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A short asymmetric synthesis of 4,4-disubstituted-γ-butyrolactones from racemic 2-methylcyclohexanone in multigram scale

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Abstract

A short and efficient asymmetric synthesis of both enantiomers (*R*)-**1a**–**c** and (*S*)-**1a**–**c** has been performed on a large scale and with high stereoselectivities from 2-methylcyclohexanone.

1. Introduction

Stereochemically defined 4,4-disubstituted-γ-butyrolactones have attracted attention because of their importance as chiral building blocks for many biologically active natural products[1] and as flavor[2] and tobacco constituents.[3] In spite of this, the methods reported in the literature for the synthesis of both racemic[4] and chiral 4,4-disubstituted-γ-butyrolactones[5] are seldom adequate in multigram scales.

Some time ago we described[6] the syntheses of racemic butenolides and γ-butyrolactones disubstituted at position 4 by oxidative cleavage of aromatic rings. Herein we report the short and large scale asymmetric syntheses of both enantiomers of 4,4-disubstituted-γ-butyrolactones (*R*)-**1a**–**c** and (*S*)-**1a**–**c** based on the highly stereoselective general method of 'deracemizing alkylation'[7] to introduce the quaternary stereogenic center.

2. Results and discussion

The 2-methylcyclohexanone **2** was directly converted into chiral α,α-disubstituted ketoester (*R*)-**3** in 81% yield and 90% e.e. as previously described in the literature[7e] employing the asymmetric Michael reaction in the presence of (*S*)-(−)-1-phenylethylamine as the chiral auxiliary (see Scheme 1).

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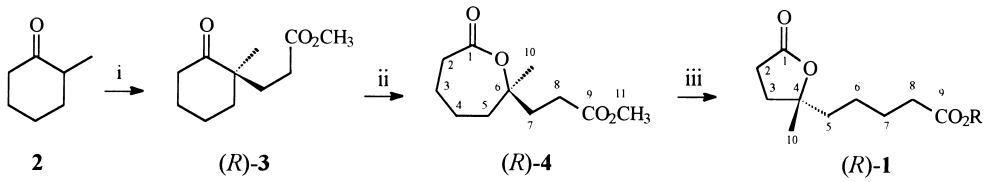

Scheme 1. (i) (*S*)-(−)-1-Phenylethylamine (1.5 equiv.), toluene, cat. TsOH, reflux, 1 h, then methyl acrylate (5.0 equiv.), r.t., 48 h and 10% aqueous HOAc, r.t., 1 h, 81% yield, 90% e.e. (see lit.[7e]); (ii) MCPBA (1.0 equiv.), Li_2CO_3 (0.78 equiv.), CH_2Cl_2, reflux, 6 h, 65% yield, 91% e.e.; (iii) ROH (ca 20 mL/mmol (*R*)-**4**), cat. HCl, reflux, 3 h: for (*R*)-**1a** (R=Me): 70%, 91% e.e., $[\alpha]_D^{25}$ +7.7 (c 2.15; $CHCl_3$); for (*R*)-**1b** (R=Et): 60%; 90% e.e., $[\alpha]_D^{25}$ +7.8 (c 1.03; $CHCl_3$); for (*R*)-**1c** (R=i-Pr): 80%, 91% e.e., $[\alpha]_D^{25}$ +4.4 (c 1.12; $CHCl_3$)

The expansion of the six-membered ring of (*R*)-**3** was achieved by Baeyer–Villiger oxidation[8] upon treatment with MCPBA on a multigram scale. This procedure led stereoselectively to the caprolactone (*R*)-**4** in 65% yield and 90% e.e., whose absolute stereochemistry is proposed based on the complete retention of configuration at the migrating chiral center for this oxidation.[9] Only one peak was observed for (*R*)-**4** from HRGC analysis using an HP-1 column, suggesting that it was obtained in high chemical purity.

The optical purity of (*R*)-**4** was determined from the ^{1}H NMR spectrum at 300 MHz in the presence of chiral Eu(hfc)$_3$. This shift reagent was added in small portions until the decomposition of the singlet at 1.45 ppm due to the hydrogens in C_{10} into two signals, one at 2.51 ppm (for (*R*)-**4**) and the other at 2.43 ppm (for (*S*)-**4**) with a 95:5 relative intensity. These signals were also identified in the spectrum of a racemic sample of **4** in the presence of this chiral shift reagent.

Typical large scale procedure for access to γ-butyrolactones by relactonization was performed by reacting 10 g of (*R*)-**4** with an excess of different alcohols in acidic media leading, after distillation at reduced pressure (10^{-2} mmHg), to (*R*)-**1a**–**c** in good yields and ca 91% e.e. The enantioselectivities of γ-butyrolactones (*R*)-**1a**–**c** were obtained by ^{1}H NMR in the presence of Eu(hfc)$_3$, as described for (*R*)-**4**.

The characteristic bands at 1718 and 1768 cm^{-1} in the IR spectra of (*R*)-**4** and (*R*)-**1**, respectively, as well as the presence of the base peaks at m/z 99 and 43 in the corresponding mass spectra of (*R*)-**1** and (*R*)-**4** were also employed to distinguish between these lactones. In addition, for (*R*)-**4** and for (*R*)-**1** the carbonyls at C_1 and C_9 were differentiated in ^{13}C NMR using the COLOC technique.

The enantiomers (*S*)-**4** and (*S*)-**1a**–**c** were also obtained as pale yellow liquids in identical chemical yields and optical purities from **2** employing (*R*)-(+)-1-phenylethylamine as a chiral auxiliary in the same synthetic protocol described in Scheme 1 above.

The 'deracemizing alkylation' is a well-known procedure[7] for the synthesis of α,α-disubstituted cycloalkanones with excellent optical purities and chemical yields that was recently used in the enantioselective synthesis of alkaloid (+)-vincamine.[10] Since this method has been successfully employed to obtain α,α-dialkylated cyclopentanones[11] and even other chiral cyclic ketones, including those having functionalities either in their rings[7,12] or at the α-position,[13] the original approach to the new chiral 4,4-disubstituted-γ-butyrolactones **1a**–**c** reported in this work by a large scale procedure can be considered as a promising extension of the 'deracemizing alkylation' method.

3. Experimental

3.1. General

(*S*)-(−)- and (*R*)-(+)-1-Phenylethylamine were purchased from Aldrich Chem. Co. HRGC analysis was performed using an HP 5890 series II chromatograph with an HP-1 column (12 m×0.2 mm×0.33

μm). Infrared spectra were recorded with a Perkin–Elmer 1760X spectrophotometer. NMR spectra were recorded on a Bruker AC-300P (300 MHz) spectrometer and COSY, HETCOR and COLOC techniques were obtained from program WIN NMR 1D/ 2D. Mass spectra (MS) were measured on an Autospec VG spectrometer. Specific rotations were measured on a Perkin–Elmer 24B polarimeter.

*3.2. (*R*)-(+)-6-Carbomethoxyethyl-6-methyl-ε-caprolactone **4***

To a suspension of *m*-chloroperbenzoic acid (70% purity, 9.42 g, 43.8 mmol) and lithium carbonate (0.138 g, 1.86 mmol) in dichloromethane (78 mL) was added a solution of ketoester (*R*)-**3** (6.0 g, 30.30 mmol) in dichloromethane (19.5 mL) and the mixture was refluxed for 6 h under an argon atmosphere. The excess peracid was reduced by addition of 10% aqueous sodium sulfite (50 mL) and the mixture was diluted with dichloromethane (150 mL). Phases were separated and the organic layer was washed with 10% aqueous K_2CO_3 (3×100 mL) and brine (3×100 mL) and dried over anhydrous Na_2SO_4. Solvent removal under vacuum was followed by distillation under reduced pressure (10^{-2} mmHg) using a vacuum-jacketed column to give (*R*)-**4** (4.21 g, 65%) as a pale yellow liquid. $[\alpha]_D^{25}$ +2.96 (c 0.9; $CHCl_3$). IR (neat, cm^{-1}): 2941; 2867; 1735; 1718; 1457; 1438; 1353; 1177; 1106; 1092; 1018. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 3.68 (s, H11); 2.69 (ddd, 12.4 Hz, 10.7 Hz, 9.7 Hz, H2); 2.51 (ddd, 16.7 Hz, 13.3 Hz, 7.5 Hz, H8); 2.16 (ddd, 16.7 Hz, 13.3 Hz, 8.0 Hz, H7); 1.94 (ddd, 16.7 Hz, 13.3 Hz, 8.0 Hz, H7); 1.88–1.83 (m, H5 and H4); 1.80–1.76 (m, H3); 1.74–1.60 (m, H3); 1.45 (s, H10). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 174.5 (s, C1); 173.8 (s, C9); 82.0 (s, C6); 51.8 (q, C11); 39.0 (t, C5); 37.1 (t, C2); 37.0 (t, C7); 28.5 (t, C8); 24.6 (q, C10); 23.7 (t, C4); 23.3 (t, C3). MS (70 eV, m/z): 199 (1); 173 (16); 127 (33); 109 (20); 99 (25); 84 (34); 81 (55); 56 (36); 55 (92); 43 (100); 28 (49). Calcd for $C_{11}H_{18}O_4$: 214.2608; found: 214.2606.

*3.3. (*R*)-(+)-4-Carbomethoxybutyl-4-methyl-γ-butyrolactone **1a***

A solution of (*R*)-**4** (10 g, 46.73 mmol) in methanol (1 L) and conc. HCl (3 mL) was refluxed for 3 h and allowed to reach room temperature. The solvent excess was removed under vacuum and the residue was diluted with dichloromethane (500 mL), washed with 5% aqueous $NaHCO_3$ (3×200 mL) and brine (3×200 mL) and dried over anhydrous Na_2SO_4. Solvent removal under vacuum was followed by distillation under reduced pressure (10^{-2} mmHg) using a vacuum-jacketed column to give (*R*)-**1a** (7.0 g, 70%) as a pale yellow liquid. Compounds **1b** and **1c** were prepared in the yields and % e.e. shown in Scheme 1 using the protocol described above. $[\alpha]_D^{25}$ +7.7 (c 2.15; $CHCl_3$). IR (neat, cm^{-1}): 2950; 2870; 1768; 1737; 1461; 1383; 1256; 1198; 1170; 1097. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 3.60 (s, H11); 2.63–2.44 (m, H2); 2.27 (t, 7.4 Hz, H8); 2.08–1.82 (m, H3); 1.66–1.53 (m, H5 and H7); 1.40–1.28 (m, H6); 1.31 (s, H10). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 176.7 (s, C1); 173.8 (s, C9); 86.6 (s, C4); 51.5 (q, C11); 40.5 (t, C5); 33.7 (t, C8); 32.9 (t, C3); 29.0 (t, C2); 25.5 (q, C10); 25.0 (t, C7); 23.3 (t, C6). MS (70 eV, m/z): 199 (2); 99 (100); 71 (12); 55 (16); 43 (39). Calcd for $C_{11}H_{18}O_4$: 214.2608; found: 214.2609.

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