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γ-Butyrolactone, an Alternative Source of Chiral Iodo Derivatives.

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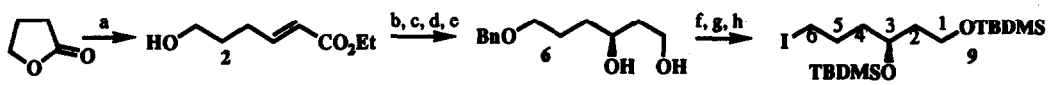
Abstract: An efficient synthesis of (3S) 1,3-di-*tert*-butyldimethylsilyloxy-6-iodohexane, a chiral iodo derivative useful for the preparation of functionalised 1,7-dioxaspiro[5.5]undecanes from γ-butyrolactone is described.

In several total syntheses of the ionophore antibiotic A.23187 and other structural analogues in this series, functionalised 1,7-dioxaspiro[5.5] undecanes were obtained by coupling iodo derivatives A (R' = H or CH_3; R_3 = R_4 = cyclohexylidene or isopropylidene; R_3 = TBDPS, R_4 = TBDMS) with a dithiane[1], a tri-*n*-butylstannyl-dihydropyran[2] or a 2-phenylsulphonyl-tetrahydropyran[3].

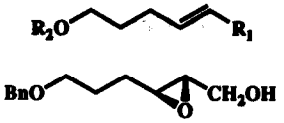
We report here the synthesis of A (R' = H, R_3 = R_4 = TBDMS) from γ-butyrolactone. Takacs *et al.*[4] performed homologation of esters to α,β-unsaturated esters using diisobutylaluminium hydride (DIBAL-H) in the presence of a lithio-trialkylphosphonate. This method applied to γ-butyrolactone afforded the trans ester **2**, the hydroxyl group of which was protected as a benzyl ether. Classical methods using NaH and benzyl bromide are not suitable because of the presence of a carbonyl function. The reaction was therefore performed with Ag_2O and benzyl bromide in DMF[5-7] leading to the ester **3** which was further reduced to allylic alcohol **4** in the presence of DIBAL-H. Sharpless epoxidation of the trans alcohol **4** with L(+) diethyltartrate introduced the chirality. The epoxide was then reduced regiospecifically to diol **6** using dimethoxyethoxyaluminium hydride (Red-Al) in THF at -20°C according to the method of Finan and Kishi.[8]



a) $(EtO)_2P(O)CH_2CO_2Et$, THF, -78°C, *n*BuLi, DIBAL-H (54%); b) Ag_2O, BnBr, DMF, RT, 48 h → **3** (69%); c) DIBAL-H, CH_2Cl_2/hexane, -78°C → **4** (95%); d) $Ti(OiPr)_4$, L(+) diethyl tartrate, CH_2Cl_2, *t*-BuOOH, -23°C (68%); e) Red-Al, THF, -20°C → **6** (85%); f) $CF_3SO_3Si(CH_3)_2t$.Bu, CH_2Cl_2, Et_3N, RT, 4h (91%); g) Na, NH_3 (84%); h) $CH_3P(OC_6H_5)_3I$, HMPA → **9** (80%).

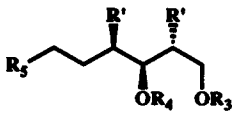
The *tert*-butyldimethylsilyl group was chosen for the protection of the 2 hydroxyl functions of diol **6**. Unlike cyclohexylidene and isopropylidene, this group is stable in subsequent coupling reactions of **9** with dithianes using *n*-butyllithium. It provides a non-volatile derivative in contrast to the acetonide which is volatile, and it is readily removed with *p*.TsOH which is used in the final cyclisation step to give spiroketals.[9]The benzyl protecting group was then removed by aminolysis. Finally, several methods were tested for the conversion of the alcohol to the iodo derivative **9**: N-iodosuccinimide, PPh_3 in CH_2Cl_2 provided **9** in only 41 % yield, the nucleophilic substitution *via* the corresponding mesylate (mesyl chloride, Et_3N, CH_2Cl_2 then KI, acetone) led to

9 in 53 % yield. The best yield (80 %) was obtained using methyl-triphenoxyphosphonium iodide $(C_6H_5O)_3P^+CH_3I^-$ in HMPA according to a method used in the chemistry of nucleosides.[10]



2 : $R_1 = CO_2Et$, $R_2 = H$
3 : $R_1 = CO_2Et$, $R_2 = Bn$
4 : $R_1 = CH_2OH$, $R_2 = Bn$

5



6 : R' = H, $R_3 = R_4 = H$, $R_5 = OBn$
7 : R' = H, $R_3 = R_4 = TBDMS$, $R_5 = OBn$
8 : R' = H, $R_3 = R_4 = TBDMS$, $R_5 = OH$
9 : R' = H, $R_3 = R_4 = TBDMS$, $R_5 = I$
A : R_5 = I, R' = H or CH_3, $R_3 = R_4$ = cyclohexylidene or isopropylidene or : R_3 = TBDPS, R_4 = TBDMS.

This reaction sequence cannot be compared with those affording methylated iodo derivatives[1,2] but involves fewer steps than that yielding the unmethylated iodo compound from benzaldehyde.[3]

References and notes

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(11) Data for 2: $\nu_{C=O}$: 1730, ν_{OH}: 3450 cm^{-1}. ^1H NMR : 1.2 (3H, t, J = 7.5 Hz, CH_3); 1.5-2.5 (4H, m, $2CH_2$); 3.2-3.8 (3H, C_1-H_2, OH); 4.2 (2H, q, J = 7.5, 15 Hz, OCH_2CH_3); 5.8 (1H, d, J = 18 Hz, C_2-H); 6.9 (1H, m, C_3-H). ^{13}C NMR : 14.2 (CH_3); 28.6; 30.9 (C_4, C_5); 60.2; 61.5 (C_6, OCH_2CH_3); 121.6 (C_2); 148.9 (C_3); 166.8 (C_1). Data for 3: $\nu_{C=O}$: 1720 cm^{-1}. ^1H NMR : 1.2 (3H, t, J = 7.5 Hz, CH_3); 1.5-2.5 (4H, 2m, $2CH_2$); 3.5 (2H, t, J = 6 Hz, C_6-H_2); 4.2 (2H, q, J = 6, 13 Hz, OCH_2CH_3); 4.6 (2H, s, $CH_2\phi$); 5.9 (1H, d, J = 17 Hz, C_2-H); 7.0 (1H, m, C_3-H); 7.5 (5H, m, aromatics). ^{13}C NMR : 13.8 (CH_3); 27.8; 78.4 (C_4, C_5); 59.6 (OCH_2CH_3); 68.8 (C_6); 72.4 ($CH_2\phi$); 121.4 (C_3); 127.1; 127.9; 138.2 (aromatics); 148.1 (C_2); 165.9 (C_1). Data for 4 : ν_{OH} : 3420cm^{-1}. ^1H NMR : 1.5-2.2 (4H, 2m, $2CH_2$); 3.1 (1H, s, OH); 3.4 (2H, t, J = 6 Hz, C_6-H_2); 4.0 (2H, m, C_1-H_2); 4.5 (2H, s, $CH_2\phi$); 5.7 (2H, m, C_2-H, C_3-H); 7.5 (5H, m, aromatics). ^{13}C NMR : 28.8; 29.2 (C_4, C_5); 63.4 (C_6); 69.6 (C_1); 72.8 ($CH_2\phi$); 127.6; 128.3; 129.6; 132.0; 148.5 (aromatics). Data for 5 : $[\alpha]_J^{25}$ = -29; ν_{OH} : 3450 cm^{-1}. ^1H NMR : 1.6-1.8 (4H, 2m, $2CH_2$); 2.9-3.0 (2H, m, C_2-H, C_3-H); 3.4-3.8 (5H, m, C_6-H_2, C_1-H_2, OH); 4.6 (2H, s, $CH_2\phi$); 7.3 (5H, m, aromatics). ^{13}C NMR : 26.1; 28.5 (C_4, C_5); 55.8; 58.7; 61.8; 69.6; (C_1, C_2, C_3, C_6); 72.9 ($CH_2\phi$); 127.7; 128.4; 138.4 (aromatics). Data for 6 : $[\alpha]_J^{25}$ = -15; ν_{OH} : 3400 cm^{-1}. ^1H NMR : 1.5-1.8 (6H, m, $3CH_2$); 3.5-4.0 (7H, m, C_1-H_2, C_3-H, C_6-H_2, 2OH); 4.5 (2H, s, $CH_2\phi$); 7.4 (5H, m, aromatics). ^{13}C NMR : 26.2; 35.0; 38.5 (C_2, C_4, C_5); 61.5; 70.6; 71.6; 73.2 (C_1, C_3, C_6, $CH_2\phi$); 127.9; 128.6; 138.3 (aromatics). Data for 7 : $[\alpha]_J^{25}$ = +11; ^1H NMR : 0.1 (12H, s, $2(CH_3)_2Si$); 0.9 (18H, s, 2*t*Bu); 1.5-1.8 (6H, m, $3CH_2$); 2.4 (2H, t, J = 6.7 Hz, C_6-H_2); 3.1 (2H, t, J = 7 Hz, C_1-H_2); 3.7 (1H, m, C_3-H); 4.5 (2H, s, $CH_2\phi$); 7.3 (5H, m, aromatics). ^{13}C NMR : 18.4 (Cquat.*t*Bu); 26.2 (*t*Bu); 26.1; 34.9; 40.9 (C_2, C_4, C_5); 60.9; 69.9; 71.4; 73.1; (C_1, C_3, C_6, $CH_2\phi$); 127.1; 127.9; 128.1 (aromatics). Data for 8 : $[\alpha]_J^{25}$ = +9; ν_{OH} : 3400 cm^{-1}. ^1H NMR : 0.0 (12H, s, $2(CH_3)_2Si$); 0.9 (18H, s, 2*t*Bu); 1.4-1.7 (6H, m, $3CH_2$); 1.8 (1H, s, OH); 3.5-3.7 (4H, m, C_1-H_2, C_6-H_2); 3.9 (1H, m, C_3-H). ^{13}C NMR : -5.0, -4.0 ($(CH_3)_2Si$); 18.3 (Cquat.*t*Bu); 25.9 (*t*Bu); 28.2; 33.7; 39.6 (C_2, C_3, C_5); 59.8 (C_6); 63.2 (C_1); 68.1 (C_4). Data for 9 : $[\alpha]_J^{25}$ = +9 ; ^1H NMR : 0.1 (12H, m, $2(CH_3)_2Si$); 0.9 (18H, s, 2*t*Bu); 1.5-1.7 (4H, 2m, C_2-H_2, C_4-H_2); 1.9 (2H, m, C_5-H_2); 3.2 (2H, t, J = 6.7 Hz, C_6-H_2); 3.6 (2H, t, J = 6.3 Hz, C_1-H_2); 3.8 (1H, m, C_3-H). The protons were assigned from ^1H-^1H COSY correlations. ^{13}C NMR : - 5.1; - 4.3 ($(CH_3)_2Si$); 7.4 (C_6); 18.4 (Cquat.*t*Bu); 26.0 (*t*Bu); 29.3; 38.2; 40.2 (C_2, C_4, C_5); 59.8 (C_1); 68.5 (C_3).

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