

Synthesis of alkyl α - and β -D-glucopyranoside-based chiral crown ethers and their application as enantioselective phase-transfer catalysts

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Abstract Chiral monoaza-15-crown-5-type lariat ethers annelated to alkyl 4,6-*O*-benzylidene- α - and β -D-glucopyranosides have been synthesized. These macrocycles generated significant asymmetric induction as phase-transfer catalysts in a few two-phase reactions. The catalytic effect of the lariat ethers with methoxy, ethoxy, and *i*-propoxy substituents on C-1 of the sugar unit in both α and β positions was compared. In liquid–liquid two-phase reactions, the nature and position of the substituents did not have much effect. The α -anomers were somewhat more efficient in terms of enantioselectivity than the β forms. In asymmetric Darzens condensations, in the epoxidation of *trans*-chalcone, in the Michael addition of β -nitrostyrene and diethyl acetamidomalonate, and in the reaction of 2-benzylidene-1,3-indandione with diethyl bromomalonate, maximum enantioselectivities of 73, 94, 78, and 72%, respectively, were obtained in presence of glucopyranoside-based lariat ethers as catalysts.

Keywords Chiral crown ether · Asymmetric reaction · Phase-transfer catalysis

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Introduction

One method for catalytic asymmetric synthesis is phase-transfer catalysis using chiral crown ethers as catalysts. Cram et al. [1] published first the asymmetric phase-transfer technique, in which the enantioselectivity was generated by a chiral crown ether catalyst. Phase-transfer catalysis has long been recognized as a versatile methodology in organic syntheses in both industrial and academic laboratories, based on its simple experimental operation and mild reaction conditions applying aqueous media, inexpensive and environmentally benign reagents and solvents, and the possibility of carrying out larger-scale preparations [2, 3]. Chiral phase-transfer catalysis has become an attractive area in the “green” chemical discipline, and many types of chiral catalysts have been developed and applied over the past few decades [4–11]. Crown ethers with carbohydrate moieties form a special group of chiral phase-transfer (PT) catalysts. The basis of our research is the previous finding that crown ethers incorporating a monosaccharide moiety in the ring can generate asymmetric induction as chiral phase-transfer (PT) catalysts in certain reactions. Building carbohydrates into the macrocycles has several advantages: (1) the starting carbohydrates are in most cases inexpensive, and easily available as commercial products; (2) they are biocompatible and available in enantiomerically pure form with known chiroptical properties; (3) the basic chemistry of these compounds is well explored; (4) carbohydrates have functionalities, which can be used to establish secondary binding sites, as well as catalytic sites. This may be achieved most easily by building the macrocycle around the “chiral ethylene glycol” unit of the carbohydrate, making use of the hydroxyl groups on the vicinal C-atoms [12]. The sugar-based crown ethers may be built from various monosaccharides, thus macrocycles of different chirality are available. In the 1970s, Stoddart et al. carried out pioneering work in preparing and investigating macrocycles built up from monosaccharides. At that time, they had not yet studied the catalytic effects of these compounds in phase-transfer reactions [13, 14].

Over the past three decades, many macrocycles containing one or more monosaccharide units (D-glucose, D-galactose, D-mannose, D- or L-xylose, etc.) have been synthesized. A few of them proved to be efficient phase-transfer catalysts in certain asymmetric reactions [15].

Previously, chiral monoaza-15-crown-5-type lariat ethers incorporating an α -D-glucopyranoside unit were synthesized in our laboratory. The attachment of a side-arm (linear or branched heteroatom-containing Pendant arms) with potential cation coordination sites to the rings leads to complexing agents, called “lasso” or lariat ethers, which have unique binding properties towards a variety of guest cations. These new chiral lariat ethers were found to be efficient catalysts in a few asymmetric reactions [16–21].

Through study of the structure–activity relationships of lariat ethers, it was found that molecules with monoaza-15-crown-5 moiety were optimal as enantioselective catalysts, where the *N* atom of the ring bears a hydroxypropyl (**1**) or methoxypropyl side arm. To benefit from its preferential catalytic properties, this structural motif was retained in the synthesis of the new glucose-based macrocycles. The chiral

scaffold of lariat ether **1** is the methyl 4,6-*O*- α -D-glucopyranoside unit. We wished to study the effect of the nature of the substituent (methyl, ethyl, isopropyl groups) on C-1 of the glucopyranoside unit, and the impact of the position (α or β anomers) on the catalytic activity, and especially on the enantioselectivity.

We report herein synthesis of a new monoaza-15-crown-5 type macrocycle family (**15a–e**) annelated to alkyl α - and β -D-glucopyranosides and the catalytic activity of the new species in a few liquid–liquid and solid–liquid phase-transfer reactions. The results obtained with lariat ether **1** were published earlier [18, 19]. In this study, the earlier results are mentioned for comparison.

Experimental

General procedures

Melting points were measured on Stuart SMP10 apparatus and are uncorrected. Specific rotation was determined using a PerkinElmer 341LC polarimeter at 22 °C. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX 500 and Bruker DRX 300 instrument in CDCl₃ or in CD₃OD, using Me₄Si as internal standard. Mass spectra were obtained on a Q-TOF Premier mass spectrometer (Waters Corporation, 34 Maple St, Milford, MA, USA) in positive electrospray ionization mode. Preparative thin-layer and analytical chromatography was carried out using silica gel (60 PF-254, Merck), while column chromatography was performed on 70–230 mesh silica gel (Merck). Enantioselectivity was determined by specific rotation and by chiral high-performance liquid chromatography (HPLC) measurement (Chiralpak AD-H or AS-H columns, Jasco PU-1580 pump, UV-1575 detector, hexane/2-propanol mixture).

Ethyl-4,6-*O*-benzylidene- β -D-glucopyranoside (12d) Ethyl β -D-glucopyranoside (**10**) (3.53 g, 17 mmol) was dissolved in dry dimethylformamide (DMF) (35 ml), then benzaldehyde dimethylacetal (3.60 ml, 24 mmol) and *p*TsOH (0.53 g, 2.8 mmol) were added. The mixture was stirred at 80 °C for 24 h under Ar. After cooling to rt, Et₃N was added, then the volatiles were removed by vacuum distillation. The residue was dissolved in CHCl₃, and the solution was washed with saturated NaHCO₃ solution (3 $\times$ 50 ml). The organic layer was dried, filtered then concentrated in vacuum. The crude product was crystallized from 2-propanol.

Yield: 69% (3.45 g); white solid; M.p. 82–84 °C; $[\alpha]_{\text{D}}^{22} = -60.5$ ($c = 1$, CHCl₃); ¹H NMR (500 MHz, CDCl₃/TMS), δ [ppm]: 7.52–7.48 (m, 2H, ArH), 7.40–7.36 (m, 3H, ArH), 5.54 (s, 1H, PhCH), 4.41 (d, $J = 8$ Hz, 1H, H-1), 4.35 (dd, $J = 10$ Hz, 5 Hz, 1H, H-6a), 4.00–3.94 (m, 1H, H-5), 3.85–3.83 (m, 2H, CH₂CH₃), 3.69–3.62 (m, 1H, H-6), 3.56 (t, $J = 10$ Hz, 1H, H-3), 3.52–3.44 (m, 2H, H-4, H-2), 2.79 (br s, 1H, OH), 2.64 (br s, 1H, OH), 1.28 (t, $J = 7$ Hz, 3H, CH₂CH₃).

Isopropyl-4,6-*O*-benzylidene- β -D-glucopyranoside (12e) Isopropyl β -D-glucopyranoside (**11**) (4.20 g, 19 mmol) was dissolved in dry DMF (40 ml), then benzaldehyde dimethylacetal (4.0 ml, 27 mmol) and *p*TsOH (0.59 g, 3 mmol) were

added. The mixture was stirred at 80 °C for 24 h under Ar. After cooling to rt, Et₃N was added, then the volatiles were removed by vacuum distillation. The residue was dissolved in CHCl₃, and the solution was washed with saturated NaHCO₃ solution (3 × 50 ml). The organic layer was dried, filtered then concentrated in vacuum. The crude product was crystallized from 2-propanol.

Yield: 68% (4.0 g); white solid; M.p. 70–71 °C; $[\alpha]_{\text{D}}^{22} = -56.5$ ($c = 1$, CHCl₃); ¹H NMR (500 MHz, CDCl₃/TMS), δ [ppm]: 7.51–7.45 (m, 2H, ArH); 7.39–7.35 (m, 3H, ArH); 5.53 (s, 1H, ArCH); 4.47 (d, $J = 8$ Hz, 1H, H-1); 4.34 (dd, $J = 10$ Hz, 5 Hz, 1H, H-6a); 4.05–4.00 (m, 1H, H-5); 3.85–3.79 (m, 2H, CHCH₃, H-6b); 3.57 (t, $J = 10$ Hz, 1H, H-3); 3.50–3.44 (m, 2H, H-4, H-2); 2.78 (br s, 1H, OH); 2.55 (br s, 1H, OH); 1.27 (d, $J = 7$ Hz, 3H, CHCH₃); 1.23 (d, $J = 7$ Hz, 3H, CHCH₃).

Synthesis of D-glucopyranoside-based lariat ethers

General procedure for preparation of bischloro compounds (13a–e)

To a mechanically stirred solution of the corresponding alkyl 4,6-*O*-benzylidene-D-glucopyranoside in bis(2-chloroethyl)ether, 50% aq. NaOH solution and equimolar amount of Bu₄NHSO₄ was added. The reaction mixture was stirred vigorously for 9 h at room temperature, then poured into a mixture of CH₂Cl₂ and water. The phases were separated, and the aqueous layer was extracted with CH₂Cl₂ three times. The combined organic layers were washed with water, dried and concentrated in vacuum. Excess bis(2-chloroethyl)ether was removed by vacuum distillation, and the crude product was purified by column chromatography.

Ethyl-4,6-*O*-benzylidene-2,3-bis-*O*-[(2-chloroethoxy)-ethyl]- α -D-glucopyranoside (13a) Ethyl-4,6-*O*-benzylidene- α -D-glucopyranoside (**12a**) (6.84 g, 23.1 mmol), bis(2-chloroethyl)ether (75.9 ml, 646.8 mmol), 50% aq. NaOH solution (75.9 ml), Bu₄NHSO₄ (7.83 g, 23.1 mmol). Column chromatography: silica gel, CHCl₃ as eluent. Yield: 94% (11.09 g), pale yellow oil. $[\alpha]_{\text{D}}^{22} = +18.8$ ($c = 1$, CHCl₃); ¹H NMR (500 MHz, CDCl₃/TMS), δ [ppm]: 7.49 (dd, $J = 7.7$ Hz, 2 Hz, 2H, ArH), 7.40–7.32 (m, 3H, ArH), 5.53 (s, 1H, PhCH), 4.98 (d, $J = 3.8$ Hz, 1H, H-1), 4.26 (dd, $J = 10.1$ Hz, 4.8 Hz, 1H, H-6a), 3.98 (ddd, $J = 11.1$ Hz, 5.6 Hz, 3.6 Hz, 1H, H-5), 3.96–3.51 (m, 21H, H-6b, H-4, H-3, OCH₂CH₃, 2 × OCH₂CH₂O, 2 × OCH₂CH₂Cl, 2 × CH₂Cl), 3.46 (dd, $J = 9.4$ Hz, 3.8 Hz, 1H, H-2), 1.27 (t, $J = 7$ Hz, 3H, CH₂CH₃).

Isopropyl-4,6-*O*-benzylidene-2,3-bis-*O*-[(2-chloroethoxy)-ethyl]- α -D-glucopyranoside (13b) Isopropyl-4,6-*O*-benzylidene- α -D-glucopyranoside (**12b**) (2.76 g, 8.9 mmol), bis(2-chloroethyl)ether (29.2 ml, 249.2 mmol), 50% aq. NaOH solution (29.2 ml), Bu₄NHSO₄ (3.02 g, 8.9 mmol). Column chromatography: silica gel, CHCl₃ as eluent. Yield: 86% (4.01 g), pale-yellow oil; $[\alpha]_{\text{D}}^{22} = +52.6$ ($c = 1$, CHCl₃); ¹H NMR (500 MHz, CDCl₃/TMS), δ [ppm]: 7.51 (dd, $J = 7.6$ Hz, 2 Hz, 2H, ArH), 7.42–7.35 (m, 3H, ArH), 5.55 (s, 1H, PhCH), 5.07 (d, $J = 3.9$ Hz, 1H, H-1), 4.27 (dd, $J = 10.2$ Hz, 4.9 Hz, 1H, H-6a), 4.01 (ddd, $J = 11.2$ Hz, 5.7 Hz,

3.6 Hz, 1H, H-5), 3.95–3.50 (m, 20H, H-6b, H-4, H-3, OCHCH_3 , $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{Cl}$, $2 \times \text{CH}_2\text{Cl}$), 3.49 (dd, $J = 9.3$ Hz, 3.9 Hz, 1H, H-2), 1.28 (d, $J = 6.1$ Hz, 3H, CHCH_3), 1.23 (d, $J = 6.1$ Hz, 3H, CHCH_3).

Methyl-4,6-*O*-benzylidene-2,3-bis-*O*-(2-chloroethoxy)-ethyl]- β -D-glucopyranoside (13c) Methyl-4,6-*O*-benzylidene- β -D-glucopyranoside (12c) (19.90 g, 71 mmol), bis(2-chloroethyl)ether (135 ml, 1.1 mol), 50% aq. NaOH solution (135 ml), Bu_4NHSO_4 (17.77 g, 52 mmol). Column chromatography: silica gel, CHCl_3 as eluent. Yield: 38% (13.19 g); pale-yellow oil; $[\alpha]_{\text{D}}^{22} = -39.8$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz, CDCl_3/TMS), δ [ppm]: 7.51–7.44 (m, 2H, ArH), 7.41–7.32 (m, 3H, ArH), 5.52 (s, 1H, PhCH), 4.37 (d, $J = 7.7$ Hz, 1H, H-1), 4.34 (dd, $J = 10.1$ Hz, 5.1 Hz, 1H, H-6a), 4.02–3.84 (m, 4H, H-6b, H-5, $\text{OCH}_2\text{CH}_2\text{O}$), 3.80–3.48 (m, 15H, H-3, $\text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{Cl}$, $2 \times \text{CH}_2\text{Cl}$), 3.55 (s, 3H, OCH_3), 3.36 (td, $J = 9.4$ Hz, 4.9 Hz, 1H, H-4), 3.22 (t, $J = 7.7$ Hz, 1H, H-2).

Ethyl-4,6-*O*-benzylidene-2,3-bis-*O*-(2-chloroethoxy)-ethyl]- β -D-glucopyranoside (13d) Ethyl-4,6-*O*-benzylidene- β -D-glucopyranoside (12d) (2.96 g, 10.0 mmol), bis(2-chloroethyl)ether (32.9 ml, 280.0 mmol), 50% aq. NaOH solution (32.9 ml), Bu_4NHSO_4 (3.39 g, 10.0 mmol). Column chromatography: silica gel, $\text{CHCl}_3:\text{CH}_3\text{OH}$ 100:1 as eluent. Yield: 75% (3.82 g); yellow oil; $[\alpha]_{\text{D}}^{22} = -37.0$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.49–7.46 (m, 2H, ArH), 7.39–7.34 (m, 3H, ArH), 5.52 (s, 1H, PhCH), 4.44 (d, $J = 7.7$ Hz, 1H, H-1), 4.32 (dd, $J = 10.5$ Hz, 5 Hz, 1H, H-6a), 4.02 (ddd, $J = 11$ Hz, 5.6 Hz, 4 Hz, 1H, H-5), 3.98–3.87 (m, 4H, H-6b, H-3, CH_2CH_3), 3.78–3.51 (m, 16H, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{Cl}$, $2 \times \text{CH}_2\text{Cl}$), 3.36 (ddd, $J = 10$ Hz, 8.7 Hz, 4.9 Hz, 1H, H-4), 3.23 (t, $J = 8$ Hz, 1H, H-2), 1.26 (t, $J = 7.1$ Hz, 3H, CH_2CH_3).

Isopropyl-4,6-*O*-benzylidene-2,3-bis-*O*-(2-chloroethoxy)-ethyl]- β -D-glucopyranoside (13e) Isopropyl-4,6-*O*-benzylidene- β -D-glucopyranoside (12e) (3.33 g, 10.7 mmol), bis(2-chloroethyl)ether (35.3 ml, 300.4 mmol), 50% aq. NaOH solution (35.3 ml), Bu_4NHSO_4 (3.64 g, 10.7 mmol). Column chromatography: silica gel, $\text{CHCl}_3:\text{CH}_3\text{OH}$ 100:1 as eluent. Yield: 76% (4.24 g); yellow oil; $[\alpha]_{\text{D}}^{22} = -24.5$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.50–7.46 (m, 2H, ArH), 7.39–7.34 (m, 3H, ArH), 5.51 (s, 1H, PhCH), 4.49 (d, $J = 7.8$ Hz, 1H, H-1), 4.31 (dd, $J = 10.5$ Hz, 5 Hz, 1H, H-6a), 4.05–3.85 (m, 5H, H-6b, H-5, CHCH_3 , $\text{OCH}_2\text{CH}_2\text{O}$), 3.80–3.50 (m, 16H, H-4, $\text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{Cl}$, $2 \times \text{CH}_2\text{Cl}$), 3.35 (td, $J = 9.5$ Hz, 5 Hz, 1H, H-4), 3.21 (t, $J = 8$ Hz, 1H, H-2), 1.25 (d, $J = 7$ Hz, 3H, CHCH_3), 1.22 (d, $J = 7$ Hz, 3H, CHCH_3).

General procedure for preparation of bisiodo podands (14a–e)

To solution of bischloro compound in dry acetone, NaI was added, and the solution was stirred at reflux temperature for 40 h. The mixture was filtered, and the filtrate

was concentrated under reduced pressure. The residue was dissolved in CHCl_3 , washed with water three times, and the aqueous phase extracted with CHCl_3 . The combined organic layer was dried and concentrated in vacuum.

Ethyl-4,6-*O*-benzylidene-2,3-bis-*O*-[(2-iodoethoxy)-ethyl]- α -D-glucopyranoside (14a) Bischloro compound **13a** (8.75 g, 17.2 mmol), dry acetone (125 ml), NaI (10.32 g, 68.8 mmol). Yield: 97% (11.50 g); yellow oil; $[\alpha]_{\text{D}}^{22} = +29.4$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.50–7.45 (m, 2H, ArH), 7.39–7.34 (m, 3H, ArH), 5.54 (s, 1H, PhCH), 4.99 (d, $J = 3.8$ Hz, 1H, H-1), 4.26 (dd, $J = 10.2$ Hz, 4.8 Hz, 1H, H-6a), 4.00–3.52 (m, 18H, H-6b, H-5, H-4, H-3, CH_2CH_3 , $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{I}$), 3.50 (dd, $J = 9.3$ Hz, 3.8 Hz, 1H, H-2), 3.26 (t, $J = 6.8$ Hz, 2H, CH_2I), 3.16 (t, $J = 7$ Hz, 2H, CH_2I), 1.28 (t, $J = 7.1$ Hz, 3H, CH_2CH_3).

Isopropyl-4,6-*O*-benzylidene-2,3-bis-*O*-[(2-iodoethoxy)-ethyl]- α -D-glucopyranoside (14b) Bischloro podand **13b** (3.71 g, 7.1 mmol), dry acetone (42 ml), NaI (4.26 g, 28.4 mmol). Yield: 99% (5.01 g); yellow oil; $[\alpha]_{\text{D}}^{22} = +36.4$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.50 (d, $J = 7.7$ Hz, 2H, ArH), 7.40–7.33 (m, 3H, ArH), 5.54 (s, 1H, PhCH), 5.06 (d, $J = 3.8$ Hz, 1H, H-1), 4.25 (dd, $J = 10.2$ Hz, 4.9 Hz, 1H, H-6a), 3.99 (ddd, $J = 11.1$ Hz, 5.8 Hz, 3.6 Hz, 1H, H-5), 3.95–3.86 (m, 4H, H-6b, H-3, $\text{OCH}_2\text{CH}_2\text{O}$), 3.84–3.59 (m, 11H, CHCH_3 , $\text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{I}$), 3.54 (t, $J = 9.4$ Hz, 1H, H-4), 3.47 (dd, $J = 9.3$ Hz, 3.9 Hz, 1H, H-2), 3.26 (t, $J = 6.8$ Hz, 2H, CH_2I), 3.17 (t, $J = 7$ Hz, 2H, CH_2I), 1.26 (t, $J = 6.3$ Hz, 3H, CHCH_3), 1.21 (t, $J = 6.1$ Hz, 3H, CHCH_3).

Methyl-4,6-*O*-benzylidene-2,3-bis-*O*-[(2-iodoethoxy)-ethyl]- β -D-glucopyranoside (14c) Bischloro compound **13c** (13.00 g, 26.3 mmol), dry acetone (260 ml) and NaI (18.19 g, 121 mmol). Yield: 92% (16.35 g); yellow oil; $[\alpha]_{\text{D}}^{22} = -28.6$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz, CDCl_3/TMS), δ [ppm]: 7.52–7.44 (m, 2H, ArH), 7.41–7.33 (m, 3H, ArH), 5.53 (s, 1H, PhCH), 4.35 (d, $J = 8$ Hz, 1H, H-1), 4.34 (dd, $J = 10.6$ Hz, 5.5 Hz, 1H, H-6a), 4.03–3.84 (m, 4H, H-6b, H-5, $\text{OCH}_2\text{CH}_2\text{O}$), 3.81–3.50 (m, 11H, H-3, $\text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{I}$), 3.56 (s, 3H, OCH_3), 3.37 (td, $J = 9.4$ Hz, 5 Hz, 1H, H-4), 3.22 (t, $J = 6.9$ Hz, 2H, CH_2I), 3.22 (t, $J = 7.1$ Hz, 1H, H-2), 3.18 (t, $J = 7$ Hz, 2H, CH_2I).

Ethyl-4,6-*O*-benzylidene-2,3-bis-*O*-[(2-iodoethoxy)-ethyl]- β -D-glucopyranoside (14d) Bischloro compound **13d** (3.82 g, 7.2 mmol), dry acetone (45 ml) and NaI (4.5 g, 30.0 mmol). 86% (4.39 g); yellow oil; $[\alpha]_{\text{D}}^{22} = -22.2$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.51–7.46 (m, 2H, ArH), 7.40–7.33 (m, 3H, ArH), 5.53 (s, 1H, PhCH), 4.44 (d, $J = 7.7$ Hz, 1H, H-1), 4.32 (dd, $J = 10.5$ Hz, 5 Hz, 1H, H-6a), 4.01 (ddd, $J = 10.7$ Hz, 5.8 Hz, 4.1 Hz, 1H, H-5), 3.98–3.87 (m, 4H, H-6b, H-3, CH_2CH_3), 3.80–3.73 (m, 4H, $2 \times \text{OCH}_2\text{CH}_2\text{O}$), 3.71–3.61 (m, 6H, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $\text{OCH}_2\text{CH}_2\text{I}$), 3.60–3.51 (m, 2H, $\text{OCH}_2\text{CH}_2\text{I}$), 3.36 (td, $J = 9.4$ Hz, 4.9 Hz, 1H, H-4), 3.27 (t, $J = 7$ Hz, 2H, CH_2I), 3.23 (t,

$J = 8.1$ Hz, 1H, H-2), 3.18 (t, $J = 6.9$ Hz, 2H, CH_2I), 1.27 (t, $J = 6.1$ Hz, 3H, CH_2CH_3).

Isopropyl-4,6-*O*-benzylidene-2,3-bis-*O*-[(2-iodoethoxy)-ethyl]- β -D-glucopyranoside (14e) Bischloro compound **13e**, (4.22 g, 8.1 mmol), dry acetone (50 ml) and NaI (4.86 g, 32.4 mmol). Yield: 90% (5.15 g); yellow oil; $[\alpha]_{\text{D}}^{22} = -22.2$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.48 (dd, $J = 7.6$ Hz, 1.9 Hz, 2H, ArH), 7.40–7.33 (m, 3H, ArH), 5.52 (s, 1H, PhCH), 4.49 (d, $J = 7.8$ Hz, 1H, H-1), 4.31 (dd, $J = 10.5$ Hz, 5 Hz, 1H, H-6a), 4.05–3.85 (m, 5H, H-5, H-6b, H-3, $\text{OCH}_2\text{CH}_2\text{O}$), 3.79–3.73 (m, 3H, CHCH_3 , $\text{OCH}_2\text{CH}_2\text{O}$), 3.71–3.61 (m, 6H, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $\text{OCH}_2\text{CH}_2\text{I}$), 3.60–3.50 (m, 2H, $\text{OCH}_2\text{CH}_2\text{I}$), 3.35 (td, $J = 9.6$ Hz, 4.9 Hz, 1H, H-4), 3.26 (t, $J = 7$ Hz, 2H, CH_2I), 3.21 (t, $J = 8.2$ Hz, 1H, H-2), 3.17 (t, $J = 7.2$ Hz, 2H, CH_2I), 1.25 (d, $J = 6.2$ Hz, 3H, CHCH_3), 1.23 (d, $J = 6.1$ Hz, 3H, CHCH_3).

General procedure for preparation of lariat ethers (15a–e)

To corresponding bisiodo compound in dry acetonitrile, Na_2CO_3 and 3-amino-propan-1-ol (or 3-methoxypropylamine) was added under argon atmosphere, and the mixture was refluxed for 40 h. The mixture was filtered and concentrated in vacuum. The residue was dissolved in CHCl_3 , washed with water, and the aqueous phase extracted with CHCl_3 . The combined organic layers were dried and concentrated under reduced pressure. Purification by column chromatography (Al_2O_3 or silica gel) was performed to obtain pure lariat ethers.

Ethyl-4,6-*O*-benzylidene-2,3-dideoxy- α -D-glucopyranosido-[2,3*h*]-*N*-(3-hydroxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (15a) Bisiodo compound **14a** (9.04 g, 13.1 mmol), dry acetonitrile (216 ml), Na_2CO_3 (8.33 g, 78.6 mmol), 3-aminopropan-1-ol (0.98 g, 13.1 mmol). Yield: 90% (5.97 g), yellow syrup; $[\alpha]_{\text{D}}^{22} = +29.9$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.48–7.45 (m, 2H, ArH), 7.38–7.32 (m, 3H, ArH), 5.53 (s, 1H, PhCH), 4.95 (d, $J = 3.8$ Hz, 1H, H-1), 4.25 (dd, $J = 10.1$ Hz, 4.8 Hz, 1H, H-6a), 4.00–3.90 (m, 2H, H-5, H-6b), 3.83–3.63 (m, 18H, H-4, H-3, CH_2CH_3 , $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{N}$, CH_2OH), 3.48 (dd, $J = 9.3$ Hz, 3.8 Hz, 1H, H-2), 2.80–2.62 (m, 6H, $3 \times \text{NCH}_2$), 1.67 (p, $J = 5.5$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{OH}$), 1.26 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). (The OH proton did not appear in the spectrum) ^{13}C NMR (125 MHz, CDCl_3/TMS), δ [ppm]: 137.47, 128.89, 128.21, 126.02, 101.23, 96.99, 82.38, 79.75, 78.00, 72.52, 70.44, 70.16, 69.89, 69.19, 69.11, 64.08, 63.57, 62.28, 56.78, 54.69, 54.46, 28.47, 15.04. EI-MS, m/z : 512.6 $[\text{M} + \text{H}]^+$; 534.6 $[\text{M} + \text{Na}]^+$.

Isopropyl-4,6-*O*-benzylidene-2,3-dideoxy- α -D-glucopyranosido-[2,3*h*]-*N*-(3-hydroxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (15b) Bisiodo compound **14b** (4.72 g, 6.7 mmol), dry acetonitrile (110 ml), Na_2CO_3 (4.26 g, 40.2 mmol), 3-aminopropan-1-ol (0.51 ml, 6.7 mmol). Yield: 94% (3.32 g); yellow oil; $[\alpha]_{\text{D}}^{22} = +32.2$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.49–7.46 (m, 2H, ArH), 7.39–7.33 (m, 3H, ArH), 5.53 (s, 1H, PhCH), 5.03 (d,

$J = 3.8$ Hz, 1H, H-1), 4.24 (dd, $J = 10.2$ Hz, 4.9 Hz, 1H, H-6a), 4.00–3.85 (m, 4H, H-6b, H-5, $\text{OCH}_2\text{CH}_2\text{O}$), 3.93–3.63 (m, 15H, CHCH_3 , H-4, H-3, $\text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{N}$, CH_2OH), 3.47 (dd, $J = 9.3$ Hz, 3.8 Hz, 1H, H-2), 2.81–2.64 (m, 6H, $3 \times \text{NCH}_2$), 1.67 (p, $J = 5.5$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{OH}$), 1.26 (d, $J = 6.3$ Hz, 3H, CHCH_3); 1.18 (d, $J = 6.1$ Hz, 3H, CHCH_3). (The OH proton did not appear in the spectrum) ^{13}C NMR (125 MHz, CDCl_3/TMS), δ [ppm]: 137.50, 128.87, 128.21, 126.01, 101.18, 95.53, 82.50, 79.68, 77.86, 72.52, 70.47, 70.09, 69.96, 69.83, 69.12, 64.01, 62.30, 56.83, 54.69, 54.51, 28.48, 23.33, 21.45. EI-MS, m/z : 525.6 $[\text{M} + \text{H}]^+$; 547.6 $[\text{M} + \text{Na}]^+$.

Methyl-4,6-*O*-benzylidene-2,3-dideoxy- β -D-glucopyranosido-[2,3*h*]-*N*-(3-hydroxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (15c) Bisiido podand **14c** (6.00 g, 8.9 mmol), acetonitrile (150 ml), Na_2CO_3 (6.27 g, 59 mmol), 3-aminopropan-1-ol (0.68 ml, 8.9 mmol). Yield: 86% (3.79 g); brownish-yellow syrup; $[\alpha]_{\text{D}}^{22} = -39.3$ ($c = 1$, CHCl_3); ^1H NMR (500 MHz, CDCl_3/TMS), δ [ppm]: 7.50–7.43 (m, 2H, ArH), 7.39–7.32 (m, 3H, ArH), 5.52 (s, 1H, PhCH), 4.35 (d, $J = 7.8$ Hz, 1H, H-1), 4.33 (dd, $J = 10.4$ Hz, 5.1 Hz, 1H, H-6a), 4.01–3.88 (m, 4H, H-6b, H-5, $\text{OCH}_2\text{CH}_2\text{O}$), 3.82–3.50 (m, 13H, H-3, $\text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{N}$, CH_2OH), 3.54 (s, 3H, OCH_3), 3.36 (td, $J = 9.5$ Hz, 5.2 Hz, 1H, H-4), 3.21 (t, $J = 8$ Hz, 1H, H-2), 2.87–2.79 (m, 2H, NCH_2), 2.75–2.65 (m, 4H, $2 \times \text{NCH}_2$), 1.75–1.60 (m, 2H, $\text{CH}_2\text{CH}_2\text{OH}$). (The OH proton did not appear in the spectrum) ^{13}C NMR (125 MHz, CDCl_3/TMS), δ [ppm]: 137.40, 128.88, 128.17, 126.05, 103.91, 101.02, 81.83, 81.69, 80.91, 72.31, 70.32, 70.27, 68.77, 68.69, 65.91, 65.93, 64.03, 56.50, 54.33, 54.25, 28.44. EI-MS, m/z : 498.6 $[\text{M} + \text{H}]^+$; 520.6 $[\text{M} + \text{Na}]^+$.

Ethyl-4,6-*O*-benzylidene-2,3-dideoxy- β -D-glucopyranosido-[2,3*h*]-*N*-(3-hydroxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (15d) Bisiido podand **14d** (4.35 g, 6.3 mmol), acetonitrile (100 ml), Na_2CO_3 (4.10 g, 37.8 mmol), 3-aminopropan-1-ol (0.48 ml, 6.3 mmol). Yield: 53% (1.71 g); white amorphous solid; $[\alpha]_{\text{D}}^{22} = -48.0$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz, CDCl_3/TMS), δ [ppm]: 7.50–7.42 (m, 2H, ArH), 7.40–7.32 (m, 3H, ArH), 5.51 (s, 1H, PhCH), 4.44 (d, $J = 7.7$ Hz, 1H, H-1); 4.31 (dd, $J = 10.5$ Hz, 5 Hz, 1H, H-6a), 4.03–3.87 (m, 6H, H-6b, H-5, CH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{O}$), 3.85–3.50 (m, 15H, H-3, $\text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{N}$, CH_2OH), 3.36 (td, $J = 9.8$ Hz, 4.9 Hz, 1H, H-4), 3.21 (t, $J = 7.9$ Hz, 1H, H-2), 2.90–2.77 (m, 2H, NCH_2), 2.76–2.62 (m, 4H, $2 \times \text{NCH}_2$), 1.77–1.60 (m, 2H, $\text{CH}_2\text{CH}_2\text{OH}$), 1.24 (t, $J = 7$ Hz, 3H, CH_2CH_3). (The OH proton did not appear in the spectrum) ^{13}C NMR (75 MHz, CDCl_3/TMS), δ [ppm]: 137.39, 128.92, 128.22, 126.01, 103.97, 101.10, 81.90, 81.72, 80.97, 72.25, 70.34, 70.26, 68.82, 68.70, 65.95, 65.89, 64.02, 56.45, 54.26, 54.21, 28.40, 15.28. EI-MS, m/z : 512.6 $[\text{M} + \text{H}]^+$; 534.6 $[\text{M} + \text{Na}]^+$.

Isopropyl-4,6-*O*-benzylidene-2,3-dideoxy- β -D-glucopyranosido-[2,3*h*]-*N*-(3-hydroxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (15e) Bisiido podand **14e** (5.00 g, 7.0 mmol), acetonitrile (120 ml), Na_2CO_3 (4.45 g, 42.0 mmol), 3-aminopropan-1-ol (0.54 ml, 7.0 mmol). Yield: 60% (2.21 g); yellow oil;

$[\alpha]_D^{22} = -37.8$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz, CDCl_3/TMS), δ [ppm]: 7.50–7.42 (m, 2H, ArH), 7.40–7.32 (m, 3H, ArH), 5.51 (s, 1H, PhCH), 4.49 (d, $J = 7.8$ Hz, 1H, H-1), 4.30 (dd, $J = 10.5$ Hz, 5 Hz, 1H, H-6a), 4.03–3.88 (m, 5H, H-6b, H-5, CHCH_3 , $\text{OCH}_2\text{CH}_2\text{O}$), 3.85–3.53 (m, 13H, H-3, $\text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{N}$, CH_2OH), 3.35 (td, $J = 9.7$ Hz, 4.9 Hz, 1H, H-4), 3.18 (t, $J = 8$ Hz, 1H, H-2), 2.91–2.79 (m, 2H, NCH_2), 2.76–2.64 (m, 4H, $2 \times \text{NCH}_2$), 1.76–1.58 (m, 2H, $\text{CH}_2\text{CH}_2\text{OH}$), 1.24 (d, $J = 6.2$ Hz, 3H, CHCH_3), 1.19 (d, $J = 6.1$ Hz, 3H, CHCH_3). (The OH proton did not appear in the spectrum) ^{13}C NMR (75 MHz, CDCl_3/TMS), δ [ppm]: 137.41, 128.90, 128.22, 126.01, 102.71, 101.06, 81.85, 81.69, 81.08, 72.81, 72.24, 70.33, 70.21, 68.86, 68.66, 65.91, 64.03, 56.45, 54.21, 54.14, 28.36, 23.54, 22.10. EI-MS, m/z : 525.6 $[\text{M} + \text{H}]^+$; 547.6 $[\text{M} + \text{Na}]^+$.

Ethyl-4,6-O-benzylidene-2,3-dideoxy- α -D-glucopyranosido-[2,3*h*]-N-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (15a') Bisiodo podand **14a** (2.05 g, 3.0 mmol), acetonitrile (55 ml), Na_2CO_3 (1.97 g, 18.6 mmol), 3-methoxypropylamine (0.28 ml, 3.0 mmol). Yield: 59% (0.95 g); yellowish-brown oil; $[\alpha]_D^{22} = +50.2$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz, CDCl_3/TMS), δ [ppm]: 7.50–7.43 (m, 2H, ArH), 7.40–7.33 (m, 3H, ArH), 5.53 (s, 1H, PhCH), 4.97 (d, $J = 3.7$ Hz, 1H, H-1), 4.26 (dd, $J = 9.9$ Hz, 4.6 Hz, 1H, H-6a), 4.01–3.34 (m, 21H, H-6b, H-5, H-4, H-3, H-2, CH_2CH_3 , $2 \times \text{OCH}_2\text{CH}_2\text{O}$, $2 \times \text{OCH}_2\text{CH}_2\text{N}$, CH_2OCH_3), 3.33 (s, 3H, OCH_3), 3.10–2.51 (m, 6H, $3 \times \text{NCH}_2$), 1.92–1.65 (m, 2H, $\text{CH}_2\text{CH}_2\text{OCH}_3$), 1.26 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, CDCl_3/TMS), δ [ppm]: 137.44, 128.83, 128.26, 126.05, 101.18, 96.94, 82.35, 79.70, 78.03, 72.47, 71.11, 70.42, 70.19, 69.94, 69.12, 69.06, 63.55, 62.29, 58.33, 56.75, 54.66, 54.42, 28.41, 15.07. EI-MS, m/z : 526.6 $[\text{M} + \text{H}]^+$; 548.6 $[\text{M} + \text{Na}]^+$.

Asymmetric syntheses

Preparation of (2*R*,3*S*)-phenyl(3-phenyloxiran-2-yl)methanone (18) via Darzens condensation α -Chloroacetophenone (0.15 g, 1 mmol) and benzaldehyde (0.15 ml, 1.5 mmol) and crown catalyst **15a–e** (15 mol%) were dissolved in toluene (3 ml), 30% aq. NaOH solution (1 ml) was added, and the mixture was stirred at room temperature. The reaction was monitored by TLC (hexane–ethyl-acetate 10:1). After completion, the reaction mixture was diluted with toluene (7 ml) and water (3 ml), and the phases were separated. The organic layer was washed with 10% aq. HCl solution (3×10 ml), dried (Na_2CO_3 and Na_2SO_4), filtered and concentrated in vacuum. The crude product was purified by preparative TLC (hexane–ethyl-acetate 10:1). Yield: 92% (0.21 g); yellowish-white powder; M.p. 64–66 °C; $[\alpha]_D^{22} = -153.2$ ($c = 1$, CH_2Cl_2); 71% ee (based on specific rotation comparison [28]). ^1H NMR (CDCl_3 , 500 MHz), δ [ppm]: 7.97–7.94 (m, 2H, ArH), 7.60–7.56 (m, 1H, ArH), 7.46–7.44 (m, 2H, ArH), 7.38–7.32 (m, 5H), 4.26 (d, $J = 1.9$ Hz, 1H, COCH), 4.05 (d, $J = 1.9$ Hz, 1H, ArCH); ^{13}C NMR (75 MHz, CDCl_3), δ [ppm]: 193.06, 135.48, 133.97, 129.04, 128.86, 128.76, 128.33, 125.78, 61.00, 59.34. ESI-MS: m/z 225.1 $[\text{M} + \text{H}]^+$.

Preparation of (2*R*,3*S*)-phenyl(3-phenyloxiran-2-yl)methanone (18) via epoxidation of *trans*-chalcone *Trans*-chalcone (0.25 g, 1.2 mmol) and crown catalyst **15a–e** (15 mol%) were dissolved in toluene (3 ml), then 60% aq. *tert*-butylhydroperoxide solution (0.5 ml) and 20% aq. NaOH solution (1 ml) were added. The mixture was stirred at room temperature. The reaction was monitored by TLC (hexane–ethyl-acetate 10:1). After completion, the mixture was diluted with toluene (7 ml) and water (3 ml), and the phases were separated. The organic layer was washed with 10% aq. HCl solution (3 × 10 ml), dried (Na₂CO₃ and Na₂SO₄), filtered and concentrated in vacuum. The crude product was purified by preparative TLC (hexane–ethyl-acetate 10:1).

Yield: 96% (0.26 g); yellowish-white powder; M.p. 64–66 °C; $[\alpha]_{\text{D}}^{22} = -195.4$ ($c = 1$, CH₂Cl₂); 94% ee (based on specific rotation comparison [28]). ¹H NMR (CDCl₃, 500 MHz), δ [ppm]: 7.97–7.94 (m, 2H, ArH), 7.60–7.56 (m, 1H, ArH), 7.46–7.44 (m, 2H, ArH), 7.38–7.32 (m, 5H), 4.26 (d, $J = 1.9$ Hz, 1H, COCH), 4.05 (d, $J = 1.9$ Hz, 1H, ArCH); ¹³C NMR (75 MHz, CDCl₃), δ [ppm]: 193.06, 135.48, 133.97, 129.04, 128.86, 128.76, 128.33, 125.78, 61.00, 59.34. ESI-MS: m/z 225.1 [M + H]⁺.

General procedure for Michael addition of malonates and MIRC reactions

The appropriate malonate (1.5 mmol), unsaturated compound (1.0 mmol), and crown catalyst **15a–e** (15 mol%) were dissolved in a mixture of dry diethyl ether and dry tetrahydrofuran (THF) (4: 1). After a short period of stirring, anhydrous Na₂CO₃ (0.22 g, 2 mmol) was added and the mixture was stirred at room temperature. The reaction was monitored by TLC (hexane–ethyl-acetate 4:1). After completion, the mixture was concentrated under reduced pressure and the residue was dissolved in CH₂Cl₂ and filtered. The filtrate was washed with 10% aq. HCl solution (3 × 10 ml), dried (Na₂CO₃ and Na₂SO₄), filtered, and concentrated in vacuum. The crude product was purified by preparative TLC (hexane–ethyl-acetate 10:1).

Diethyl-2-acetamido-2-(2-nitro-1-phenylethyl)malonate (22) Yield: 67% (0.25 g); white powder; M.p. 135–136 °C; $[\alpha]_{\text{D}}^{22} = -33.7$ ($c = 1$, CHCl₃); 78% ee; major enantiomer $t_r = 8.5$ min, minor enantiomer $t_r = 11.1$ min (Chiralpak AS-H column, 85/15 hexane/2-propanol, 0.8 ml/min, 20 °C) (Fig. 1).

¹H NMR (CDCl₃, 500 MHz), δ [ppm]: 7.31–7.28 (m, 3H, ArH), 7.22–7.18 (m, 2H, ArH), 6.89 (br s, 1H, NH), 5.51 (dd, $J = 20$ Hz, 10.5 Hz, 1H, CH₂NO₂), 4.73–4.66 (m, 2H, CH₂NO₂, PhCH), 4.34–4.23 (m, 2H, OCH₂), 4.20–4.13 (m, 1H, OCH₂), 4.08–4.01 (m, 1H, OCH₂), 2.12 (s, 3H, CH₃CONH), 1.27 (t, $J = 7$ Hz, 3H, CH₂CH₃), 1.25 (t, $J = 7$ Hz, 3H, CH₂CH₃). ¹³C NMR (75 MHz, CDCl₃), δ [ppm]: 170.10, 166.43, 165.71, 133.78, 128.75, 128.70, 128.69, 76.83, 67.21, 63.56, 62.75, 48.30, 22.97, 13.84, 13.76. ESI-MS: m/z 367.1 [M + H]⁺.

Diethyl-1',3'-dioxo-3-phenyl-1'3'-dihydrospiro[cyclopropane-1,2'-indene]-2,2-dicarboxylate (25) Yield: 67% (0.27 g); yellow oil; $[\alpha]_{\text{D}}^{22} = -69.2$ ($c = 1$, CHCl₃); ee 72%; major enantiomer $t_r = 7.5$ min, minor enantiomer $t_r = 5.7$ min (Chiralpak AD-H column, 80/20 hexane/2-propanol, 2 ml/min, 20 °C) (Fig. 2).

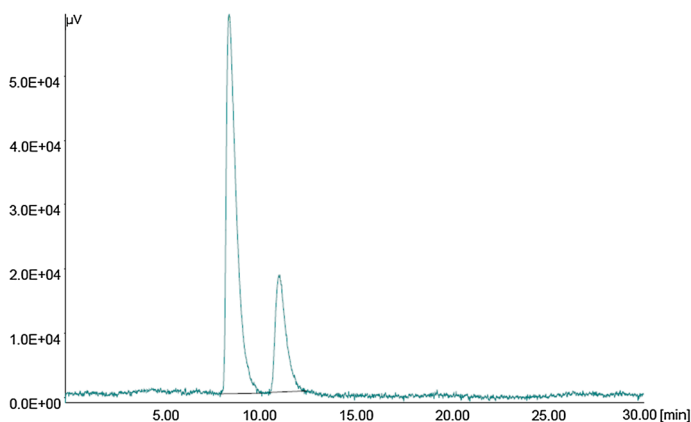


Fig. 1 Determination of optical purity of compound **22** by chiral HPLC

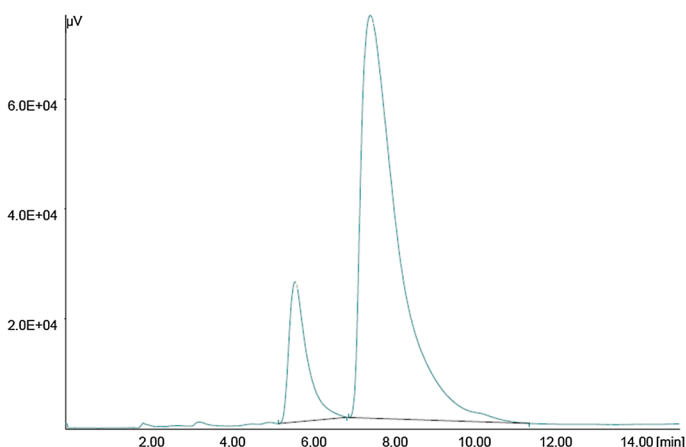


Fig. 2 Determination of optical purity of compound **25** by chiral HPLC

^1H NMR (300 MHz, CDCl_3), δ (ppm): 8.04–7.93 (m, 2H, ArH), 7.88–7.81 (m, 2H, ArH), 7.35–7.25 (m, 5H, ArH), 4.40–4.25 (m, 2H, OCH_2), 4.25–4.15 (m, 2H, OCH_2), 4.16 (s, 1H, PhCH), 1.31 (t, $J = 7.2$ Hz, 3H, CH_3), 1.18 (t, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (75 MHz, CDCl_3), δ (ppm): 194.69, 191.41, 164.37, 162.53, 143.10, 141.24, 135.58, 135.25, 130.17, 127.86, 123.18, 62.89, 62.39, 51.74, 45.23, 42.35, 13.98, 13.71. ESI-MS: m/z 393.1 $[\text{M} + \text{H}]^+$.

Results and discussion

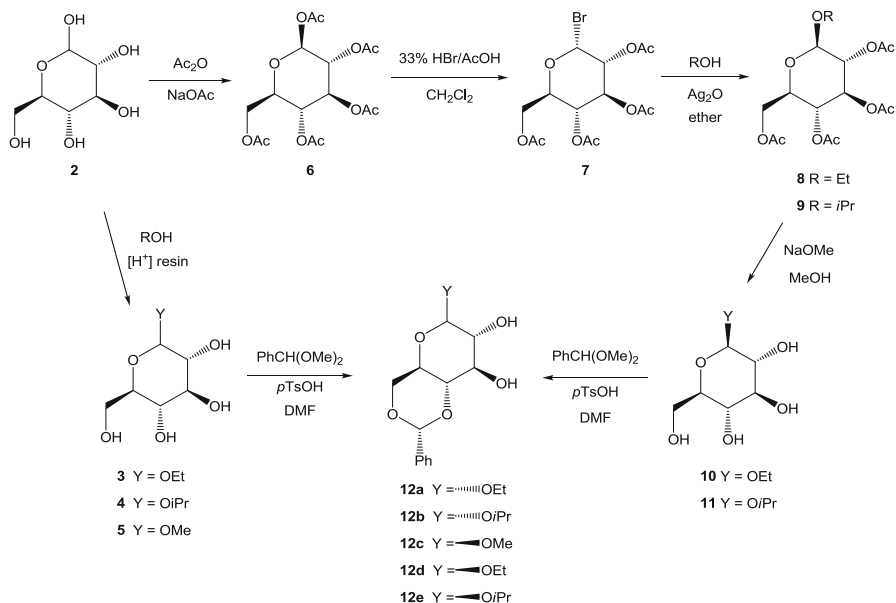
Synthesis of D-glucopyranoside-based crown ethers

Synthesis of methyl α -glucopyranoside-based lariat ether **1** was described earlier [22]. In this study, the macrocycles containing ethyl and isopropyl substituents

instead of the methyl group in series α (**15a**, **a'**, **b**) were prepared. The starting alkyl 4,6-*O*-benzylidene- α -D-glucopyranosides were prepared in a somewhat different way as described in literature. D-Glucose and excess of corresponding alcohol (methanol, ethanol, 2-propanol) was stirred at boiling point in presence of ion-exchange resin to furnish the products (**3**–**5**) as anomeric mixtures. The alkyl glucosides **3**–**5** were converted to benzylidene derivatives (**12a**–**e**) by reaction with benzaldehyde dimethylacetal in presence of *p*TsOH as catalyst. The ethyl 4,6-*O*-benzylidene- α -D-glucopyranoside (**12a**) [23], the α -isopropyl derivative (**12b**) [24], and the β -methyl derivative (**12c**) [25] were isolated by repeated crystallization of solid crude mixtures (Scheme 1).

The first four steps of the synthesis of sugar derivatives with β -ethyl and β -isopropyl group were carried out according to literature methods (Scheme 1). D-Glucose (**2**) was acetylated with acetic anhydride in presence of NaOAc [26]. The resulting β -pentaacetyl compound **6** was then brominated using dry HBr in glacial acetic acid to afford intermediate **7** formed by inversion [27]. Acetobromoglucose **7** was reacted with ethanol and 2-propanol using Ag_2O as base to give derivatives **8** and **9** by inversion according to the Koenigs–Knorr glycosylation protocol [28, 29]. Glucose derivatives **8** and **9** were deacetylated by the method of Zemplén applying NaOMe in methanol [30, 31]. Finally, intermediates **10** and **11** were converted to benzylidene derivatives **12d** and **12e** by reaction with benzaldehyde dimethylacetal in presence of *p*TsOH as catalyst. These compounds have so far been known only as anomeric mixture in literature [32].

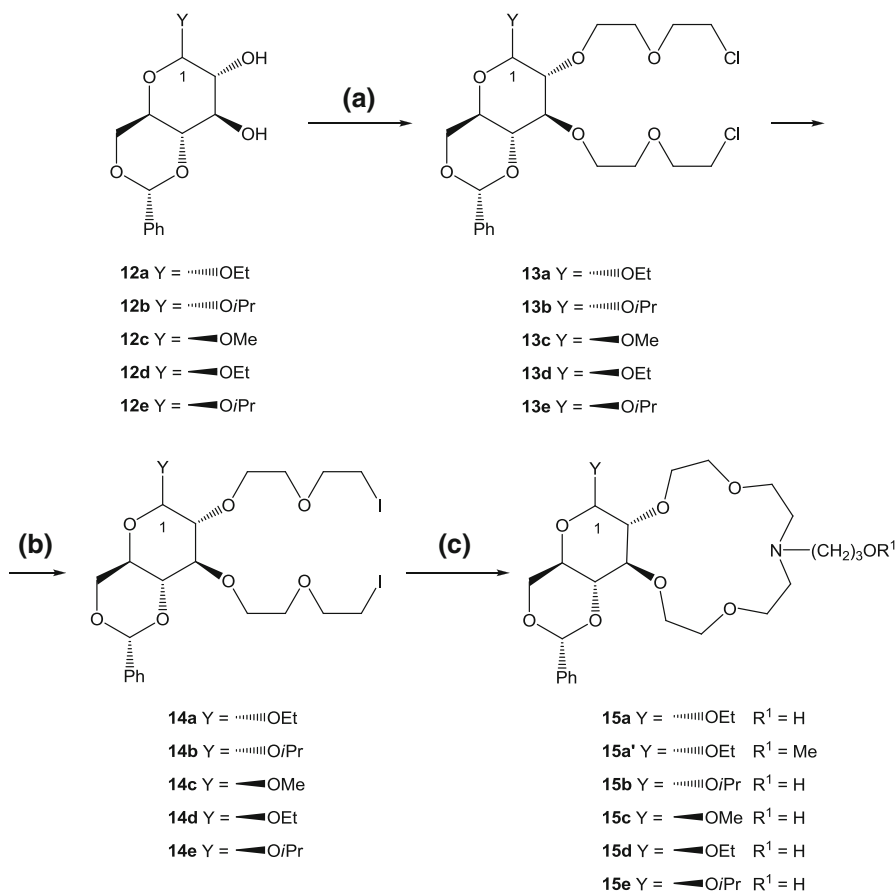
Annulation of the crown ring in positions 2 and 3 of the alkyl α - and β -benzylidene acetals (**12a**–**e**) was performed in three steps, as described earlier



Scheme 1 Synthesis of alkyl 4,6-*O*-benzylidene- α - and β -D-glucopyranosides

(Scheme 2) [22]. The vicinal hydroxyl groups of the sugar derivatives were alkylated with bis(2-chloroethyl)ether in presence of tetrabutylammonium hydrogensulfate (Bu_4NHSO_4) as catalyst and 50% aq. NaOH in a liquid–liquid two-phase system to give intermediates **13a–e**. The bis(2-chloroethyl)ether was not only the reagent, but also the solvent. The corresponding bischloro podands **13a–e** were obtained in yields of 38–94% after column chromatography.

Exchange of chlorine to iodine in the intermediates was accomplished by reaction with NaI in boiling acetone to afford bisiodo derivatives **14a–e** in high yields (86–99%). These compounds were then cyclized with two kinds of primary amines, such as 3-aminopropanol or 3-methoxypropylamine, using the high-dilution technique in boiling acetonitrile, in presence of anhydrous Na_2CO_3 to afford azacrown ethers **15a–e**, which were purified by column chromatography. The yield of lariat ethers **15a–e** lay in the range of 53–94% (Scheme 2).



Scheme 2 Synthesis of glucose-based crown ethers; Reagents and conditions: **a** $(\text{ClCH}_2\text{CH}_2)_2\text{O}$, 50% aq. NaOH, Bu_4NHSO_4 , rt; **b** NaI, acetone, reflux; **c** $\text{H}_2\text{N}-(\text{CH}_2)_3-\text{OH}$ or $\text{H}_2\text{N}-(\text{CH}_2)_3-\text{OMe}$, anhydrous Na_2CO_3 , CH_3CN , reflux

Asymmetric syntheses

The catalytic efficiency of the new glucopyranoside-based lariat ethers (**15a–e**) was investigated in asymmetric liquid–liquid and solid–liquid two-phase reactions to test their ability to induce enantioselectivity. Comparison of the results promoted understanding of the structure–activity relationship. In most cases, 15 mol% catalyst was used in the phase-transfer reactions. After the usual work-up procedure, the products were purified by preparative TLC. The asymmetric induction was expressed in term of the enantiomeric excess (ee), determined either by measuring the specific rotation of the products and comparing it with data for the pure enantiomer obtained from literature, or performing chiral HPLC analysis.

Darzens condensation

Darzens condensation is a powerful method to form epoxides with a new carbon–carbon bond. Epoxyketones have significant relevance as intermediates in syntheses of biologically active compounds, thus these reactions have to be performed in a stereoselective way. Different methods have been applied to achieve this goal. Herein, we discuss Darzens condensation between α -chloroacetophenone (**16**) and benzaldehyde (**17**) in a liquid–liquid two-phase (toluene–water) system using 30% aq. NaOH as base [22]. Two new stereogenic centers are established in this reaction, so theoretically four stereoisomers could be formed. However, due to steric hindrance, the reaction showed > 99% diastereoselectivity in favor of the *trans* product. Complete conversion was observed within 1 h in all cases. The results are summarized in Table 1.

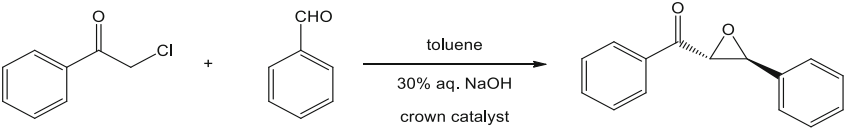
As seen from Table 1, when using catalysts **1**, **15a**, **b** belonging to series α , epoxyketone **18** was obtained in excellent yields of 92–94% and enantioselectivities of 71–73%. Change in the C-1 substituents had practically no effect on the enantioselectivity. When the side-arm was changed from hydroxypropyl to methoxypropyl, a dramatic decrease in enantioselectivity was observed: the ee of 73% induced by crown **15a** decreased to 15% in presence of catalyst **15a'**. In presence of lariat ethers belonging to series β with OMe, OEt, and OiPr substituents (**15c–e**), epoxyketone **18** was prepared in good yields (87–89%) and moderate ee values (62–66%) (Table 2, entries 5–7). The nature of the C-1 substituents had no effect in this instance. In all cases, the (2*R*,3*S*) antipode of **18** was formed.

It can be concluded that the lariat ethers with α -C-1 substituents are somewhat more efficient in terms of asymmetric induction than the analogues belonging to the series β . The small, but significant, differences between the effects of the anomers are related to the impact of steric factors on the asymmetric induction.

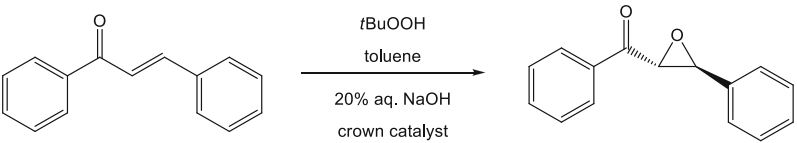
Epoxidation of *trans*-chalcone

Another convenient method for preparation of chiral epoxyketone **18** is epoxidation of *trans*-chalcone (**19**). The reaction was carried out in toluene–20% aq. NaOH liquid–liquid two-phase system, using *tert*-butylhydroperoxide as oxidant [17]. Similarly to the Darzens condensation, the reaction showed >99%

Table 1 Asymmetric Darzens condensation of α -chloroacetophenone (**16**) and benzaldehyde (**17**) using D-glucose-based lariat ethers

					
	16	17		18	
Entry	Catalyst	R	R ¹	Yield of 18 (%) ^a	ee (%) ^b
1	1	α -OMe	H	92	71 ^c
2	15a	α -OEt	H	94	73
3	15b	α -OiPr	H	94	70
4	15a'	α -OEt	Me	78	15
5	15c	β -OMe	H	87	62
6	15d	β -OEt	H	89	66
7	15e	β -OiPr	H	85	63

^aAfter isolation by preparative TLC^bDetermined by specific rotation^cLit: 22**Table 2** Asymmetric epoxidation of *trans*-chalcone (**19**)

					
	19			18	
Entry	Catalyst	R	R ¹	Yield of 18 (%) ^a	ee (%) ^b
1	1	α -OMe	H	82	94 ^c
2	15a	α -OEt	H	96	94
3	15b	α -OiPr	H	93	93
4	15a'	α -OEt	Me	85	21
5	15c	β -OMe	H	87	84
6	15d	β -OEt	H	93	78
7	15e	β -OiPr	H	86	73

^aAfter isolation by preparative TLC^bDetermined by specific rotation^cLit: 17

diastereoselectivity for the *trans* isomer. The reaction time was 1 h in all cases. The results are summarized in Table 2.

It can be seen from Table 2 that application of lariat ethers **1**, **15a**, **b** with α -OMe, OEt, and OiPr substituents allowed isolation of epoxyketone **18** in good yields of 82–96% and in ee values of 93–94% (Table 2, entries 1–3). In presence of OMe-, OEt-, and OiPr-substituted lariat ethers belonging to anomer series β (**15c**, **d**, **e**), the oxiran product **18** was obtained again in good yields (82–93%) and in ee values of 84, 78, and 73%, respectively. The slight, but significant, decrease in the ee values is in accord with the increase in the size of the C-1 substituent.

It can also be seen that the crown ethers belonging to series α generated somewhat higher asymmetric induction than those in the β series. When the side-arm was changed from hydroxypropyl to methoxypropyl, a dramatic decrease in the enantioselectivity was observed: the enantioselectivity of 94% generated by lariat ether **15a** decreased to 21% in presence of catalyst **15a'**. During all epoxidations, the (2*R*,3*S*)-**18** product was formed.

Asymmetric Michael additions

Michael addition provides an effective way to establish a new carbon–carbon bond. In these reactions, an electron-deficient olefin derivative is reacted with a CH-acidic compound. It is a new trend to develop new catalysts for asymmetric Michael additions.

β -Nitrostyrene (**20**) and diethyl acetamidomalonate (**21**) were reacted in a liquid–solid two-phase system employing the starting materials and 15 mol% crown ether in 1:4 mixture of THF–diethyl ether as organic phase, and 2 equivalents of anhydrous Na₂CO₃ as solid phase at ambient temperature [19]. After reaction times of 1–5 h, product **22** was obtained by preparative TLC, and the enantiomeric purity was measured by chiral HPLC. The results are given in Table 3.

From Table 3 it can be seen that, in presence of methyl-, ethyl-, and isopropyl-containing catalysts belonging to the α anomer series (**1**, **15a**, **b**), adduct **22** could be isolated in yields of 67–74% and in ee values of 94, 78 and 69%. Here again, increase in the size of the substituent resulted in a decrease in the enantioselectivities. Using the β -series of the anomers involving catalysts **15c**, **d**, **e**, the yields of product **22** lay in the range of 67–75% and the ee values were somewhat lower (70, 68, and 66%, respectively).

Change in the C-1 substituents in series α caused a more significant difference in the enantioselectivity (69–94%), than in series β (66–70%). Again, the methyl derivatives allowed the highest ee values (Table 2, entries 1, 5). The negative effect of the change of the hydroxypropyl side-arm (as in **15a**) to methoxypropyl substituent (as in **15a'**), was again observed, as the ee value of 78% decreased to 27%.

Asymmetric Michael-initiated ring closure (MIRC) reaction

The MIRC reaction is a convenient alternative to create cyclopropane moieties, which could act as important building blocks for more complex molecules. MIRC

Table 3 Asymmetric Michael addition of diethyl acetamidomalonate (**21**) to β -nitrostyrene (**20**) using glucose-based crown ether catalysts

	20	21		22	
Entry	Catalyst	R	R ¹	Yield of 22 (%) ^a	ee (%) ^b
1	1	α -OMe	H	70	94 ^c
2	15a	α -OEt	H	67	78
3	15b	α -OiPr	H	74	69
4	15a'	α -OEt	Me	74	27
5	15c	β -OMe	H	67	70
6	15d	β -OEt	H	71	68
7	15e	β -OiPr	H	75	66

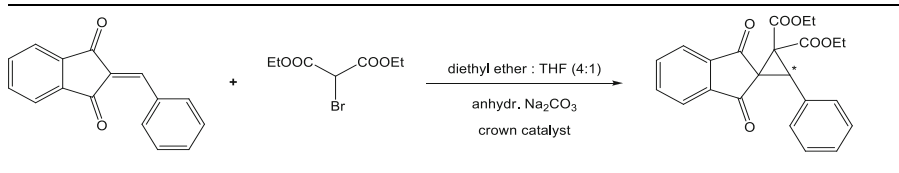
^aAfter isolation by preparative TLC^bDetermined by specific rotation^cLit: 19

reactions have several advantages (such as reaction simplicity and use of environmentally friendly solvents and reagents) over other reactions for cyclopropane formation (e.g., organometallic reactions, or reactions involving diazo compounds). Lattanzi et al. published the asymmetric phase-transfer-catalyzed cyclopropanation of dimethyl bromomalonate with 2-arylidene-1,3-indandiones in presence of cinchona alkaloids and α,α -diarylprolinols as organocatalysts using K_2CO_3 as base [33].

In our experiments, 2-benzylidene-1,3-indandione (**23**) was reacted with diethyl bromomalonate (**24**) in a solid–liquid two-phase system at room temperature. The reaction conditions were similar to those in the previous reaction. The reactions were stopped after 168 h, however, no full conversion could be observed within this period of time. The results are listed in Table 4.

Table 4 shows that the cyclopropanation reactions performed in presence of α -OMe-, α -OEt-, and α -OiPr-substituted lariat ether catalysts (**1**, **15a**, **b**) were characterized by medium yields of 54–62% and ee values of 68, 70, and 67% (Table 4, entries 1–3).

The different substituents did not cause a significant change in the optical purity. It is noteworthy that, even with application of the lariat ether with methoxypropyl side-arm (**15a'**), an ee value of 72% was observed (Table 4, entry 4). Regarding the results with the catalysts belonging to series β (**15c**, **d**, **e**), the yields lay in the range of 52–67% and the ee values were 70, 71, and 59%. One can see that presence of isopropyl group decreased the ee value to 59%, likely due to the steric requirement. It is also noteworthy that, in the cyclopropanation reactions, the position of the

Table 4 Asymmetric MIRC reaction of 2-benzylidene-1,3-indandione (**23**)


Entry	Catalyst	R	R ¹	Yield of 25 (%) ^a	ee (%) ^b
1	1	α -OMe	H	62	68
2	15a	α -OEt	H	54	70
3	15b	α -OiPr	H	56	67
4	15a'	α -OEt	Me	61	72
5	15c	β -OMe	H	67	70
6	15d	β -OEt	H	52	71
7	15e	β -OiPr	H	67	59

^aAfter isolation by preparative TLC^bDetermined by chiral HPLC measurement

substituents (either α or β) had practically no effect on the enantioselectivity (67–71% ee).

Conclusions

A new family of chiral lariat ethers annelated to alkyl 4,6-*O*-benzylidene- α - and β -D-glucopyranosides have been synthesized. These macrocycles generated significant asymmetric induction as phase-transfer catalysts in a few two-phase reactions. It was found that, in two liquid–liquid two-phase reactions (Darzens condensation and epoxidation of chalcone), the lariat ethers with different α -alkoxy substituents had approximately the same effect, and the catalysts with β -alkoxy groups generated, in all cases, lower enantioselectivity. The situation was different in the solid–liquid two-phase reactions (Michael reaction of nitrostyrene with diethyl acetamidomalonate and cyclopropanation reaction of 2-benzylidene-1,3-indandione with diethyl bromomalonate). In the reaction of nitrostyrene with diethyl acetamidomalonate, the optical purity decreased in the order OMe > OEt > OiPr, which can be explained based on steric reasons. Interestingly, in the MIRC reaction, the steric effect was observed only in the case of the OiPr group. It was also seen that, with the exception of the MIRC reaction, change of the hydroxypropyl side-arm to methoxypropyl substituent resulted in dramatically decreased enantioselectivity.

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