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Note

Stereospecific synthesis of chiral caprolactone monomers from D-glucose[☆]

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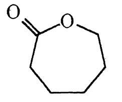
Abstract

The synthesis and characterisation of a novel chiral bicyclic oxacaprolactone is reported. The choice of diisopropylidene-D-glucose as a starting material allowed selective introduction of the synthetic equivalent necessary for the formation of the seven-membered ring of the lactone, i.e., one carbon atom and the carbonyl of the ester which was to become the carbonyl group of the lactone. In order to complete the formation of the seven-membered ring, via intramolecular lactonisation, it was necessary to excise carbon six and to establish a primary alcohol group at C-5. The lactone was fully characterised and available for ring-opening polymerisation. © 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Caprolactone; Diisopropylidene-D-glucose; NMR; Stereospecific synthesis

As part of a wider programme of design and synthesis of wholly synthetic chiral polymers possessing intrinsic main chain chirality and in which the stereochemical properties of the polymeric matrix are closely controlled, we have been interested in synthetic routes to chiral caprolactones from chiral templates derived from carbohydrates. Speciality chiral polymers have found commercial application as chromatographic media for the separation of racemates in high performance liquid chromatography,[1] as drug delivery systems [2–4] and in asymmetric synthesis.[5,6] Early syntheses of polyesters derived from carbohydrates are reported in the literature, e.g., the formation of polyterephthalates obtained by condensation of dichloroterephthalic acid with 1,9:3,6 dianhydrohexitols.[7] Since the late 1970s, some aliphatic polyesters, e.g., poly(ε-caprolactone) are well-known for their low toxicity and their hydrolytic and enzymatic biodegradability,[8] properties which make them especially suitable for medical uses. The ring-opening polymerisation of lactones [9,10] (e.g., unsubstituted ε-caprolactone **1**) has proved very efficient for controlling the molecular characteristics and the end-functionalisation of the derived polyesters.



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Towards the design of chiral membranes with the potential to separate enantiomers, we have focused on monomers which would furnish poly-(etheresters). In particular, we report a facile, stereospecific synthesis of a highly functionalised caprolactone derivative **8**, from D-glucose. The synthetic sequence, starting from the readily available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **2**, is outlined in Scheme 1.

Thus, the reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5 g, 19.2 mmol) with 1.1 equiv of sodium hydride in dried THF (50 mL) at 0 °C over 1.5 h gave the 3-alkoxide which, when treated with ethyl bromoacetate (2 equiv) at reflux over 2.5 h gave the

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[☆] The assignment of the ^{1}H and ^{13}C NMR data was made with the help of ^{1}H–^{13}C correlation experiments for compounds **3**, **4**, **6**, **7** and ^{1}H–^{13}C correlation and COSY experiments for compound **8**.

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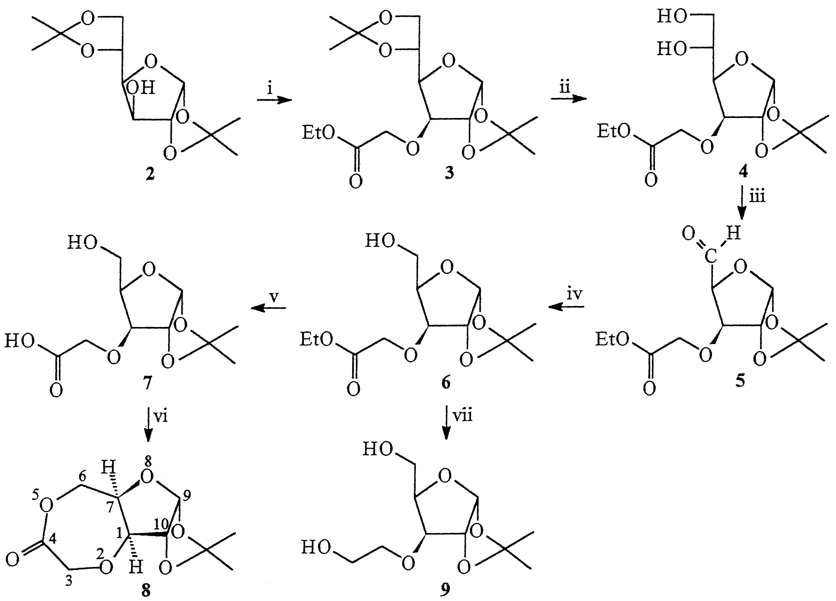

Scheme 1. *Reagents and conditions:* (i) NaH, 0 °C then $BrCH_2COOC_2H_5$, THF, reflux; (ii) AcOH (75% aq), 40 °C; (iii) $NaIO_4$ (1.1 equiv), MeOH, 0 °C; (iv) $NaBH_4$ (1.1 equiv), EtOH, rt; (v) NaOH, reflux then H_3O^+; (vi) *p*-toluene sulphonic acid, toluene, reflux; (vii) $NaBH_4$ (excess), EtOH, rt.

crystalline 3-*O* alkylated ester **3**, in 78% yield, after a single chromatographic purification on silica gel in 4:1 $CHCl_3$–EtOAc (solvent system A), mp 85–86 °C, $[\alpha]_D$ $-6.0°$ (*c* 0.99, $CHCl_3$), R_f value 0.82 (solvent system A). The structure of **3** was confirmed by its IR [e.g., ν(KBr) 1751 cm^{-1} (C=O)], ^1H and ^{13}C NMR spectra ($CDCl_3$) [e.g., the presence of a typical ethoxy group: δ_H (400 MHz) 1.30 (3 H, t, CH_3), 4.23 (2 H, q, CH_2), and full assignment of all other protons; δ_C (100 MHz) 14.2 ($-COO-CH_2-CH_3$), 61.1 ($-COO-CH_2-CH_3$), and full assignment of all other carbons], by the EI mass spectrum [e.g., *m*/*z* 346 [M^+], 331 $[M-CH_3]^+$, 101 (100%, base peak, 5,6-*O*-isopropylidene fragment from h-rupture of the C-4, C-5 bond)]. Anal. Calcd for $C_{16}H_{26}O_8$: C, 55.49; H, 7.57. Found: C, 55.47; H, 7.61.

The following degradation sequence effects a D-*gluco* to D-*xylo* conversion and many examples exist in the literature to carry out this standard procedure. Removal of the 5,6-*O*-isopropylidene group with aqueous acid followed by periodate cleavage of the 5,6-diol to give a 1,4-dialdofuranose could be performed independent of the C-3 substituent. Thus, treatment of **3** (6 g, 17.3 mmol) with 75% aq AcOH (40 mL) at 45 °C for 2 h readily removed the 5,6-*O*-isopropylidene group to afford an almost quantitative yield of the diol **4** as a chromatographically homogeneous pale yellow oil, $[\alpha]_D$ $-58.2°$ (*c* 1.03, $CHCl_3$), R_f value 0.20 (solvent system A). The IR spectrum (neat) had a strong OH signal at 3463 cm^{-1}. The structure of **4** was confirmed by its ^1H and ^{13}C NMR spectra ($CDCl_3$) which showed the presence of only one isopropylidene group [δ_H (400 MHz), 1.32 (3 H, s, CH_3), 1.49 (3 H, s, CH_3); δ_C (100 MHz) 26.3, 26.7 ($2\times CH_3$)]. In addition, the FAB(+) mass spectrum had *m*/*z* 307 (19%, MH^+) and 291 $[M-CH_3]^+$. Anal. Calcd for $C_{13}H_{22}O_8$: C, 50.98; H, 7.24. Found: C, 49.26; H, 7.05.

Oxidative cleavage of the diol **4** (1 g, 3.27 mmol) was readily achieved with sodium metaperiodate (1.1 equiv) in aq MeOH (50%, 25 mL) at 0 °C to give, in near quantitative yield, the D-*xylo*-dialdofuranose **5**, homogeneous on TLC: $[\alpha]_D$ $-37.0°$ (*c* 1.00, $CHCl_3$), R_f value 0.40 (solvent system A), IR ν(neat) 1751 cm^{-1} (C=O, ester), 1740 cm^{-1} (C=O, aldehyde); the FAB(+) mass spectrum had *m*/*z* 275 $[MH]^+$. The aldehyde was unstable on standing at room temperature (rt) and was therefore used immediately for subsequent reactions.

A solution of the aldehyde **5** (1.79 g, 6.54 mmol) in aq EtOH (75% v/v, 50 mL) upon treatment with $NaBH_4$ (1.1 equiv) at rt over 1 h afforded the D-*xylo*-furanose **6** in 74% yield as a chromatographically pure oil, $[\alpha]_D$ $-91.9°$ (*c* 1.07, $CHCl_3$), R_f value 0.45 (solvent system A). The IR spectrum of compound **6** showed the disappearance of the aldehydo carbonyl stretching absorption with retention of the ester group signal [ν(neat) 1735 cm^{-1} (C=O, ester)]. The structure was further confirmed by full assignment of all signals in the ^1H and ^{13}C NMR spectra and by the FAB(+) mass spectrum which had *m*/*z* 553 [$(2M+H)^+$, dimer] and 277 [MH^+]. Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30. Found: C, 50.85; H, 7.19.

Prolonged exposure to excess reducing agent (3 equiv) resulted in reduction of the ester group to afford the diol **9** as an oil in 78%, $[\alpha]_D$ $-51.6°$ (*c* 1.05, $CHCl_3$), R_f value 0.08 (solvent system A). The FAB(+)

mass spectrum had *m*/*z* 235 [MH^+] and 219 [$M - CH_3$]$^+$. Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.28; H, 7.69. Found: C, 49.53; H, 7.26.

The ester **6** (2.69 g, 9.75 mmol) was subsequently hydrolysed with NaOH (2 equiv) in water (30 mL) in 0.5 h reflux to afford, after acidification and extraction with ether, the carboxylic acid **7** as an analytically pure solid in 73% yield, mp 127° C, $[\alpha]_D$ $-48.5°$ (*c* 1.03, C_2D_6SO), R_f value 0.05 (solvent system A). The IR spectrum had ν(KBr) 1704 cm^{-1} (C=O, carboxylic acid). The ^1H and ^{13}C NMR spectra (C_2D_6SO) were consistent with the structure of the hydroxy acid **7**. The FAB(+) mass spectrum had signals at *m*/*z* 249 [MH^+] and *m*/*z* 233 [$M - CH_3$]$^+$. Anal. Calcd for $C_{10}H_{16}O_7$: C, 48.39; H, 6.50. Found: C, 48.39; H, 6.60.

Finally, compound **7** (2.94 g, 11.85 mmol) underwent intramolecular cyclisation by treatment with trace amounts of *p*-toluene sulphonic acid in $C_6H_5CH_3$ (500 mL) at reflux temperature (5 h) above the β face of the sugar to afford the crystalline bicyclic oxacaprolactone **8**, in 73% yield, mp > 200° C dec, $[\alpha]_D$ $-64.8°$ (*c* 1.00, C_2D_6SO), R_f value 0.43 (solvent system A). The IR spectrum showed ν(KBr) 1738 cm^{-1} (C=O lactone) and disappearance of the acid carbonyl and alcohol stretching absorptions. All signals in the ^1H NMR spectrum (400 MHz, C_2D_6SO) were assigned. In particular, the methylene protons at C-3 and C-6 of the seven-membered ring, could be distinguished. The protons at C-3 (non-equivalent due to the proximity of the chiral centre C-1) were two coupled, symmetrical one-proton doublets centred at 4.19 and 4.57 ppm (J_{gem} 14.8 Hz). The non-equivalence of the protons at C-6 further confirmed that the seven-membered ring was formed; H-6 and H-6′ gave rise to two coupled signals: a one-proton doublet centred at 4.76 ppm (J_{gem} 14.1 Hz) was assigned to the pro-S H-6, which has a dihedral angle of 90° with H-7 (in a model of **8** with the furanose ring E_4 or $^3T_4$ and the lactone ring in a chair-like arrangement, the planarity of the lactone unit maintained). A one-proton double doublet centred at 4.41 ppm (J_{gem} 14.1, $J_{6,7}$ 4.3 Hz) was assigned to the pro R H-6. The ^{13}C NMR spectrum (50 MHz, C_2D_6SO) was also in agreement with the structure of the bicyclic lactone. The FAB(+) mass spectrum had *m*/*z* 231 [MH^+]. Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.18; H, 6.13. Found: C, 52.06; H, 6.09.

More details about the experimental procedures and techniques used can be found in Ref. 11.

The entire sequence could be conducted to give multi-gram quantities of the chiral caprolactone **8**, which is a substrate for ring-opening polymerisation.

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