m, CH_2OBn), 3.66(3H, s, OCH_3), 3.20(1H, m, CH_aH_bC=C), 2.89(1H, qtd, J=1.5, 9, and 18.5Hz, CH_aH_bC=C), 2.21-2.11(1H, m), 1.96-1.61(3H, m), and 1.77(3H, t, J=1.5Hz, C=CCH_3); vmax (neat) 1695 and 1650 cm^{-1}; m/z (EI) 290(M^+), 259, and 91. Found M^+ 290.1514 $C_{17}H_{22}O_4$ requires 290.1519.

Preparation of (±)-(2-hydroxyethyl)-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (12). (±)-[2-(Benzyloxy)ethyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (**11**) (500mg, 1.7mmol) was dissolved in methanol (20ml) containing 10% palladium-on-carbon (50mg), 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 crude (±)-(2-hydroxyethyl)-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (**12**) (342mg, 1.7mmol, 100%) as a colourless oil, ^{1}H nmr (300MHz, $CDCl_3$) δ 4.48(1H, quintet, J=6.5Hz, C*H*OR), 3.77(2H, t, J=6Hz, CH_2OH), 3.63(3H, s, OCH_3), 3.19(1H, m, CH_aH_bC=C), 2.87(1H, qtd, J=1.5, 9, and 18Hz, CH_aH_bC=C), 2.24-2.12(1H, m), 2.06(1H, br.s, O*H*), 1.88-1.60(3H, m), and 1.73(3H, t, J=1.5Hz, CH_3); vmax (neat) 3450, 1710, and 1630cm^{-1}; m/z (EI) 200(M^+), 168, 115, 98, 83, and 71. Found M^+ 200.1033 $C_{10}H_{16}O_4$ requires 200.1050. This material was sufficiently pure for use in subsequent reactions.

Preparation of (±)-2(R)-[1(R)-(methoxycarbonyl)ethyl]-5(S)-(2-hydroxyethyl)tetrahydrofuran (13). Crude 2-(S)-(2-hydroxyethyl)-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (**12**) (342mg, *ca.* 1.7mmol) was dissolved in methanol (25ml), the solution placed in a glass bomb, and the mixture degassed. Fresh 5% rhodium-on-alumina (0.4g) 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 2(R)-[1(R)-(methoxycarbonyl)ethyl]-5(S)-(2-hydroxyethyl)tetrahydrofuran (**13**) (320mg, 1.6mmol, 93%) as a colourless oil. This material appeared to be *ca.* 8:1 mixture of diastereoisomers by ^{1}H nmr. (Major diastereoisomer); ^{1}H nmr (300MHz, $CDCl_3$) δ 4.05-3.88(2H, m, C*H*OCH_2), 3.69(2H, br.t, J=5.5Hz, CH_2OH), 3.64(3H, s, CO_2CH_3), 2.81(1H, br.s, O*H*), 2.48(1H, qd, J=7 and 8Hz, C*H*(Me)CO_2Me), 2.02-1.89(2H, m), 1.77-1.48(4H, m), and 1.07(3H, d, J=7Hz, CHCH_3), vmax (neat) 3400 and 1730cm^{-1}; m/z (EI) 203(M+ H^+), 115, 97, 73, and 71, (CI, NH_3) 220(M+NH_4^+) and 203(M+H^+). Found M+H^+ 203.1272 $C_{10}H_{19}O_4$ requires 203.1284.

Reduction of (±)-(2-benzyloxyethyl)-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (11) with Raney nickel. A slurry of W2 Raney nickel* (*ca.* 0.1g) in methanol was added to a solution of (±)-[2-(Benzyloxy)ethyl]-5-(E)-[1-(methoxycarbonyl)ethylidene] tetrahydrofuran (**11**) (500mg, 1.7mmol) in methanol (20ml) in a steel bomb. The mixture was degassed, placed under an atmosphere of hydrogen pressurised at 80atm, and shaken at 70°C for 50h. After cooling to room temperature the pressure was released, and the mixture filtered through a pad of silica to remove the catalyst. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (diethyl ether) gave (±)-2(R)-[1(R)-(methoxycarbonyl)ethyl]-5(S)-(2-hydroxyethyl)tetrahydrofuran (**13**) (263mg, 1.3mmol, 76%) as a colourless oil. This material appeared to be ca. 4:1 mixture of diastereoisomers by ^{1}H nmr, the major product being identical to the material obtained above.

* Supplied by Aldrich Chemical Co. as a slurry in water, washed with methanol until neutral.

Preparation of (±)-2(R)-[1(R)-(methoxycarbonyl)ethyl]-5(S)-(formylmethyl)tetrahydrofuran (6). A solution of (±)-2(R)-[1(R)-(methoxycarbonyl)ethyl]-5(S)-(2-hydroxyethyl)tetrahydrofuran (13) (250mg, 1.2mmol) in dry dimethylsulphoxide (3ml) was added dropwise to a vigorously stirred solution of pyridine-sulphur trioxide (1.25g, 7.8mmol) and triethylamine (1.1ml, 7.8mmol) in dry dimethylsulphoxide (4ml) at room temperature under argon. The resulting mixture was stirred at room temperature for 3h, water (20ml) added, and the mixture extracted with diethyl ether (3x40ml). The ether extracts were dried over magnesium sulphate and the solvent removed under reduced pressure. Chromatography of the residue on silica gel gave (±)-2(R)-[1(R)-(methoxycarbonyl)ethyl]-5(S)-(formylmethyl)tetrahydrofuran (6) (213mg, 1.1mmol, 86%) as a colourless oil **^{1}H nmr** (300MHz, $CDCl_3$) δ 9.70(1H, t, J=2Hz, C*H*O), 4.26(1H, m, C*H*OR), 3.99(1H, q, J=7Hz, C*H*OR), 3.62(3H, s, CO_2CH_3), 2.62(1H, ddd, J=2, 7, and 16Hz, CH_aH_bCHO), 2.54-2.42(2H, m), 2.14-1.89(2H, m), 1.65-1.44(2H, m), and 1.05(3H, d, J=7Hz, $CHCH_3$); **vmax** (neat) 1740cm^{-1}; **m/z** (NH_3, CI) 218($M+NH_4^+$). Found $M+NH_4^+$ 218.1393 $C_{10}H_{20}NO_4$ requires 218.1394. This material was stored at -10°C under argon.

Preaparation of (±)-methyl homononactate (4b). (±)-2(R)-[1(R)-(Methoxycarbonyl)ethyl]-5(S)-(formylmethyl) tetrahydrofuran (6) (70mg, 0.35mmol) was dissolved in dry dichloromethane (10ml) and the solution cooled to -78°C under argon. Titanium tetrachloride (70µl, 0.35mmol) was added dropwise, the mixture stirred for 10min, then diethyl zinc (1.59ml, 1.1M solution in toluene, 1.75mmol) added. The reaction was stirred at -78°C for 1h, saturated aqueous sodium bicarbonate (10ml) added, and the mixture allowed to warm to room temperature. Extraction with diethyl ether (3x20ml) followed by drying of the organic extracts over magnesium sulphate and removal of the solvent under reduced pressure gave the crude product. Chromatography on silica gel (50% diethyl ether - 50% petroleum ether) gave (±)-methyl 8-*epi* homononactate (5b) (13mg, 0.056mmol, 16%) as a colourless oil **^{1}H nmr** (300MHz, $CDCl_3$) δ 4.05-3.94(2H, m), 3.69-3.64(1H, m), 3.66(3H, s, CO_2CH_3), 3.56(1H, br.s, O*H*), 2.51(1H, dq, J=7 and 8Hz, C*H*CH_3), 2.04-1.92(2H, m), 1.69-1.32(6H, m), 1.09(3H, d, J=7Hz, $CHCH_3$), and 0.89(3H, t, J=7.5Hz, CH_2CH_3); **vmax** (neat) 3540 and 1740cm^{-1}; **m/z** (NH_3, CI) 248($M+NH_3^+$) and 231 ($M+H^+$). Found $M+NH_3^+$ 248.1859, $C_{12}H_{26}NO_4$ requires 248.1863. and (±)-methyl homononactate (4b) (56mg, 0.23mmol, 69%) as a colourless oil, **^{1}H nmr** (300MHz, $CDCl_3$) δ 4.15-4.06(1H, m), 3.98-3.91(1H, m), 3.74-3.66(1H, m), 3.66(3H, s, CO_2CH_3), 2.79(1H, br.s, O*H*), 2.51(1H, dq, J=7 and 8Hz, C*H*CH_3), 2.04-1.90(2H, m), 1.78-1.36(6H, m), 1.09(3H, d, J=7Hz, $CHCH_3$), and 0.90(3H, t, J=7.5Hz, CH_2CH_3); **vmax** (neat) 3540 and 1740cm^{-1}; **m/z** (NH_3, CI) 248($M+NH_3^+$) and 231 ($M+H^+$). Found $M+NH_3^+$ 248.1856, $C_{12}H_{26}NO_4$ requires 248.1863.

Preaparation of (±)-methyl 8-*epi*-homononactate (5b). (±)-2(R)-[1(R)-(Methoxycarbonyl)ethyl]-5(S)-(formylmethyl)tetrahydrofuran (6) (68mg, 0.34mmol) was dissolved in dry dichloromethane (10ml) and the solution cooled to -78°C under argon. Boron trifluoride etherate (84µl, 0.72mmol) was added, and the mixture stirred at -78°C for 10min, then diethyl zinc (1.54ml, 1.1M solution in toluene, 1.7mmol) was added dropwise. The resulting mixture was stirred at -78°C for 6h, quenched with saturated aqueous sodium bicarbonate (5ml) and warmed to room temperature. Extraction with diethyl ether (3x20ml) followed by drying of the organic extracts over magnesium sulphate and removal of the solvent under reduced pressure gave the crude product. Chromatography on silica gel (50% diethyl ether - 50% petroleum ether) gave (±)-methyl 8-*epi* homononactate (5b) (59mg, 0.26mmol, 75%) as a colourless oil and (±)-methyl homononactate (4b) (4mg, 0.017mmol, 5%) as a colourless oil, both products being identical to the previously prepared samples.

REFERENCES

1. M. Dobler, "Ionophores and their Structure", Wiley, New York, 1981, and references therein.

2. W.Keller-Schierlein and H. Gerlach, *Fortschr. Chem. Org. Natursh.*, 1968, **26**, 161.

3. H. Gerlach and H. Wetter, Helv. Chim. Acta, 1974, 57, 2306.

4. J. Gombos, E. Haslinger, H. Zak, and U. Schmidt, *Tetrahedron Lett.*, 1975, 3391; U. Schmidt, J. Gombos, E. Haslinger, and H. Zak, *Chem. Ber.*, 1976, **109**, 2628.

5. P.A. Bartlett, J.D. Meadows, and E. Ottow, *J. Am. Chem. Soc.*, 1984, **106**, 5304.

6. U. Schmidt and J. Werner, *J. Chem. Soc., Chem. Commun.*, 1986, 996; U. Schmidt and J. Werner, *Synthesis*, 1986, 986.

7. a) G. Beck and E. Henseleit, *Chem. Ber.*, 1971, **104**, 21; b) J. Gombos, E. Haslinger, H. Zak, and U. Schmidt, *Montash Chem.*, 1975, **106**, 219; c) H. Zak and U. Schmidt, *Angew. Chem. Int. Ed. Engl.*, 1975, 14, 432; d) M.J. Arco, M.H. Trammell, and J.D. White, *J. Org. Chem.*, 1976, **41**, 2075; e) P.A. Bartlett and K.K. Jernstedt, *Tetrahedron Lett.*, 1980, **21**, 1607; f) K.M. Sun and B. Fraser-Reid, *Can. J. Chem.*, 1980, **58**, 2732; g) R.E. Ireland and J.P. Vevert, *J. Org. Chem.*, 1980, **45**, 4259; h) R.E. Ireland and J.P. Vevert, *Can. J. Chem.*, 1981, **59**, 572; i) A.G.M. Barrett and H.G. Sheth, *J. Chem. Soc., Chem. Commun.*, 1982, 170; j) A.G.M. Barrett and H.G. Sheth, *J. Org. Chem.*, 1983, **48**, 5017; k) W.C. Still, L.J. MacPherson, T. Harada, J.F. Callahan, and A.L. Rheingold, *Tetrahedron*, 1984, **40**, 2275; l) P.C. Bulman Page, J.F. Carefull, L.H. Powell, and I.O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1985, 822; m) S. Batmangherlich and A.H. Davidson, *J. Chem. Soc., Chem. Commun.*, 1985, 1399; n) S.V. Ley, *Chem. Ind.*, 1985, 101; o) A. Warm and P. Vogel, *Tetrahedron Lett.*, 1986, **27**, 5615; p) S.W. Baldwin and J.M. McIver, *J. Org. Chem.*, 1987, **52**, 320; q) B. Lygo and N. O'Connor, *Tetrahedron Lett.*, 1987, **28**, 3597.

8. See accompanying paper.

9. Active samples of 5% Rh/Al_2O_3 were obtained from Fluka agents: Fluorochem Ltd., Glossop, Derbyshire. Old samples (3 yrs) appeared to be no longer effective.

10. Oxidation of optically-pure aldehyde (6) has also been carried out using Swern conditions, see ref. 7h.

11. G. Brussani, S.V. Ley, J.L. Wright, and D.J. Williams, *J. Chem. Soc., Perkin Trans. I*, 1986, 303.

12. Debenzylation is not effected using Rh/Al_2O_3 catalyst, reduction of the aromatic ring being the preferred process.

13. For example, see: M.T. Reetz, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 556; M.T. Reetz and K. Kesseler, *J. Chem. Soc., Chem. Commun.*, 1984, 1079.

14. Intramolecular addition of allyl silanes to β-chiral β-alkoxy has recently been shown to be selective for either isomer depending upon the conditions employed; M.T. Reetz, A. Jung, and C. Bolm, *Tetrahedron*, 1988, **44**, 3889.