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Enantioselective synthesis of pantolactone analogues from an ephedrine-derived morpholine-dione

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Abstract—An efficient enantioselective synthesis of β,β-dialkyl α-hydroxy γ-butyrolactones, analogues of pantolactone, has been developed employing a stereoselective Prins reaction of chiral alkylidene morpholinones, as the key step. Enantioselective synthesis of a naturally occurring pantolactone homologue and a spiro analogue of pantolactone was achieved with this protocol.

The enantioselective synthesis of α-hydroxy γ-butyrolactones has been the subject of several recent investigations.[1] The synthesis of such lactones has attracted attention since they comprise crucial components in several naturally occurring chiral molecules.[2] A number of these lactones are natural products and this has spurred interest in their total synthesis.[3] β,β-Dialkyl α-hydroxy γ-butyrolactones have recently been employed as components of interleukin inhibitors.[4] This particular class of butyrolactones and the parent hydroxy acids are also of interest due to their structural similarity to pantolactone[5] and the potential for application as pantothenic acid analogues in biologically relevant molecules.[6] Herein, we describe the application of an ephedrine-derived morpholine-dione in a general, stereoselective synthesis of β,β-disubstituted α-hydroxy butyramides and the corresponding butyrolactones.

The reaction of ephedrine and oxalyl chloride at ambient temperature generates the morpholine-dione **1** in 63% yield.[1e] Dione **1** reacts readily with a variety of Grignard and organolithium reagents[7] at the lactone carbonyl to generate the corresponding hemiacetals **2** (Scheme 1). Thus, treatment of **1** with cyclohexyl magnesium bromide generates **2a** (80%, ds=2.5/1) and reaction with *sec*-butyl magnesium chloride gives a mixture of diastereomers **2b–e** (84%, dr=3/3/1/1, stereochemistry at the hemiacetal carbon and the *sec*-butyl carbon for **2b–e** has not been established). Although the dehydration of these hemiacetals can be achieved by treatment with trifluoroacetic acid in dichloromethane, the procedure of choice is treatment with $BF_3{\cdot}OEt_2$ at ambient temperature and the cyclohexylidene morpholinone **3a** is obtained from **2a** in 82% yield under these conditions. Dehydration of the **2b–e** mixture gives **3b/c** (90%, 1/1 mixture of *E*/*Z* isomers, Scheme 1). The stereochemistry of **3b** and **3c** is based on the downfield shift of the methylene hydrogens in **3b** (δ 2.6–2.8) as compared to **3c** (δ 2.2–2.4).[8] Olefins **3b** and **3c** are separable by chromatography and further reactions were conducted on the pure *E* and *Z* isomers.

The synthesis of a spiro analogue of pantolactone was examined with **3a** as the starting material. The Prins reaction[9] [$(CH_2O)_n$, acetic acid, cat. H_2SO_4, 85°C] of **3a** efficiently generates the spiro bis-acetal **4a** (90%, Scheme 2) as a single diastereomer. This reaction is remarkably rapid and all of **3a** is consumed within 2 min. Prolonged heating of the reaction mixture results in decomposition of the desired product **4a**. The alkylidene morpholinones **3b** and **3c** are also converted into the spiro bis-acetals **4b** and **4c** in an analogous manner. The stereochemistry at the spiro acetal stereocenter in **4a–c** is assigned by analogy to other reactions of the oxocarbenium ion intermediate in the ephedrine-derived template.[10] At this stage, the stereochemistry at the quaternary carbon (bearing the methyl and ethyl groups) in **4b** and **4c** was tentatively assigned as shown (Scheme 2). The assignment was later confirmed by synthesis of the derived lactones and by correlation.

Morpholinones **4** incorporate all the required carbons for the target α-hydroxy butyrates and possess a spiro acetal stereocenter that can be reduced stereoselectively with a combination of Lewis acid and silanes. Accordingly, treatment of **4a–c** with excess $TiCl_4$/triethylsilane efficiently generates the morpholinones **5a–c** as single diastereomers. The reaction probably proceeds by preferential cleavage of the anomeric carbon–oxygen

Keywords: asymmetric synthesis; lactones; Prins reaction; dehydration; reduction.

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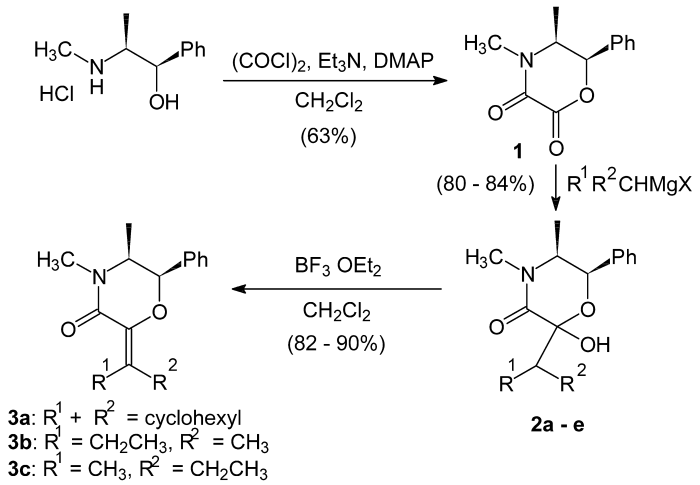
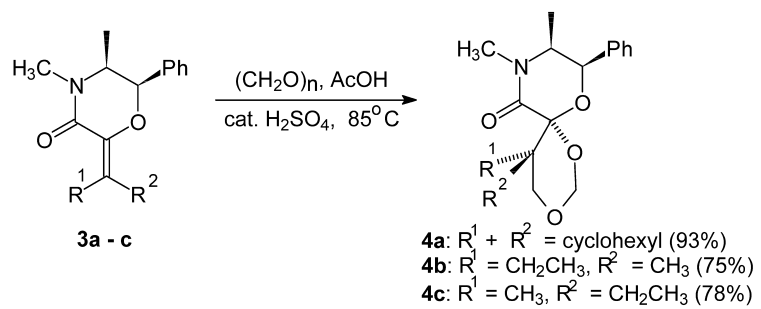


Scheme 1.



Scheme 2.

bond (C–O(1), Fig. 1) in **4a–c** to generate the endocyclic oxocarbenium ion which is reduced under stereoelectronic control.[11] Further reduction of the resulting methylenedioxy functionality generates **5a–c**. The stereochemistry of the newly generated stereocenter was assigned as *S* from previous observations in a related system.[5b]

It should be noted that an excess of triethylsilane (20 equiv.) is essential for the conversion of **4a–c** into **5a–c**. Use of lesser equivalents of triethylsilane results in the retro-Prins reaction of the intermediate oxocarbenium ion and variable amounts of the olefin **3a** (from **4a**) and mixtures of **3b** and **3c** (from **4b** and **4c**) are obtained as side products (Fig. 2).

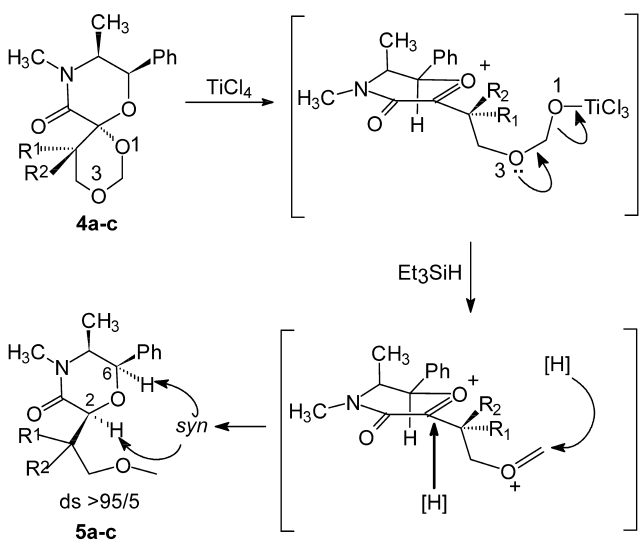


Figure 1.

Morpholinones **5a–c** are protected versions of the α,γ-dihydroxy butyric acid precursors of the target lactones. Dissolving metal reduction of **5a–c** generates the α-hydroxy γ-methoxy butyramides **6a–c** (50–52%). Conversion of **6** into the lactones **7** is readily achieved by a one-pot reaction sequence. Liberation of the primary hydroxyl group in **6** by demethylation (BBr_3) and subsequent acid catalyzed lactonization (H_2SO_4/H_2O, −15°C to rt) generates the lactones **7a–c** in good yield (70–86% Scheme 3).

Thus, the spiro analogue of pantolactone (*S*)-**7a** is obtained in 86% yield (98% e.e. by chiral GC analysis). One of the pantolactone homologues **7** is a natural product isolated from *Marshallia tenuifolia*, the absolute configuration of which has been unambiguously established as 3*S*,4*S* by synthesis from D-glucose.[12] A synthesis from (*S*)-malic acid has also been reported recently.[13] The specific rotation ($[\alpha]_D^{25}$=+4.45 (*c*=0.25, $CHCl_3$); lit.[14] $[\alpha]_D^{20}$=+4.7 (*c*=0.26, $CHCl_3$)) and spectroscopic data of **7b** (97% e.e.) obtained from our study are in agreement with those of the natural product[14] and **7b** therefore has the 3*S*,4*S* configuration.

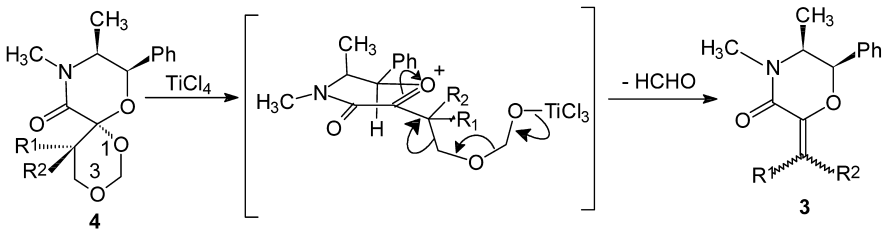
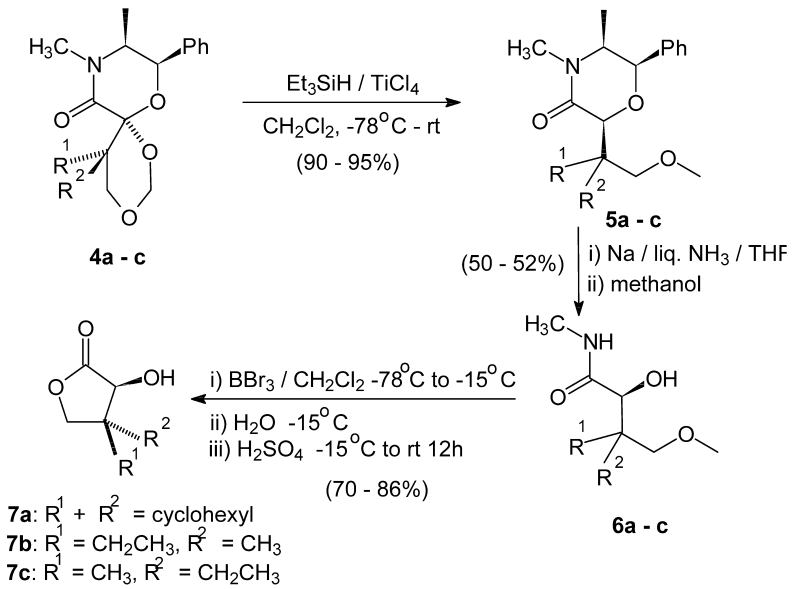


Figure 2.



Scheme 3.

Since the stereochemistry of the α-hydroxy bearing carbon has been established as *S* in the present as well as other related systems[5b] and **7b** and **7c** are diastereomers, it follows that **7c** has the 3*S*,4*R* configuration. The Prins reaction of the alkylidene morpholinones **3** is therefore stereospecific and proceeds with retention of the olefin geometry. Thus, the *E*-isomer **3b** generates **4b** whereas the *Z*-isomer **3c** generates **4c** (Fig. 3).

In conclusion, we have demonstrated that the ephedrine derived morpholine dione **1** is a convenient precursor for chiral alkylidene morpholinones that are key substrates in a highly stereoselective Prins reaction/acetal reduction protocol. A general, enantioselective route to β,β-disubstituted α-hydroxy butyrolactones has been established. The above procedure should provide access to a variety of enantiomerically enriched β,β-disubstituted α-hydroxy γ-butyrolactones in either enantiomeric form, since both enantiomers of ephedrine are commercially available. Current efforts focus on other applications of the dione **1** in the enantioselective synthesis of α-hydroxy acids and derivatives.

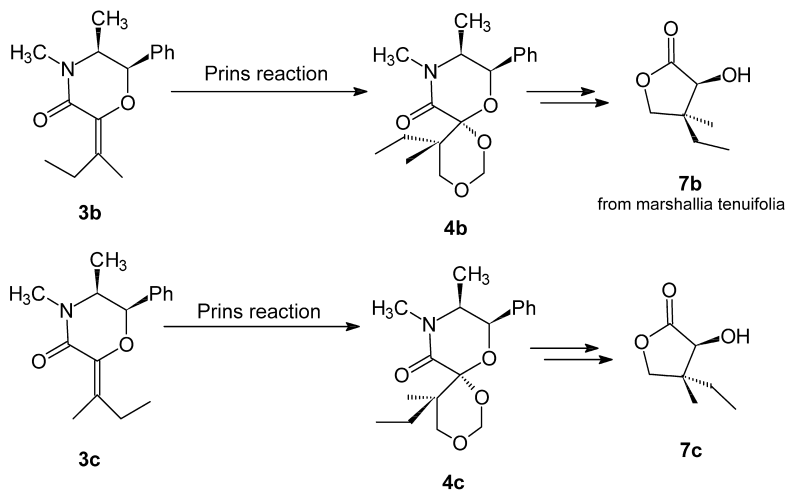


Figure 3.

1. Experimental

1.1. General

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120°C). THF was distilled from sodium and benzophenone. Dichloromethane, triethylamine were distilled from calcium hydride. Solvents for chromatography were distilled at their respective constant boiling point. Petroleum ether refers to the fraction in the 60–80°C range. Commercially available $TiCl_4$ was distilled and used. Grignard reagents were freshly prepared. Triethylsilane and boron tribromide were obtained from Aldrich Chemical Company. Reactions were monitored by TLC on commercial precoated silica (Merck 60F-254) by staining in phosphomolybdic acid (10% solution in ethanol) followed by charring at 200°C. Silica gel for column chromatography was 230–400 mesh. ^1H and ^{13}C NMR spectra were recorded on Bruker MSL-300 or Ac-200 instruments. IR spectra was recorded on FTIR-8400 Fourier Transform, (Shimadzu) instrument. Optical rotations were measured at the sodium D line on a JASCO P-1020 polarimeter. Mass spectra (EI) were recorded on a Finnigan-Mat 1020C mass spectrometer at ionization potential of 70 eV. High resolution mass spectra were recorded on a Jeol JMS-SX-102 spectrometer. All melting points are uncorrected. The enantiomeric excess of the lactones **7a–c** was determined by gas chromatography (Agilent 6890 series GC system) using a flame ionization detector and a Supelco β-DEX 120 (20% permethylated β-cyclodextrin) capillary column (30 m×0.32 mm×0.25 μm). Temperature gradient: 40°C (5 min); 5°C/min to 240°C (10 min); carrier gas: nitrogen; flow rate: 2 mL/min. Elemental analyses were performed by the microanalysis facility at NCL, Pune.

1.1.1. 5*S*,6*R*-4,5-Dimethyl-6-phenyl-morpholin-2,3-dione (1). This was prepared from ephedrine hydrochloride and oxalyl chloride according to the reported procedure.[1e] Mp: 182°C; $[\alpha]_D^{25}=-184.0$ (c=0.8, $CHCl_3$); lit.[1e] $[\alpha]_D^{25}=-184.3$ (c=0.82, $CHCl_3$). Spectroscopic data consistent with that reported in the literature.[1e]

1.1.2. Synthesis of hemiacetals 2. General procedure for the reaction of 1 with Grignard reagents. To a solution of **1** (n mmol) at an ambient temperature in anhydrous THF was added the Grignard reagent (n×1.5 mmol) over a period of 30 min and the reaction mixture was stirred for 1 h. Saturated aqueous NH_4Cl solution was added and the precipitated solids were dissolved by adding sufficient water. The mixture was extracted with dichloromethane and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated to furnish the crude product. This was used further without purification.

1.1.3. (5*S*,6*R*-2-Cyclohexyl-2-hydroxy-4,5-dimethyl-6-phenyl-morpholin-3-one 2a. Reaction of **1** (1 mmol, 219 mg) and cyclohexyl magnesium bromide (1.5 mL, 1.5 mmol, 1 M solution in THF) in anhydrous THF (5 mL) afforded **2a** as a mixture of diastereomers (242 mg, 80%). This was used without purification. An analytical sample was obtained by flash column chromatography (2/3 ethyl acetate/pet. ether).

^1H NMR (200 MHz, $CDCl_3$): δ 7.53–7.24 (m, 5H, Ar*H*), 5.49 (d, 1H, J=3.0 Hz, PhC*H*), 3.46 (dq, 1H, J=3.0, 6.3 Hz, CH_3CH), 3.03 (s, 3H, NCH_3), 2.23–1.11 (m, 11H, cyclohexyl CH_2, C*H*), 0.95 (d, 3H, J=6.3 Hz, $CHCH_3$). Visible peaks of the minor diastereomer: δ 5.49 (d, 1H, J=3.0 Hz, PhC*H*), 3.55 (dq, 1H, J=3.0, 6.3 Hz, CH_3CH), 0.98 (d, 3H, J=6.3 Hz, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.0 (*C*=O), 137.6 (ArC_{ipso}), 128.1 (Ar*C*H), 127.3 (Ar*C*H), 125.5 (Ar*C*H), 98.8 (OCO_{quat}), 70.8 (Ph*C*H), 59.0 (N*C*H), 45.4 (*C*H, cyclohexyl), 33.4 (NCH_3), 28.2 (CH_2, cyclohexyl), 26.4 (CH_2, cyclohexyl), 26.0 (CH_2, cyclohexyl), 24.4 (CH_2, cyclohexyl), 12.5 (CH_3CH). IR ($CHCl_3$): 3353, 2931, 2854, 1643, 1452, 1380, 1215, 1145, 1020, 756, 700 cm^{-1}. MS (EI, 70 eV): m/z 58 (14), 91 (11), 118 (100), 146 (20), 197 (10), 220 (26), 275 (3). Analysis for $C_{18}H_{25}NO_3$: calcd: C, 71.25; H, 8.23; N, 4.61, found: C, 71.28; H, 8.34; N, 4.38.

1.1.4. (5*S*,6*R*)-2-*sec*-Butyl-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (2b–e). Reaction of **1** (1.01 g, 4.63 mmol) and *sec*-butylmagnesium chloride (6.95 mL, 1 M solution in ether) in anhydrous THF (10 mL) furnished a 3:3:1:1 mixture of diastereomers **2b–e** as a gum (1.08 g, 84%) which was used further without purification. An analytical sample was obtained by flash column chromatography (1/1 ethyl acetate/pet. ether).

^1H NMR (200 MHz, $CDCl_3$). Major diastereomers: δ 7.49–7.24 (m, 5H, Ar*H*), 5.5 (br, 1H, PhC*H*), 3.62–3.41 (m, 2H, $CHCH_3$, $CHOH$), 3.03 (s, 3H, NCH_3), 2.26–2.07 (m, 1H, $CHCH_2$), 2.02–1.80 (m, 1H, CH_2), 1.50–1.19 (m, 1H, CH_2), 1.14–0.91 (m, 9H, 2×$CHCH_3$, CH_2CH_3). Visible peaks for the minor diastereomers: δ 5.72 (d, 1H, J=2.5 Hz, PhC*H*), 5.61 (d, 1H, J=3.0 Hz, PhC*H*), 3.12 (s, 3H, NCH_3), 3.05 (s, 3H, NCH_3), 1.15 (d, 3H, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.3 (*C*=O), 137.9 (ArC_{ipso}), 128.4 (Ar*C*H), 127.6 (Ar*C*H), 125.8 (Ar*C*H), 99.8 (*C*OH), 99.5 (*C*OH, diastereomer), 71.0 (Ph*C*H), 59.3 (N*C*H), 42.8 ($CHCH_2$), 42.5 ($CHCH_2$, diastereomer), 33.7 (NCH_3), 25.2 (CH_2CH_3), 21.4 (CH_2CH_3, diastereomer), 14.8 ($CHCH_3$), 12.7 (CH_2CHCH_3), 12.4 (CH_2CHCH_3, diastereomer), 10.8 (CH_2CH_3). IR ($CHCl_3$): 3332, 2969, 1738, 1632, 1452, 1147, 700 cm^{-1}. MS (EI, 70 eV): m/z 58 (53), 91 (14), 118 (100), 160 (14), 220 (13), 277 (M^+, 1). HRMS for $C_{16}H_{23}NO_3$: calcd: 277.1678, found: 277.1673.

1.2. General procedure for dehydration of hemiacetals 2a–e

To a solution of hemiacetal in anhydrous dichloromethane, at 0°C, was added $BF_3{\cdot}Et_2O$ at 0°C and the mixture was warmed to ambient temperature. After stirring for 6 h, cold water was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product which was purified by flash column chromatography on silica gel to furnish olefins **3a–c**.

1.2.1. 5*S*,6*R*-2-Cyclohexylidene-4,5-dimethyl-6-phenyl-morpholin-3-one (3a). Reaction of **2a** (1.108 g, 3.65 mmol) with $BF_3{\cdot}Et_2O$ (4.62 mL, 36.5 mmol) in anhydrous dichloromethane (20 mL), gave after purification

by flash column chromatography (1/4 ethyl acetate/pet. ether) 1.04 g (89%) of **3a** as colourless liquid which solidified upon refrigeration.

Mp 184–185°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.32 (m, 5H, ArH), 5.12 (d, 1H, J=2.2 Hz, PhCH), 3.55 (dq, 1H, J=2.2, 6.7 Hz, CH_3CH), 3.22–2.84 (m, 1H, CH_2, cyclohexyl), 3.06 (s, 3H, NCH_3), 2.96–2.88 (m, 1H, CH_2, cyclohexyl), 2.53–2.34 (m, 2H, CH_2, cyclohexyl), 1.73–1.51 (m, 6H, CH_2, cyclohexyl) 0.98 (d, 3H, J=6.7 Hz, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.7 (*C*=O), 137.3 (ArC_{ipso}), 135.7 (OC=*C*), 134.0 (OC=*C*), 128.0 (Ar*C*H), 127.3 (Ar*C*H), 125.1 (Ar*C*H), 76.7 (Ph*C*H), 58.4 (N*C*H), 33.1 (NCH_3) 28.3 (CH_2C=C), 28.0 (CH_2C=C), 27.7 (CH_2, cyclohexyl), 27.4 (CH_2, cyclohexyl), 26.1 (CH_2, cyclohexyl), 11.5 (CH_3CH). IR ($CHCl_3$): 2948, 2850, 1649, 1622, 1448, 1292, 1016, 756, 707 cm^{-1}. MS (EI, 70 eV): *m/z* 67 (11), 77 (16), 91 (20), 118 (100), 168 (4), 205 (14), 285 (M^+, 8). Analysis for $C_{18}H_{23}NO_2$: calcd: C, 75.75; H, 8.05, N, 4.90, found: C, 76.08; H, 8.03; N, 4.77. $[\alpha]_D^{25}$=−148.3 (c=2.1, $CHCl_3$).

1.3. Olefins 3b and 3c

Reaction of **2b–e** (1.08 g, 3.9 mmol) with $BF_3{\cdot}Et_2O$ (4.95 mL, 39 mmol) in anhydrous dichloromethane (30 mL) gave crude **3** a mixture of diastereomers. Careful chromatography (crude mixture loaded on 1/19 ethyl acetate/pet. ether and eluted with 3/17 ethyl acetate/pet. ether) gave 450 mg (45%) of **3b** as a white solid and 450 mg (45%) of **3c** as a gum.

1.3.1. (2,1′)*E*,5*S*,6*R*-4,5-Dimethyl-2-(1-methylpropylidene)-6-phenylmorpholin-3-one (3b). Mp 80–81°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41–7.35 (m, 5H, Ar*H*), 5.14 (d, 1H, J=2.9 Hz, ArC*H*), 3.56 (dq, 1H, J=2.9, 6.8 Hz, CH_3CH), 3.07 (s, 3H, NCH_3), 2.81–2.65 (m, 2H, CH_2CH_3), 1.90 (s, 3H, CCH_3), 1.14 (t, 3H, J=7.3 Hz, CH_2CH_3), 0.98 (d, 3H, J=6.8 Hz, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 160.3 (*C*=O), 138.0 (ArC_{ipso}), 137.6 (O*C*O), 132.5 (CCH_2CH_3), 128.2 (Ar*C*H), 127.6 (Ar*C*H), 125.3 (Ar*C*H), 76.7 (Ph*C*H), 58.6 (N*C*H), 33.2 (NCH_3), 26.3 (CH_2CH_3), 17.4 (CH_2CH_3), 12.9 (CCH_3), 11.7 ($CHCH_3$). IR ($CHCl_3$): 3031, 2957, 2872, 1657, 1498, 1378, 1286, 1172, 1069, 1018, 706 cm^{-1}. MS (EI, 70 eV): *m/z* 69 (22), 98 (31), 118 (100), 126 (8), 142 (4), 186 (5), 259 (M^+, 12). Analysis for $C_{16}H_{21}NO_2$: calcd: C, 74.08; H, 8.16; N, 5.40, found: C, 73.71; H, 8.48; N, 5.62. $[\alpha]_D^{25}$=−180.0 (c=0.5, $CHCl_3$).

1.3.2. (2,1′)*Z*,5*S*,6*R*-4,5-Dimethyl-2-(1-methylpropylidene)-6-phenylmorpholin-3-one (3c). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.30 (m, 5H, Ar*H*), 5.13 (d, 1H, J=3.0 Hz, ArC*H*), 3.60 (dq, 1H, J=2.9 Hz, 6.8, CH_3CH), 3.07 (s, 3H, NCH_3), 2.41–2.28 (m, 2H, CH_2CH_3), 2.25 (s, 3H, CCH_3), 1.09 (t, 3H, J=7.4 Hz, CH_2CH_3), 0.97 (d, 3H, J=6.8 Hz, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 160.4 (*C*=*O*), 137.6 (ArC_{ipso}), 137.2 (O*C*O), 131.7 (CCH_2CH_3), 127.9 (Ar*C*H), 127.2 (Ar*C*H), 124.9 (Ar*C*H), 76.3 (Ph*C*H), 58.3 (N*C*H), 32.9 (NCH_3), 26.4 (CH_2CH_3), 17.4 (CH_2CH_3), 11.5 (CCH_3), 11.3 ($CHCH_3$). IR ($CHCl_3$): 2972, 2874, 1657, 1498, 1378, 1260, 1171, 1067, 1020, 707 cm^{-1}. MS (EI, 70 eV): 69 (15), 91 (19), 118 (100), 142 (5), 205 (1), 259 (M^+, 19). Analysis for $C_{16}H_{21}NO_2$: calcd: C, 74.08; H, 8.16; N, 5.40, found: C, 73.70; H, 7.85; N, 5.10.

1.4. General procedure for the Prins reaction of olefins 3a–c

To a solution of the olefin **3** and paraformaldehyde in glacial acetic acid was added conc. H_2SO_4 (two drops) and the mixture was heated rapidly for 90 s in a preheated oil-bath set at 85°C. After cooling reaction mixture it was neutralized with saturated aqueous sodium bicarbonate solution. The mixture was extracted with ether and the combined extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. Removal of ether under reduced pressure gave crude product which was purified by flash column chromatography.

1.4.1. 2*R*,3*S*,6*R*-3,4-Dimethyl-2-phenyl-1,14,16-trioxa-4-aza-dispiro[5.0.5.4]hexadecane-5-one (4a). Reaction of **3a** (830 mg, 2.9 mmol) with paraformaldehyde (437 mg, 14.6 mmol) in glacial acetic acid (10 mL) gave after purification by flash column chromatography (1/4 ethyl acetate/pet. ether) on silica gel 939 mg (93%) **4a** as a white solid.

Mp 74°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.29 (m, 5H, Ar*H*), 5.42 (d, 1H, J=3.0 Hz, PhC*H*), 5.12 (d, 1H, J=5.4 Hz, OCH_2O), 5.09 (d, 1H, J=5.4 Hz, OCH_2O), 4.39 (d, 1H, J=11.0 Hz, OCH_2C), 4.13 (d, 1H, J=11.0 Hz, OCH_2C), 3.47 (dq, 1H, J=3.0, 6.4 Hz, CH_3CH), 3.02 (s, 3H, NCH_3), 2.09–1.19 (m, 10H, cyclohexyl), 1.00 (d, 3H, J=6.4 Hz, CH_3CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.7 (*C*=O), 137.1 (Ar*C*H), 128.2 (Ar*C*H), 127.4 (Ar*C*H), 125.2 (Ar*C*H), 99.5 (OCO$_{quat}$, cyclohexyl), 88.0 (OCH_2O), 70.4 (Ph*C*H), 66.7 (CCH_2O), 58.6 (N*C*H), 40.6 (C*quat*), 33.4 (NCH_3), 27.7 (CH_2, cyclohexyl), 27.3 (CH_2, cyclohexyl), 25.7 (CH_2, cyclohexyl), 20.9 (CH_2, cyclohexyl), 12.2 (CH_3CH). IR ($CHCl_3$): 4214, 3631, 3450, 3018, 2931, 2866, 2401, 1654, 1454, 1215, 985, 765, 669, 451 cm^{-1}. MS (EI, 70 eV): 81 (17), 91 (23), 118 (100), 130 (4), 146 (5), 192 (5), 220 (21), 345 (M^+, 4). HRMS for $C_{20}H_{27}NO_4$: calcd: 345.1941, found: 345.1941. $[\alpha]_D^{25}$=−81.1 (c=1.4, $CHCl_3$).

1.4.2. (5*S*,8*R*,9*S*)-5-Ethyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (4b). Reaction of **3b** (382 mg, 1.5 mmol) with paraformaldehyde (221 mg, 7.4 mmol) in glacial acetic acid (9 mL) gave after purification by flash column chromatography (3/17 ethyl acetate/pet. ether) 352 mg (75%) of **4b** as white solid.

Mp 110°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.31 (m, 5H, Ar*H*), 5.48 (d, 1H, J=3.0 Hz, PhC*H*), 5.24 (d, 1H, J=5.4 Hz, OCH_2O), 5.03 (d, 1H, J=5.4 Hz, OCH_2O), 4.26 (d, 1H, J=11.0 Hz, OCH_2C), 3.83 (d, 1H, J=11.0 Hz, OCH_2C), 3.50 (dq, 1H, J=3.0, 6.4 Hz, CH_3CH), 3.01 (s, 3H, NCH_3), 1.79 (m, 2H,CCH_2CH_3), 1.16 (s, 3H, CCH_3), 0.99 (d, 3H, J=6.4 Hz, $CHCH_3$), 0.89 (t, 3H, J=7.4 Hz, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.8 (*C*=O), 137.0 (ArC_{ipso}), 128.1 (Ar*C*H), 127.4 (Ar*C*H), 125.1 (Ar*C*H), 99.1 (OCO_{quat}), 88.5 (OCH_2O), 70.6 (OCH_2C), 70.6 (Ph*C*H), 58.5 (N*C*H), 40.6 (CCH_2CH_3), 33.2 (NCH_3), 25.3 (CCH_2CH_3), 17.2 (CCH_3), 12.2 (CH_3CH), 7.5

(CH_2CH_3). IR ($CHCl_3$): 3018, 2979, 2885, 1650, 1497, 1215, 1095, 975, 757 cm^{-1}. MS (EI, 70 eV): *m/z* 69 (23), 103 (19), 118 (100), 146 (4), 220 (6), 319 (M^+, 1). Analysis for $C_{18}H_{25}NO_4$: calcd: C, 67.67; H, 7.89; N, 4.38, found: C, 67.29; H, 8.22; N, 4.13. $[\alpha]_D^{25}=-136.0$ (*c*=0.5, $CHCl_3$).

1.4.3. (5*R*,8*R*,9*S*)-5-Ethyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (4c). Reaction of **3c** (342 mg, 1.3 mmol) with paraformaldehyde (198 mg, 6.6 mmol) in glacial acetic acid (8 mL) gave after purification by flash column chromatography (3/17 ethyl acetate/pet. ether) 328 mg (78%) of **4c** as a colourless liquid.

Mp 85°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.31 (m, 5H, Ar*H*), 5.42 (d, 1H, *J*=2.9 Hz, PhC*H*), 4.99 (AB system, *J*=7.0 Hz, 2H, OCH_2O), 4.05 (d, 1H, *J*=11.0 Hz, OCH_2C), 3.76 (d, 1H, *J*=11.0 Hz, OCH_2C), 3.53 (dq, 1H, *J*=2.9, 6.3 Hz, CH_3CH), 3.00 (s, 3H, NCH_3), 1.63–1.48 (m, 2H, CH_2CH_3), 1.41 (s, 3H, CH_3), 0.99 (d, 3H, *J*=6.3 Hz, CH_3CH), 0.90 (t, 3H, *J*=7.3 Hz, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.6 (*C*=O), 136.9 (ArC_{ipso}), 128.3 (Ar*C*H), 127.6 (Ar*C*H), 125.2 (Ar*C*H), 99.5 (OCO_{quat}), 87.3 (OCH_2O), 72.1 (OCH_2C), 70.3 (Ph*C*H), 58.8 (N*C*H), 40.7 (CCH_2CH_3), 33.6 (NCH_3), 25.7 (CCH_2CH_3), 18.4 (CCH_3), 12.2 (CH_3CH), 7.4 (CH_2CH_3). IR ($CHCl_3$): 3018, 2883, 1658, 1461, 1400, 1215, 1095, 977, 756 cm^{-1}. MS (EI, 70 eV): *m/z* 73 (81), 103 (100), 118 (73), 133 (10), 220 (3), 319 (M^+, 3). Analysis for $C_{18}H_{25}NO_4$: calcd: C, 67.67; H, 7.89; N, 4.38, found: C, 67.77; H, 8.05; N, 4.49. $[\alpha]_D^{25}=-93.1$ (*c*=0.58, $CHCl_3$).

1.5. General procedure for reductive cleavage of spirobisacetals 4

To a solution of the Prins product **4** in anhydrous dichloromethane was added at −78°C titanium tetrachloride followed by triethylsilane. The reaction mixture was warmed to ambient temperature and stirred for 24 h. It was then cooled to −5°C and saturated aqueous ammonium chloride was added and warmed to ambient temperature. Water was added to dissolve the precipitated solids and the solution was extracted with dichloromethane. The dichloromethane layer was dried (Na_2SO_4), and concentrated to obtain crude product which on purification by flash column chromatography rendered **5a**–**c** as colourless oils.

1.5.1. 2*S*,5*S*,6*R*-2-((1-Methoxymethyl)cyclohexyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (5a). Reduction of **4a** (840 mg, 2.4 mmol) with titanium tetrachloride (4.6 mL, 42 mmol) and triethylsilane (7.8 mL, 48.6 mmol) in anhydrous dichloromethane (28 mL) gave after purification by flash column chromatography (1/4 ethyl acetate/pet. ether) 747 mg (93%) of **5a** as colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.39 (m, 5H, Ar*H*), 4.92 (d, 1H, *J*=3.0 Hz, PhC*H*), 4.32 (s, 1H, C*H*O), 3.73 (d, 1H, *J*=9.1 Hz, CH_2), 3.52 (d, 1H, *J*=9.1 Hz, CH_2), 3.51 (dq, 1H, *J*=3.0, 6.3 Hz, CH_3CH), 3.30 (s, 3H, OCH_3), 2.99 (s, 3H, NCH_3), 2.00–1.35 (m, 10H, cyclohexyl), 0.96 (d, 3H, *J*=6.3 Hz, CH_3CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.0 (*C*=O), 138.1 (Ar*C*H), 127.9 (Ar*C*H), 127.1 (Ar*C*H), 125.1 (Ar*C*H), 79.5 (*C*HO), 76.1 (Ph*C*H), 74.2 (CH_2O), 58.6 (OCH_3), 58.4 (CH_3CH), 42.6 (C_{quat}, cyclohexyl), 33.2 (NCH_3), 29.6 (CH_2, cyclohexyl), 29.4 (CH_2, cyclohexyl), 25.8 (CH_2, cyclohexyl), 21.4 (CH_2, cyclohexyl), 21.3 (CH_2, cyclohexyl), 12.4(CH_3CH). IR ($CHCl_3$): 3452, 3005, 2929, 2865, 1642, 1453, 1379, 1249, 1188, 1105, 1061, 702, 666 cm^{-1}. MS (EI, 70 eV): 58 (26), 67 (15), 91 (20), 105 (17), 148 (10), 205 (99), 267 (7), 331 (M^+, 2). HRMS for $C_{20}H_{29}NO_3$: calcd: 331.2147, found: 331.2128. $[\alpha]_D^{25}=-123.2$ (*c*=3.4, $CHCl_3$).

1.5.2. (2*S*,5*S*,6*R*)-2-[(1*S*)-1-(Methoxymethyl)-1-methyl-propyl]-4,5-dimethyl-6-phenylmorpholin-3-one (5b). Reduction of **4b** (334 mg, 1 mmol) with titanium tetrachloride (3.3 mL, 30 mmol) and triethylsilane (3.3 mL, 21 mmol) in anhydrous dichloromethane (15 mL) gave after purification by flash column chromatography (1/4 ethyl acetate / pet. ether) 747 mg (93%) of **5b** as colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.24 (m, 5H, Ar*H*), 4.93 (d, 1H, *J*=3.0 Hz, PhC*H*), 4.26 (s, 1H, C*H*O), 3.64 (d, 1H, *J*=8.8 Hz, OCH_2), 3.51 (dq, 1H, *J*=3.0, 6.4 Hz, CH_3CH), 3.43 (d, 1H, *J*=8.8 Hz, OCH_2), 3.33 (s, 3H, OCH_3), 3.00 (s, 1H, NCH_3), 1.95–1.47 (m, 2H, CCH_2CH_3), 1.13 (s, 3H, CCH_3), 0.97 (d, 3H, *J*=6.4 Hz, $CHCH_3$), 0.89 (t, 3H, *J*=7.4 Hz, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.9 (*C*=O), 138.2 (ArC_{ipso}), 128.1 (Ar*C*H), 127.2 (Ar*C*H), 125.2 (Ar*C*H), 80.7 (*C*HO), 76.8 (OCH_2), 76.3 (Ph*C*H), 58.8 (OCH_3), 58.6 (CH_3CH), 42.6 (C_{quat}), 33.3 (NCH_3), 26.9 (CH_2CH_3), 19.1 (CCH_3), 12.8 ($CHCH_3$), 7.9 (CH_2CH_3). IR ($CHCl_3$): 4214, 3016, 2935, 2881, 1641, 1461, 1380, 1215, 756 cm^{-1}. MS (EI, 70 eV): *m/z* 58 (9), 97 (21), 105 (7), 118 (100), 148 (6), 205 (37), 260 (2), 290 (4), 305 (M^+, 7). HRMS for $C_{18}H_{27}NO_3$: calcd: 305.1991, found: 305.1978. $[\alpha]_D^{25}=-166.8$ (*c*=1.7, $CHCl_3$).

1.5.3. (2*S*,5*S*,6*R*)-2-[(1*R*)-1-(Methoxymethyl)-1-methyl-propyl]-4,5-dimethyl-6-phenylmorpholin-3-one (5c). Reduction of **4c** (238 mg, 0.75 mmol) with titanium tetrachloride (1.40 mL, 12.75 mmol) and triethylsilane (3.0 mL, 18.75 mmol) in anhydrous dichloromethane (13 mL) for 12 h gave after purification by flash column chromatography (1/5 ethyl acetate/pet. ether) 212 mg (93%) of **5c** as a colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.20 (m, 5H, Ar*H*), 4.93 (d, 1H, *J*=2.4 Hz, PhC*H*), 4.25 (s, 1H, C*H*O), 3.65–3.41 (m, 3H, OCH_2, CH_3CH), 3.34 (s, 3H, OCH_3), 3.00 (s, 3H, NCH_3), 1.74 (q, 2H, *J*=7.3 Hz, CCH_2CH_3), 1.07 (s, 3H, CH_3), 0.99–0.85 (m, 6H, $CHCH_3$, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.7 (*C*=O), 137.9 (ArC_{ipso}), 127.9 (Ar*C*H), 127.0 (Ar*C*H), 124.9 (Ar*C*H), 80.0 (*C*HO), 76.0 (OCH_2), 75.9 (Ph*C*H), 58.6 (OCH_3), 58.2 (CH_3CH), 42.3 (C_{quat}), 33.1 (NCH_3), 26.6 (CH_2CH_3), 18.6 (CCH_3), 12.6 ($CHCH_3$), 7.7 (CH_2CH_3). IR ($CHCl_3$): 3475, 2972, 2877, 1649, 1452, 1251, 1108, 1064, 702 cm^{-1}. MS (EI, 70 eV): 58 (9), 97 (13), 117 (27), 148 (7), 205 (50), 290 (10), 305 (M^+, 6). HRMS for $C_{18}H_{27}NO_3$: calcd: 305.1991, found: 305.1983. $[\alpha]_D^{25}=-177.6$ (*c*=1.2, $CHCl_3$).

1.6. General procedure for dissolving metal reduction of morpholinones 5

To anhydrous liquid ammonia (distilled over sodium), was added sodium metal at −78°C and the mixture was stirred

for 15 min. To the resulting blue solution was added a solution of **6a–c** dissolved in anhydrous THF. The mixture was stirred at −78°C for three and a half minutes, methanol was added and the mixture was stirred at room temperature till the ammonia was completely removed. The methanol was removed under reduced pressure and the residue was partitioned in ethyl acetate and water. The ethyl acetate layer was separated and the aqueous layer was extracted several times with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated to obtain crude product which on purification by flash column chromatography gave **6** as colourless oils.

1.6.1. 2*S*-2-Hydroxy-2-((1-methoxymethyl)cyclohexyl)-*N*-methyl acetamide (6a). Prepared from **5a** (293 mg, 0.9 mmol) in THF (2 mL) and Na (116 mg, 4.8 mmol) in ammonia (10 mL). Purification by flash column chromatography (3/2 ethyl acetate/pet. ether) furnished 95 mg (50%) of **6a** as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.79 (br s, 1H, N*H*), 4.28 (d, 1H, *J*=6.0 Hz, O*H*), 4.04 (d, 1H, *J*=6.0 Hz, C*H*), 3.61 (d, 1H, *J*=9.3 Hz, OCH_2), 3.35 (s, 3H, OCH_3), 3.33 (d, 1H, *J*=9.3 Hz, OCH_2), 2.86 (d, 3H, *J*=5.3 Hz, NCH_3), 2.09–1.37 (m, 10H, cyclohexyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.1 (*C*=*O*), 78.2 (*C*HOH), 77.4 (OCH_2), 59.4 (OCH_3), 40.8 (C_{quat}), 30.0 (CH_2, cyclohexyl), 28.9 (CH_2, cyclohexyl), 26.0 (CH_2, cyclohexyl), 25.7 (NCH_3), 21.5 (CH_2, cyclohexyl), 21.4 (CH_2, cyclohexyl). IR ($CHCl_3$): 3306, 2920, 1650, 1531, 1409, 1203, 1094, 799 cm^{-1}. MS (EI, 70 eV): 58 (8), 81 (15), 89 (100), 95 (23), 139 (14), 183 (5), 215 (M^+, 3). HRMS: calcd: 215.1521, found: 215.1525. $[\alpha]_D^{25}$=−41.6 (*c*=3.2, $CHCl_3$).

1.6.2. (2*S*,3*S*)-2-Hydroxy-3-(methoxymethyl)-*N*,3-dimethylpentanamide (6b). Prepared from **5b** (86 mg, 0.28 mmol) in THF (0.5 mL) and Na (34 mg, 1.4 mmol) in ammonia (4 mL). Purification by flash column chromatography (3/2 ethyl acetate/pet. ether) gave 27 mg (50%) of **6b** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.84 (br s, 1H, N*H*), 4.39 (br s, 1H, O*H*), 4.05 (s, 1H, C*H*), 3.35 (s, 5H, CH_2OCH_3), 2.85 (d, 3H, *J*=4.9 Hz, NCH_3), 1.74–1.39 (m, 2H, CCH_2CH_3), 0.97 (s, 3H, CCH_3), 0.92 (t, 3H, *J*=7.4 Hz, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.3 (*C*=O), 79.6 (OCH_2), 77.6 (*C*HOH), 59.2 (OCH_3), 40.9 (C_{quat}), 27.6 (CH_2CH_3), 25.6 (NCH_3), 17.8 (CCH_3), 7.6 (CH_2CH_3). IR ($CHCl_3$): 3380, 2968, 2881, 2812, 1658, 1411, 1286, 1108, 732 cm^{-1}. MS (EI, 70 eV): 58 (60), 71 (37), 89 (100), 113 (13), 189 (M^+, 4). ESMS for $C_9H_{19}NO_3Na$: calcd: 212.1263, found: 212.1264. $[\alpha]_D^{25}$=−34.75 (*c*=0.28, $CHCl_3$).

1.6.3. (2*S*,3*R*)-2-Hydroxy-3-(methoxymethyl)-*N*,3-dimethylpentanamide (6c). Prepared from **5c** (199 mg, 0.65 mmol) in THF (1 mL) and Na (78 mg, 3.26 mmol) in ammonia (7 mL). Purification by flash column chromatography (3/2 ethyl acetate/pet. ether) gave 62 mg (50%) of **6c** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.81 (br, s, 1H, N*H*), 4.46 (br s, 1H, O*H*), 3.99 (s, 1H, C*H*), 3.43–3.19 (m, 5H, CH_2OCH_3), 2.79 (d, 3H, *J*=4.9 Hz, NCH_3), 1.70–1.50 (m, 1H, CCH_2CH_3), 1.38–1.17 (m, 1H, CCH_2CH_3) 0.90 (s, 3H, CCH_3), 0.84 (t, 3H, *J*=7.4 Hz, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8 (*C*=O), 79.1 (OCH_2), 78.3 (*C*HOH), 59.0 (OCH_3), 40.9 (C_{quat}), 25.4 (NCH_3), 24.9 (CH_2CH_3), 18.0 (CCH_3), 7.6 (CH_2CH_3). IR ($CHCl_3$): 3382, 2968, 1650, 1537, 1107, 1031 cm^{-1}. MS (EI, 70 eV): 58 (43), 71 (28), 81 (7), 89 (100), 113 (13), 131 (10), 189 (M^+, 2). ESMS for $C_9H_{19}NO_3Na$: calcd: 212.1263, found: 212.1263. $[\alpha]_D^{25}$=−33.86 (*c*=0.9, $CHCl_3$).

1.7. General procedure for lactonization of 6a–c to 7a–c

To a stirred solution of **6** in anhydrous dichloromethane was added at −78°C boron tribomide in anhydrous dichloromethane and the resulting reaction mixture was gradually warmed to −15°C with continuous stirring for 4 h. Water was then added over a period a 5 min, the mixture was stirred for 15 min and 6 M H_2SO_4 was added. The mixture was then stirred overnight (approximately 12 h) during which time it warmed to ambient temperature. The mixture was then cooled in an ice bath and neutralized with saturated sodium bicarbonate solution. It was then extracted with dichloromethane and the combined dichloromethane extracts were dried (Na_2SO_4) and concentrated to obtain the crude lactone which was purified by flash column chromatography.

1.7.1. 4*S*-4-Hydroxy-2-oxa-spiro[4,5]decan-3-one: (7a). Demethylation of **6a** (70 mg 0.32 mmol) in anhydrous dichloromethane (4 mL) with boron tribromide (0.26 mL, 2.8 mmol diluted in 1 mL anhydrous dichloromethane) followed by addition of water (1 mL) and 6 M H_2SO_4 (1.5 mL), gave after purification by flash column chromatography (1/4 ethyl acetate/pet. ether) 53 mg (86%) of **7a** as a white crystalline solid.

Mp 92–93°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.38 (d, 1H, *J*=9.3 Hz, CH_2), 4.12 (s, 1H, C*H*OH), 3.91 (d, 1H, *J*=9.3 Hz, CH_2), 3.46 (br, s, 1H, O*H*), 1.84–1.1 (m, 10H, cyclohexyl). ^{13}C NMR (50 MHz, $CDCl_3$): 177.9 (*C*=O), 75.6 (*C*HOH), 73.6 (OCH_2), 44.0 (C_{quat}), 33.7 (CH_2, cyclohexyl), 25.8 (CH_2, cyclohexyl), 25.3 (CH_2, cyclohexyl), 22.9 (CH_2, cyclohexyl), 21.7 (CH_2, cyclohexyl). IR ($CHCl_3$): 3425, 2931, 2857, 1778, 1455, 1166, 1005, 731 cm^{-1}. MS (EI, 70 eV): *m*/*z* 55 (97), 67 (100), 79 (51), 83 (59), 95 (77), 108 (14), 170 (M^+, 7). HRMS: calcd: 170.0943, found: 170.0942. $[\alpha]_D^{25}$=+13.9 (*c*=0.55, $CHCl_3$).

1.7.2. (3*S*,4*S*)-4-Ethyl-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one (7b).[14] Demethylation of **6b** (17 mg, 0.09 mmol) in anhydrous dichloromethane (4 mL) with boron tribromide (0.08 mL, 0.79 mmol) diluted in anhydrous dichloromethane (0.5 mL), followed by addition of water (0.4 mL) and 6 M H_2SO_4 (0.3 mL) gave after purification by flash column chromatography (3/7 ethyl acetate/pet. ether) gave 9 mg (70%) of **7b** as a syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.23 (d, 1H, *J*=9.3 Hz, CH_2), 4.16 (s, 1H, C*H*OH), 3.89 (d, 1H, *J*=9.3 Hz, CH_2), 3.0 (br s, 1H, O*H*), 1.50 (m, 2H, CH_2CH_3), 1.19 (s, 3H, CH_3), 0.96 (t, 3H, *J*=7.3 Hz, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 177.5 (*C*=O), 75.9 (*C*HOH), 73.7 (CH_2), 43.5 (C_{quat}), 24.2 (CH_2CH_3), 20.9 (CH_3), 8.2 (CH_2CH_3).

$[\alpha]_D^{25}$=+4.45 (c=0.25, $CHCl_3$) (lit.[14] $[\alpha]_D^{20}$=+4.7 (c=0.26, $CHCl_3$)).

1.7.3. (3*S*,4*R*)-4-Ethyl-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one (7c). Demethylation of **6c** (45 mg, 0.24 mmol) in anhydrous dichloromethane (5 mL), with boron tribromide (0.20 mL, 2.1 mmol) diluted in anhydrous dichloromethane (1 mL) followed by addition of water (1 mL) and 6 M H_2SO_4 (0.6 mL) gave after purification by flash column chromatography (3/7 ethyl acetate/pet. ether) 26 mg (76%) of **7c** as colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.21 (s, 1H, C*H*OH), 4.05–3.95 (AB system, J=10.8 Hz, 2H, CH_2), 3.45 (br s, 1H, O*H*), 1.60 (m, 2H, CH_2CH$_3$), 1.08 (s, 3H, CH_3), 1.01 (t, 3H, J=7.4 Hz, CH$_2$CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 177.8 (*C*=O), 75.6 (*C*HOH), 75.0 (*C*H$_2$), 44.1 (C_{quat}), 30.1 (*C*H$_2$CH$_3$), 15.9 (*C*H$_3$), 8.5 (CH$_2$*C*H$_3$). IR ($CHCl_3$): 3444, 2968, 1776, 1460, 1112, 999, 715 cm^{-1}. ESMS for $C_7H_{12}O_3Na$: calcd: 167.0684, found: 167.0687. $[\alpha]_D^{25}$=+25.65 (c=0.35, $CHCl_3$).

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