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A simple route to enantiopure bis-lactones: synthesis of both enantiomers of *epi*-nor-canadensolide, nor-canadensolide, and canadensolide

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Abstract

A simple strategy has been developed for the synthesis of both enantiomers of nor-canadensolide, *epi*-nor-canadensolide, and an intermediate to canadensolide. An orthoester Claisen rearrangement of an appropriately constructed allyl alcohol derivative prepared from *R*-(+)-2,3-di-*O*-cyclohexylidine glyceraldehyde followed by epoxidation of the resulting unsaturated esters produced hydroxy-lactones, which on oxidation gave keto-lactones. Stereoselective reduction of the keto-carbonyl using either a chelation controlled or a non-chelation controlled process led to the natural or the *epi*-series, respectively. The interplay of the electronic effect between the polar groups and the steric effect of the β-substituent during reduction of the keto-lactones turned out to be the key factors in deciding the stereochemical outcome. Regeneration of the aldehyde functionality latent in the ketal moiety of the hydroxy-lactones provided the lactols, which on oxidation gave the bis-lactones.

Keywords: Asymmetric synthesis; Bis-lactones; Chelation; Stereocontrol

1. Introduction

The bis-lactone represented by the general structure **1** is found in a number of structurally related natural products such as canadensolide **1a**,[1] sporothriolide **1b**,[2] and xylobovide **1c**.[3] They differ only in the length of the side chain. These compounds exhibit important biological activities. For example, canadensolide **1a**, a mold metabolite formed by *Penicillium canadense*, possesses an antigerminative activity against fungi. Sporothriolide is an antibacterial, fungicidal, algicidal, and herbicidal agent while xylobovide is a phytotoxic agent. Due to the novel structure with three contiguous stereocenters and interesting biological activities, considerable attention has been focused on the development of new methodology for their synthesis.[4–21] As part of our interest in the synthesis of natural products containing fused butyro-lactones,[22] we initiated a program for developing a general flexible route toward the synthesis of these bis-lactones.

We envisaged the bicyclic lactols **2** with appropriate alkyl chain (R) as the intermediates to the bis-lactones (Scheme 1). In a few earlier approaches to canadensolide, the lactol **2a** has served as an intermediate. The lactol **2** would become available from the keto-lactone **3**. The ketal moiety in **3** would provide the aldehyde functionality and a stereocontrolled hydride reduction of the carbonyl group would deliver the hydroxyl group required for lactol formation. The keto-lactone **3** in principle should be available from the unsaturated ester **4** through lactonisation initiated by addition of an electrophile to the carbon–carbon double bond. Hydride reduction of the carbonyl group with a heteroatom at the α-chiral center generally proceeds with high diastereoselectivity especially when the reaction proceeds through a metal chelated intermediate. The keto-lactone **3** possesses a heteroatom (ring oxygen) next to the carbonyl group. In addition, it has a bulky substituent at β to the carbonyl group. Presumably, the stereochemical outcome during reduction of the keto-carbonyl in **3** would be determined by the interplay of the electronic effect exerted by the lactone oxygen and the steric hindrance posed by the ketal substituent. During the present synthetic investigation we had the opportunity to explore the stereochemical

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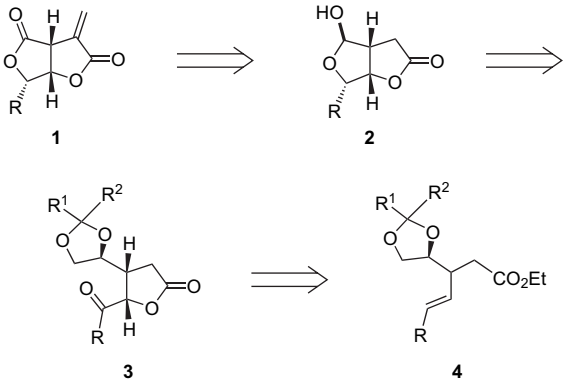
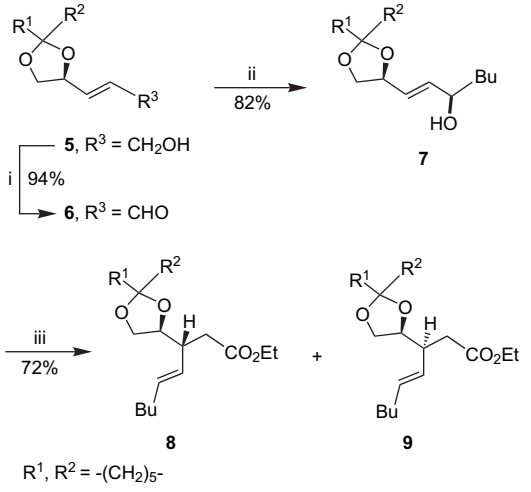
outcome in the reduction of the keto-lactone **3** along with its other three possible diastereomers. This investigation has allowed access to either the natural series or the *epi*-series of the bis-lactones. In this paper the approach is illustrated by a total synthesis of both enantiomers of nor-canadensolide, *epi*-nor-canadensolide and a formal synthesis of (+)-canadensolide and (−)-canadensolide.



Scheme 1.

2. Results and discussion

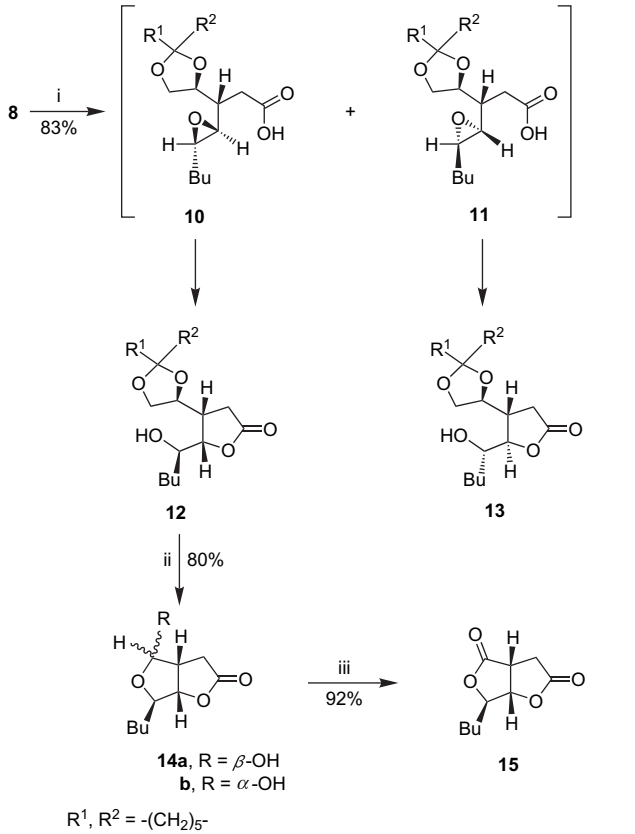
The unsaturated ester required for canadensolide was prepared from the allylic alcohol **5** as delineated in Scheme 2. The allylic alcohol **5** was obtained from *R*-(+)-2,3-di-*O*-cyclohexylidine glyceraldehyde according to the known procedure.[23] Oxidation of the alcohol **5** with Dess–Martin periodinane (DMP)[24] afforded the aldehyde **6** in excellent yield. Addition of *n*-BuLi to the aldehyde **6** followed by orthoester Claisen rearrangement of the resulting alcohol **7** led to a 1:1 mixture of the two diastereomers **8** and **9** in 37% and 35% yields, respectively.



Scheme 2. (i) DMP, CH_2Cl_2, 2 h; (ii) *n*-BuLi, THF, −78 °C; (iii) $H_3CC(OEt)_3$, propionic acid (cat.), 140 °C, 4 h.

The gross structure of the compounds **8** and **9** was easily ascertained from spectroscopic data. Stereochemical assignment to the compounds **8** and **9** followed from their transformation to (+)-nor-canadensolide **35** and (−)-nor-canadensolide (vide infra). Toward this end, the ester **8** was hydrolyzed with aqueous ethanolic KOH and the resulting acid was treated with *m*-CPBA to produce the lactones **12** and **13** in 46% and 45% isolated yields, respectively (Scheme 3). The lactone **12** was treated with 75% aqueous acetic acid and the liberated vicinal diol was cleaved with $NaIO_4$ to afford an inseparable mixture of the lactols **14a** and **14b** in 1:2 ratio as determined by integration of the proton attached to the anomeric carbon at δ 5.36 (s) for **14a** and at δ 5.54 (d, J=4.5 Hz) for **14b**. The stereochemical assignment to **14a** and **14b** is based on comparison of the observed coupling constants to those reported in the literature.[25] The mixture of the lactols **14a** and **14b** on Jones oxidation produced the bis-lactone **15**, $[\alpha]_D^{26}$ +25.03 (*c* 1.67, $CHCl_3$). The spectral data of the bis-lactone thus obtained were found to be comparable with those reported[18] for *epi*-nor-canadensolide. This confirmed the structure of the hydroxy-lactone as **12** and the intermediate epoxide as **10**. That the vicinal substituents in the lactone **13** are trans to each other was confirmed by its failure to undergo lactonisation when subjected to the reaction sequence for conversion of **12** to **15**.

A similar protocol was employed to establish the structure of the unsaturated ester **9**. Thus, the acid obtained from the



Scheme 3. (i) (a) KOH–EtOH–H_2O, 85 °C, 2 h; (b) *m*-CPBA, $ClCH_2CH_2Cl$, 0 °C to rt, 6 h; (ii) (a) AcOH–H_2O; (b) $NaIO_4$, 80% (two steps); (iii) Jones reagent, acetone, 0 °C.

ester **9** on treatment with *m*-CPBA afforded a mixture of the hydroxy-lactones **16** and **17** in 35% and 44% yields, respectively (Scheme 4). The hydroxy-lactone **16** was converted to the bis-lactone **18** using the protocol for transformation of the hydroxy-lactone **12** to the bis-lactone **15**. The bis-lactone **18** has specific rotation $[\alpha]_D^{26}$ −28.73 (*c* 1.41, $CHCl_3$) nearly equal and opposite to that observed for **15**. Thus, a synthesis of (+)-*epi*-nor-canadensolide and (−)-*epi*-nor-canadensolide from an *R*-(+)-glyceraldehyde derivative is achieved.

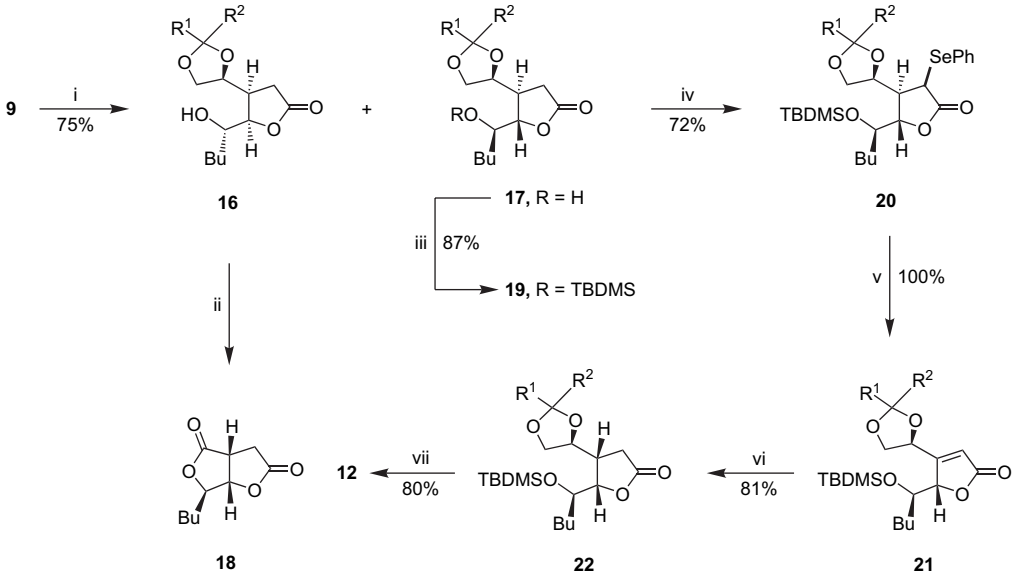
By analogy to the formation of the lactones **12** and **13** from the ester **8**, the hydroxy-lactone obtained along with **16** from the ester **9** was assigned the structure **17**. This assignment was further corroborated by its transformation to the hydroxy-lactone **12** as delineated in Scheme 4.

The hydroxyl group in **17** was protected to afford the silyl ether **19** in 87% yield. Reaction of lithium enolate of **19** with PhSeBr afforded the lactone **20**, which on treatment with hydrogen peroxide underwent selenoxide elimination to give the butenolide **21**. Hydrogenation of the butenolide **21** in the presence of PtO_2 as catalyst afforded exclusively the cis-disubstituted lactone **22**. Desilylation finally afforded **12**, the structure of which has already been established (Scheme 3).

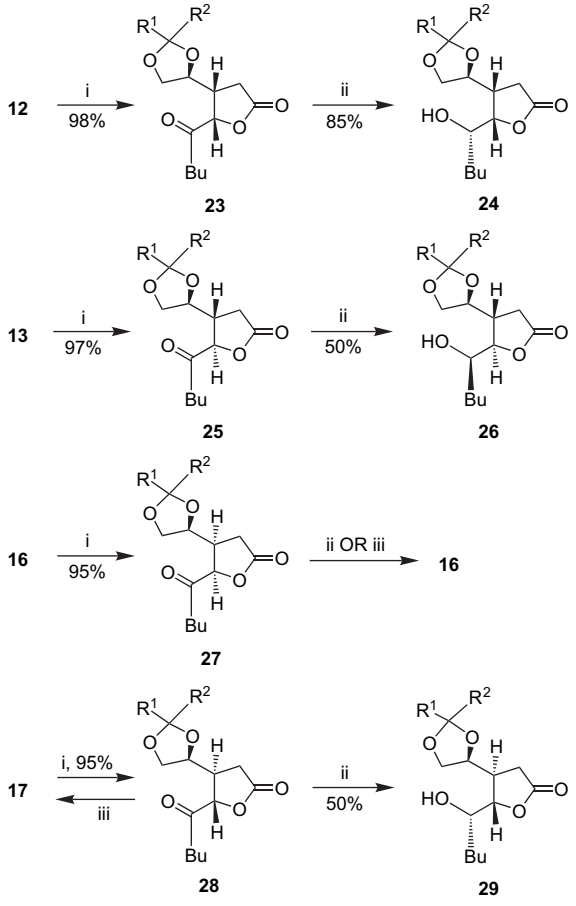
After achieving the synthesis of both enantiomers of nor-*epi*-canadensolide, we next focused our attention on the synthesis of canadensolide. For this purpose it is necessary to invert the stereochemistry of the butyl group in the *cis*-hydroxy-lactones **12** and **16**. An inversion of configuration at C-4 and the stereocenter bearing the butyl group in **13** and **17** can also be considered toward this end. We decided to pursue both this approach so that all the diastereomeric lactones obtained above can be converted to canadensolide. We thought that reduction of the keto-lactones derived from these hydroxy-lactones would be the simplest way of inverting the stereochemistry of the butyl group. This led us to investigate the reduction of all the four possible diastereoisomers of the keto-lactones **23**, **25**, **27**, and **28**. The keto-lactones **23**, **25**, **27**, and **28** were obtained by oxidation of the hydroxy-lactones **12**, **13**, **16**, and **17**, respectively, with DMP in excellent yields. Reduction of these ketones was carried out using $NaBH_4$–MeOH (condition A) as well as with $NaBH_4$–MeOH–$CeCl_3$ (condition B) (Scheme 5). The results are summarized in Table 1.

Reduction of the ketone **23** with $NaBH_4$ in MeOH gave a mixture of the hydroxy-lactones **12** and **24** in1:1 ratio. When the reduction was carried out in the presence of $CeCl_3$, the hydroxy-lactones **12** and **24** were obtained in a ratio of 1:9 (entry 1, Table 1). The predominant formation of **24** in the presence of $CeCl_3$ dictates that the latter plays a significant role in determining stereoselectivity and could be attributed to hydride delivery from the convex face of the chelated intermediate **30** (Fig. 1). Chromatographic purification of this mixture afforded the pure diastereomer **24** in 85% yield. Interestingly reduction of the ketone **27** with $NaBH_4$ alone or in the presence of $CeCl_3$ produced exclusively the hydroxy-lactone **16** (entry 2, Table 1). Inspection of the Drieding model revealed that of the two different conformers **31** and **32** of the keto-lactone **27**, the conformer **32** is preferred over **31** due to the presence of a steric interaction between the butyl residue and the ketal group in the latter.

In order to delve into the matter, we have performed some semi-empirical quantum mechanical calculations[26] on the conformers **31** and **32** in regard to their minimum energies by AM1 method developed by Dewar et al.[27] The results indicate that the conformer **32** (*E*=−4796.8791 kcal/mol) in which the butyl residue is away from the ketal is more stable than the conformer **31** (*E*=−4796.2877 kcal/mol) by ca. 0.6 kcal/mol.



Scheme 4. (i) (a) KOH–EtOH–H_2O, 85 °C, 2 h; (b) *m*-CPBA, $ClCH_2CH_2Cl$, 0 °C to rt, 6 h; (ii) (a) AcOH–H_2O–$NaIO_4$, 82%; (b) Jones reagent, acetone, 0 °C, 90%; (iii) TBDMSOTf, 2,6-lutidine, DCM, 0 °C; (iv) LDA, THF, −78 °C, HMPA, PhSeBr; (v) H_2O_2, Py, DCM–THF (2:1), 8 h; (vi) H_2–PtO_2, MeOH, 5 h; (vii) TBAF, THF, 0 °C–rt.



Scheme 5. (i) DMP, CH_2Cl_2, 2–2.5 h; (ii) $NaBH_4$, MeOH, $CeCl_3 \cdot 7H_2O$, −20 °C, 30 min; (iii) $NaBH_4$, MeOH, 0 °C, 30 min.

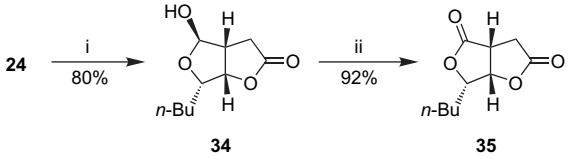
Table 1
Reduction of keto-lactones

Entry	Keto-lactones	Hydroxy-lactones	Product ratio
1	23	12+24	50:50[a]
			5:95[b]
2	27	16	100[a,b]
3	25	13+26	50:50[a]
			40:60[b]
4	28	17	100[a]
		29	100[b]

[a] Condition A.
[b] Condition B.

Thus reduction of the carbonyl group under both the conditions proceeds through the conformation **32** by addition of hydride from the *Re*-face to produce exclusively the hydroxy-lactone **16**.The observed diastereoselectivity may also be attributed by Felkin–Anh model as depicted in structure **33**. Reduction of the ketone **25** with $NaBH_4$ gave 1:1 mixture of the hydroxy-lactones **13** and **26**. However, in the presence of $CeCl_3$ the ratio of the hydroxy-lactones did not change significantly producing **13** and **26** in 2:3 ratio (entry 3). The ketal unit and the chain bearing the carbonyl group in the lactone **25** are *anti* to each other ruling out the possibility of chelation. Thus, no significant face selectivity was observed during reduction in the presence of $CeCl_3$. The major diastereomer **26** was isolated in 50% yield through column chromatography. The reduction of the ketone **28** (entry 4) with $NaBH_4$ produced the hydroxy-lactone **17** exclusively while with $NaBH_4$–$CeCl_3$ it gave the hydroxy-lactone **29** exclusively. Thus, a combination of electronic factor and steric factor influences the reduction of the carbonyl group in the keto-lactones **23**, **25**, **27**, and **28**.

The hydroxy-lactone **24** has the desired stereochemistry at C-4 and the center bearing the butyl group for synthesis of nor-canadensolide. Thus, treatment of the hydroxy-lactone **24** with aqueous acetic acid followed by cleavage of the resulting diol produced exclusively the lactol **34**, $[\alpha]_D^{26}$ +9.8 (*c* 1.64, $CHCl_3$) (Scheme 6). The stereochemical assignment to the lactol **34** follows from the coupling constant (J=0) of the proton attached to the anomeric center, which appeared as a singlet at δ 5.32. Notably, under identical conditions the ketal derivative **12** produced a mixture of the lactols **14a** and **14b** in 1:2 ratio (Scheme 3). The contrasting behavior of the ketals toward the formation of the bicycles is probably guided by the thermodynamic stability of the products leading predominantly the lactol **14b** from **12** and exclusively **34** from **24**. Jones oxidation of the lactol **34** finally afforded (+)-nor-canadensolide **35**, $[\alpha]_D^{24}$ +24.50 (*c* 1.2, $CHCl_3$); [lit.[6] $[\alpha]_D^{23}$ +26.2 (*c* 0.50, $CHCl_3$)]. The lactol **34** has already been converted to (+)-canadensolide.[6]



Scheme 6. (i) HOAc–H_2O then $NaIO_4$; (ii) Jones reagent, acetone, 0 °C.

Finally, the hydroxy-lactone **26** obtained by reduction of the ketone **25** was transformed to (−)-nor-canadensolide (−)-**35** as delineated in Scheme 7. To this end, the hydroxy group in **26** was protected to give the silyl ether **36**. The lactone **36** was then converted to selenophenyl derivative **37** in 73% yield through alkylation of its lithium enolate with

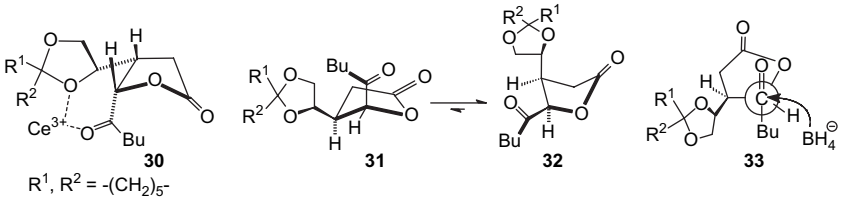
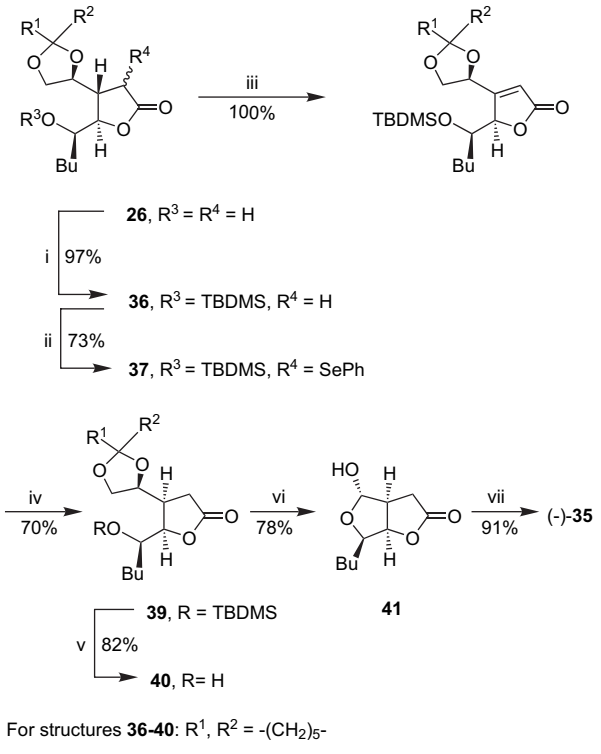


Figure 1.



Scheme 7. (i) TBDMSOTf, 2,6-lutidine, DCM, 0 °C–rt; (ii) LDA, THF, −78 °C, HMPA, PhSeBr; (iii) H_2O_2, Py, DCM–THF (2:1), 8 h; (iv) H_2–PtO_2, MeOH, 5 h; (v) TBAF, THF, 0 °C to rt; (vi) HOAc–H_2O then $NaIO_4$; (vii) Jones reagent, acetone, 0 °C.

phenylselenyl bromide. Elimination of selenoxide from **37** afforded the butenolide **38** in near quantitative yield. Hydrogenation of the butenolide **38** over PtO_2 afforded after chromatographic purification the cis compound **39** (70%). Desilylation of the lactone **39** gave the hydroxy-lactone **40**. Treatment of **40** with aqueous acetic acid followed by cleavage of the resulting diol with periodate afforded the lactol **41**, $[\alpha]_D^{25}$ −10.0 (*c* 0.2, $CHCl_3$) [lit.[5] $[\alpha]_D$ −14.9 (*c* 1.0, $CHCl_3$) (for an anomeric mixture of lactols)]. Jones oxidation of the lactol **41** gave (−)-nor-canadensolide (−)-**35**. The spectral data and $[\alpha]_D^{26}$ −21.5 (*c* 1.09, $CHCl_3$) [lit. $[\alpha]_D^{23}$ −18.9 (c 4.79, $CHCl_3$)] for the sample prepared by us were comparable with those reported in the literature.[10] The lactol **41** has already been converted to (−)-canadensolide by earlier workers.[4,5,10] Thus, starting with *R*-(+)-2,3-di-*O*-cyclohexylidine glyceraldehyde a formal synthesis of both enantiomers of canadensolide is achieved.

3. Conclusion

We have developed a general strategy for synthesis of the bis-lactone **1** in enantiomerically pure form. The strategy has been illustrated by a formal synthesis of both enantiomers of canadensolide starting from *R*-(+)-2,3-di-*O*-cyclohexilidine glyceraldehyde. Stereocontrolled reduction of the carbonyl group in an appropriately constructed keto-lactone gave both canadensolide and *epi*-canadensolide. The stereochemical outcome during reduction of the carbonyl group in the keto-lactones has been demonstrated to be influenced significantly by steric and electronic effects imposed by the polar groups present in the keto-lactones.

4. Experimental section

4.1. General

Melting points were taken in open capillaries in a sulfuric acid bath. Petroleum ether refers to the fraction having bp 60–80 °C. A usual workup of the reaction mixture consists of extraction with ether, washing with brine, drying over Na_2SO_4, and removal of the solvent in vacuo. Column chromatography was carried out with silica gel (60–120 mesh). Peak positions in ^1H and ^{13}C NMR spectra are indicated in parts per million downfield from internal TMS in δ units. NMR spectra were taken in $CDCl_3$ at 300 MHz for ^1H and 75 MHz for ^{13}C. ^{13}C peak assignment is based on DEPT experiment. IR spectra were recorded as neat for liquid and in KBr for solids. Unless otherwise indicated, all reactions were carried out under blanket of Ar.

4.1.1. (1E)-1-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]hept-1-en-3-ol 7

To a magnetically stirred suspension of Dess–Martin periodinane (7.7 g, 18.2 mmol) in dichloromethane (30 mL) at 0 °C, the allylic alcohol **5** (3.0 g, 15.2 mmol) in dichloromethane (15 mL) was added drop-wise. The reaction mixture was stirred for 30 min and was quenched with 10% $Na_2S_2O_3$ solution (15 mL) doped with $NaHCO_3$. The organic layer was separated and the aqueous part extracted with diethyl ether (2×100 mL). The combined organic layer was dried to afford the enal **6** (2.8 g, 94%). Without further purification, it was used in the next step. To a solution of the enal **6** (2.8 g, 14.2 mmol) in THF (40 mL) cooled to −78 °C *n*-BuLi (14.4 mL, 17.2 mmol, 1.5 M in hexane) was added drop-wise. The reaction mixture was stirred for 30 min at −78 °C and then warmed to −30 °C and quenched with saturated aqueous NH_4Cl (3 mL). Usual workup of the reaction mixture with diethyl ether (2×80 mL) followed by column chromatography (ether–petroleum ether 1:5) afforded the allylic alcohol **7** (1.5 g, 82%) as a colorless liquid. IR 3419.6, 1448.4 cm^{-1}; ^1H NMR (of the diastereomeric mixture) δ 0.87 (3H, t, *J*=6.5 Hz), 1.24–1.45 (6H, m), 1.47–1.60 (10H, m), 1.87 (1H, br s), 3.52–3.58 (1H, m), 4.03–4.10 (2H, m), 4.49 (1H, q, *J*=6.8 Hz), 5.63 (1H, m), 5.77 (1H, m); ^{13}C NMR δ 14.1, 14.2, 22.7, 23.9, 24.0, 24.1, 25.2, 27.7, 35.5, 35.6, 36.3, 36.6, 36.9, 69.2, 69.3, 72.0, 72.2, 76.3, 110.08, 110.12, 128.1, 128.3, 137.2, 137.3; HRMS (ESI) calcd for $C_{15}H_{26}O_3Na$ $(M+Na)^+$, 277.1780; found, 277.1772.

4.1.2. Ethyl (3R,4E)-3-[(2S)-1,4-dioxaspiro[4.5]dec-2-yl]hex-4-enoate 8 and ethyl (3S,4E)-3-[(2S)-1,4-dioxaspiro[4.5]dec-2-yl]hex-4-enoate 9

A mixture of the allylic alcohol **7** (1.26 g, 5.0 mmol), triethylorthoacetate (7.2 mL, 50.0 mmol), propionic acid (10 mg,

172.0 μmol), and xylene (20 mL) was heated at 140 °C for 4 h. The excess triethylorthoacetate and xylene was removed by distillation at reduced pressure. The residual mass was then purified by flash chromatography (ether–petroleum ether 1:20) to afford the ester **8** (570 mg, 37%): R_f=0.6 (EtOAc–petroleum ether 1:9); $[\alpha]_D^{24}$ +7.20 (*c* 1.5, $CHCl_3$); IR 1737.7 cm^{-1}; ^1H NMR δ 0.84 (3H, t, *J*=7.0 Hz), 1.21 (3H, t, *J*=7.2 Hz), 1.25–1.29 (4H, m), 1.36 (2H, br s), 1.54 (4H, br s), 1.58 (4H, br s), 1.94 (2H, dt, *J*=6.7, 6.6 Hz), 2.25 (1H, dd, *J*=9.3, 14.5 Hz), 2.57 (1H, m), 2.69 (1H, dd, *J*=4.5, 14.5 Hz), 3.63 (1H, dd, *J*=5.7, 7.3 Hz), 3.87 (1H, dd, *J*=4.8, 7.3 Hz), 3.91 (1H, q, *J*=6.1 Hz), 4.09 (2H, q, *J*=7.2 Hz), 5.14 (1H, dd, *J*=8.8, 15.4 Hz), 5.52 (1H, td, *J*=6.7, 15.4 Hz); ^{13}C NMR δ 13.9, 14.4, 22.1, 23.9, 24.1, 25.3, 31.5, 32.3, 35.2, 36.6, 37.6, 44.6, 60.3, 67.9, 77.8, 110.0, 128.0, 134.3, 172.6; HRMS (ESI) calcd for $C_{19}H_{32}O_4Na$ $(M+Na)^+$, 347.2198; found, 347.2191 and the ester **9** (550 mg, 35%): R_f=0.5 (EtOAc–petroleum ether 1:9); $[\alpha]_D^{24}$ +35.75 (*c* 1.6, $CHCl_3$); IR 1737.7 cm^{-1}; ^1H NMR δ 0.84 (3H, t, *J*=6.8 Hz), 1.20 (3H, t, *J*=7.1 Hz), 1.27 (4H, m), 1.35 (2H, br s), 1.53 (4H, br s), 1.56 (4H, br s), 1.97 (2H, dt, *J*=7.8, 7.8 Hz), 2.31 (1H, dd, *J*=9.3, 15.0 Hz), 2.49 (1H, dd, *J*=5.3, 15.0 Hz), 2.70 (1H, m), 3.60 (1H, t, *J*=7.6 Hz), 3.90 (1H, t, *J*=7.6 Hz), 4.04–4.11 (3H, m), 5.26 (1H, dd, *J*=8.5, 15.4 Hz), 5.48 (1H, td, *J*=6.7, 15.4 Hz); ^{13}C NMR δ 14.0, 14.3, 22.1, 23.9, 24.0, 25.3, 31.5, 32.3, 34.9, 35.9, 36.5, 41.7, 60.4, 66.2, 77.2, 109.6, 127.4, 134.2, 172.6; HRMS (ESI) calcd for $C_{19}H_{32}O_4Na$ $(M+Na)^+$, 347.2198; found, 347.2197.

*4.1.3. (4S,5S)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-[(1R)-1-hydroxypentyl]dihydrofuran-2(3H)-one **12** and (4S,5R)-4-[(2S)-1,4-dioxaspiro[4.5]dec-2-yl]-5-[(1S)-1-hydroxypentyl]dihydrofuran-2(3H)-one **13***

A solution of the ester **8** (1.8 g, 5.6 mmol) in EtOH (15 mL) was heated under reflux with KOH (1.6 g, 28.0 mmol) and water (4 mL) for 2.5 h. After removing ethanol under reduced pressure the residual mass at ice-cold condition was diluted with water (3 mL) and was acidified carefully with HCl (5 mL, 4 N). The organic compound was then worked up to afford the acid (1.5 g, 91%) as sticky yellowish liquid. To a magnetically stirred cooled (0 °C) solution of the unsaturated acid (1.7 g, 5.7 mmol) in 1,2-dichloroethane (25 mL) was added *m*-CPBA (1.7 g, 7.6 mmol) portion-wise. Stirring was continued for 6 h at rt. The precipitated white solid was filtered off and washed thoroughly with diethyl ether. The combined filtrate and washing was washed sequentially with saturated Na_2SO_3 (3×2 mL) and saturated $NaHCO_3$ (3×2 mL), and dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography of the residual mass afforded the hydroxy-lactone **12** (810 mg, 46%): R_f=0.3 (EtOAc–petroleum ether 1:1); IR 3419.6, 1766.7 cm^{-1}; $[\alpha]_D^{26}$ +7.56 (*c* 1.5, $CHCl_3$); ^1H NMR δ 0.90 (3H, t, *J*=6.8 Hz), 1.35 (6H, br s), 1.43–1.60 (10H, m), 1.80 (1H, br s), 2.49 (1H, dd, *J*=8.4, 17.1 Hz), 2.60 (1H, dd, *J*=5.1, 17.1 Hz), 2.68–2.73 (1H, m), 3.58 (1H, t, *J*=7.6 Hz), 3.88 (1H, dt, *J*=2.0, 7.5 Hz), 4.10 (1H, t, *J*=7.6 Hz), 4.23 (1H, t, *J*=7.3 Hz), 4.60 (1H, dt, *J*=2.3, 6.7 Hz); ^{13}C NMR δ 14.1, 22.7, 23.9, 24.0, 25.1, 27.3, 29.8, 34.2, 34.3, 35.7, 40.0, 67.6, 70.0, 72.4, 83.4, 110.8, 176.1; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $(M+Na)^+$, 335.1834; found, 335.1837 and the hydroxy-lactone **13** (800 mg, 45%): R_f=0.4 (EtOAc–petroleum ether 1:1); IR 3446.6, 1774.4 cm^{-1}; $[\alpha]_D^{25}$ −9.2 (*c* 1.75, $CHCl_3$); ^1H NMR δ 0.91 (3H, t, *J*=6.9 Hz), 1.32–1.41 (6H, m), 1.46 (2H, m), 1.54 (4H, br s), 1.59 (4H, br s), 2.93 (1H, br s), 2.47–2.64 (2H, m), 2.72 (1H, m), 3.55 (1H, dd, *J*=6.7, 8.1 Hz), 3.83 (1H, dt, *J*=3.5, 8.2 Hz), 4.04 (1H, t, *J*=7.5 Hz), 4.17 (1H, dt, *J*=3.8, 6.4 Hz), 4.29 (1H, t, *J*=3.1 Hz); ^{13}C NMR δ 14.1, 22.7, 23.8, 24.0, 25.2, 27.9, 30.1, 32.2, 34.4, 36.1, 37.4, 66.9, 72.3, 75.9, 85.0, 110.3, 177.3; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $(M+Na)^+$, 335.1834; found, 335.1832.

*4.1.4. (3aR,6R,6aS)-6-Butyl-4-hydroxytetrahydrofuro[3,4-b]furan-2(3H)-one **14***

A solution of the hydroxy-lactone **12** (110 mg, 0.35 mmol) in CH_3CN (0.5 mL) was treated with 75% aqueous AcOH (2 mL) at rt for 6 h. To the resulting solution cooled to 0 °C $NaIO_4$ (374 mg, 1.75 mmol) was added pinch-wise. After stirring for 4 h at rt the reaction mixture was diluted with diethyl ether (20 mL). The entire mass was transferred to a separatory funnel and washed with saturated $NaHCO_3$ solution (3×1 mL) until alkaline. The organic layer was dried (Na_2SO_4) and concentrated to afford a mixture of the lactols **14a** and **14b** (57 mg, 80%) as a low melting solid (mp 42–45 °C). IR 3444.6, 1770.5 cm^{-1}; ^1H NMR (of the anomeric mixture) δ 0.91 (3H, t, *J*=6.0 Hz), 1.37–1.49 (4H, m), 1.62–1.74 (2H, m), 2.50–2.60 (1H, m), 2.74–2.88 (1H, m), 2.96–3.06 (1H, m), 4.21 (1H, t, *J*=7.7 Hz), 4.27–4.32 (1H, m), 4.60 (1H, dd, *J*=3.0, 7.8 Hz), 4.89 (1H, m), 5.36 (1H, s), 5.54 (1H, d, *J*=4.4 Hz); ^{13}C NMR δ 14.0, 14.1, 22.4, 22.6, 27.6, 28.0, 29.2, 32.0, 32.8, 34.2, 43.8, 46.3, 82.8, 85.6, 86.7, 87.4, 97.4, 104.7, 176.3, 177.3; HRMS (ESI) calcd for $C_{10}H_{16}O_4Na$ $(M+Na)^+$, 223.0946; found, 223.0920.

*4.1.5. (3aR,6R,6aS)-6-Butyltetrahydrofuro[3,4-b]furan-2,4-dione **15***

The lactol **14** (50 mg, 2.5 mmol) in acetone (1 mL) as obtained above was immediately treated with Jones reagent at 0 °C until the color of the reagent persisted. Workup of the reaction mixture with diethyl ether followed by column chromatography (ethyl acetate–petroleum ether 1:3) afforded bis-lactone **15** (46 mg, 92%) as a white crystalline solid. Mp 85–86 °C (lit. (±)-**15**, mp 85–86 °C); IR 1772.5 cm^{-1}; $[\alpha]_D^{26}$ +25.03 (*c* 1.67, $CHCl_3$); ^1H NMR δ 0.92 (3H, t, *J*=6.8 Hz), 1.44 (4H, m), 1.67 (2H, dt, *J*=7.2, 7.2 Hz), 2.82–2.95 (2H, m), 3.45 (1H, ddd, *J*=3.4, 6.3, 9.2 Hz), 4.67 (1H, t, *J*=7.0 Hz), 4.87 (1H, d, *J*=6.5 Hz); ^{13}C NMR δ 13.9, 22.3, 26.7, 31.0, 32.6, 39.8, 82.0, 84.2, 173.4, 175.4; HRMS (ESI) calcd for $C_{10}H_{14}O_4Na$ $(M+Na)^+$, 221.0790; found, 221.0799.

*4.1.6. (4R,5R)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-[(1S)-1-hydroxypentyl]dihydrofuran-2(3H)-one **16** and (4R,5S)-4-[(2S)-1,4-dioxaspiro[4.5]dec-2-yl]-5-[(1R)-1-hydroxypentyl]dihydrofuran-2(3H)-one **17***

Following the procedure similar to the conversion of the ester **8** to the hydroxy-lactones **12** and **13**, the ester **9**

(550 mg, 1.7 mmol) was converted to a diastereomeric mixture of the hydroxy-lactone **16** (110 mg, 35%). R_f=0.4 (EtOAc–petroleum ether 1:1); IR 3444.6, 1770.5 cm^{-1}; $[\alpha]_D^{24}$ −42.3 (*c* 1.2, $CHCl_3$); ^1H NMR δ 0.90 (3H, t, *J*=6.9 Hz), 1.24–1.43 (6H, m), 1.47–1.60 (10H, m), 2.15 (1H, dd, *J*=4.2, 17.7 Hz), 2.58 (1H, m), 2.76 (1H, dd, *J*=9.8, 17.7 Hz), 3.60 (1H, m), 3.82 (1H, m), 4.08 (2H, m), 4.41 (1H, t, *J*=3.5 Hz); ^{13}C NMR δ 14.1, 22.7, 23.8, 24.0, 25.1, 27.7, 32.0, 32.4, 34.7, 36.4, 39.6, 67.5, 72.8, 76.8, 85.2, 110.7, 176.6; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $(M+Na)^+$, 335.1834; found, 335.1832 and the hydroxy-lactone **17** (140 mg, 44%): R_f=0.5 (EtOAc–petroleum ether 1:1); IR 3431.1, 1780.2 cm^{-1}; $[\alpha]_D^{24}$ −10.32 (*c* 2.0, $CHCl_3$); ^1H NMR δ 0.91 (3H, t, *J*=7.1 Hz), 1.33–1.43 (6H, m), 1.45–1.60 (8H, m), 1.75 (2H, m), 2.08 (1H, dd, *J*=5.5, 21.0 Hz), 2.74 (1H, m), 2.76 (1H, dd, *J*=8.1, 20.6 Hz), 3.60 (1H, t, *J*=7.6 Hz), 3.87 (1H, dt, *J*=2.6, 8.2 Hz), 4.15 (1H, t, *J*=7.2 Hz), 4.18–4.28 (2H, m); ^{13}C NMR δ 14.2, 22.9, 24.0, 24.1, 24.9, 27.3, 32.9, 33.6, 35.1, 36.2, 42.2, 68.6, 69.3, 73.1, 84.6, 111.6, 174.9; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $(M+Na)^+$, 335.1834; found, 335.1831.

*4.1.7. (3aS,6S,6aR)-6-Butyltetrahydrofuro[3,4-b]furan-2,4-dione **18***

Following the procedure for the conversion of the hydroxy-lactone **12** to the bis-lactone **15**, the hydroxy-lactone **16** (100 mg, 0.32 mmol) was first converted to a cyclic hemiacetal (52 mg, 82%) followed by Jones oxidation to afford the bis-lactone **18** (46 mg, 90%), an enantiomer of the bis-lactone **15** as a white crystalline solid. $[\alpha]_D^{26}$ −28.73 (*c* 1.41, $CHCl_3$); HRMS (ESI) calcd for $C_{10}H_{14}O_4Na$ $(M+Na)^+$, 221.0790; found, 221.0799.

*4.1.8. 5-[1(R)-1-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-(4R,5S)-4-[(2S)-1,4-dioxa-spiro[4.5]dec-2-yl]dihydro-furan-2-one **19***

To a stirring solution of the secondary alcohol **17** (140 mg, 0.45 mmol) in dichloromethane (8 mL) 2,6-lutidine (0.1 mL, 0.90 mmol) was added drop-wise. After stirring for 5 min at rt the reaction mixture was cooled to 0 °C. TBDMSOTf (0.14 mL, 0.58 mmol) was then added drop-wise and stirred for 10 min at the same temperature. The solvent was removed by blowing nitrogen and the residual organic material was chromatographed (ether–petroleum ether 1:9) to afford the lactone **19** (167 mg, 87%) as a colorless liquid. IR 1782.1 cm^{-1}; $[\alpha]_D^{25}$ −24.54 (*c* 2.07, $CHCl_3$); ^1H NMR δ 0.00 (3H, br s), 0.03 (3H, br s), 0.82 (12H, br s), 1.20–1.32 (6H, m), 1.50–1.54 (10H, m), 2.23 (1H, dd, *J*=9.1, 16.8 Hz), 2.42 (1H, dd, *J*=11.3, 16.7 Hz), 2.72 (1H, m), 3.44 (1H, t, *J*=7.7 Hz), 4.00 (2H, dd, *J*=6.0, 7.9 Hz), 4.45–4.56 (2H, m); ^{13}C NMR δ −4.4, −4.3, 14.4, 18.3, 23.2, 24.2, 24.3, 25.5, 26.3 ($3CH_3$), 28.5, 31.9, 33.9, 35.5, 36.9, 42.7, 68.6, 73.9, 76.0, 83.0, 110.5, 176.3; HRMS (ESI) calcd for $C_{23}H_{42}O_5SiNa$ $(M+Na)^+$, 449.2699; found, 449.2671.

*4.1.9. 5-[1(R)-1-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-(4R,5S)-4-[(2S)-1,4-dioxa-spiro[4.5]dec-2-yl]-3-phenylselanyl-dihydro-furan-2-one **20***

To a magnetically stirred solution of diisopropylamine (0.16 mL, 1.08 mmol) in anhydrous THF (3 mL) cooled to −20 °C under argon atmosphere was added drop-wise *n*-BuLi (0.57 mL, 0.85 mmol, 1.5 M in hexane), and stirred for 40 min. The solution was then cooled to −78 °C and a solution of the protected lactone **19** (180 mg, 0.42 mmol) in THF (4 mL) was added drop-wise. The reaction mixture was then slowly warmed to −30 °C and stirred at that temperature for 30 min. The temperature of the reaction mixture was again brought to −78 °C and to it HMPA (0.1 mL) and phenylselenyl bromide (120 mg, 0.50 mmol) in THF (3 mL) were added sequentially. The reaction mixture was then allowed to attain rt. After quenching with saturated NH_4Cl solution, the reaction mixture was worked up in the usual way with diethyl ether (3×12 mL) to afford after column chromatography (ether–petroleum ether 1:8) the lactone **20** (200 mg, 81%) as a light yellow liquid. ^1H NMR δ 0.00 (3H, br s), 0.02 (3H, br s), 0.80 (12H, m), 1.22 (4H, m), 1.40 (2H, br s), 1.51 (10H, br s), 2.68 (1H, q, *J*=7.5 Hz), 3.79 (1H, d, *J*=7.7 Hz), 3.88 (2H, m), 4.01 (1H, dd, *J*=5.8, 8.7 Hz), 4.33 (1H, dd, *J*=3.3, 7.3 Hz), 4.45 (1H, q, *J*=7.0 Hz), 7.30 (3H, m), 7.62 (2H, d, *J*=6.6 Hz); ^{13}C NMR δ −4.3, −4.1, 14.5, 18.4, 23.2, 24.2, 24.3 25.5, 26.3 ($3CH_3$), 27.9, 33.9, 35.4, 36.7, 40.9, 47.6, 67.6, 73.7, 74.5, 81.7, 109.4, 127.0, 129.6, 129.8 (2CH), 136.3 (2CH), 175.9; HRMS (ESI) calcd for $C_{29}H_{46}O_5SeSiNa$ $(M+Na)^+$, 605.2180; found, 605.2188.

*4.1.10. 5-[1(R)-1-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-(5S)-4-[(2S)-1,4-dioxa-spiro[4.5]dec-2-yl]-5H-furan-2-one **21***

To a solution of the lactone **20** (200 mg, 0.34 mmol) in dichloromethane (6 mL) and THF (3 mL), pyridine (0.05 mL, 0.57 mmol) was added followed by addition of 30% H_2O_2 (5 mL) drop-wise. The reaction mixture was stirred at rt for about 8 h. It was then worked up with diethyl ether to afford after column chromatography (ether–petroleum ether 1:10) the unsaturated lactone **21** (145 mg, 100%) as a light yellow liquid. IR 1760.9 cm^{-1}; $[\alpha]_D^{25}$ +48.3 (*c* 1.0, $CHCl_3$); ^1H NMR δ 0.05 (3H, br s), 0.06 (3H, br s), 0.83–0.92 (12H, m), 1.31 (4H, m), 1.41 (4H, m), 1.60 (8H, br s), 3.91 (1H, dd, *J*=6.6, 8.2 Hz), 4.12 (1H, t, *J*=6.4 Hz), 4.28 (1H, dd, *J*=6.4, 8.2 Hz), 4.81 (1H, t, *J*=6.2 Hz), 5.08 (1H, s), 5.92 (1H, s); ^{13}C NMR δ −4.7, −4.5, 14.1, 18.1, 22.7, 23.9, 24.0, 25.0, 25.9 ($3CH_3$), 28.4, 32.7, 35.1, 36.0, 68.4, 71.8, 72.6, 86.6, 111.1, 117.6, 167.8, 172.4; HRMS (ESI) calcd for $C_{23}H_{40}O_5SiNa$ $(M+Na)^+$, 447.2543; found, 447.2541.

*4.1.11. 5-[1(R)-1-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-(4S,5S)-4-[(2S)-1,4-dioxa-spiro[4.5]dec-2-yl]dihydro-furan-2-one **22***

To a solution of the unsaturated lactone **21** (110 mg, 0.26 mmol) in methanol (8 mL) at rt was added PtO_2 (10 mg). The reaction mixture was stirred under hydrogen atmosphere for 5 h and then filtered through filter paper.

Removal of methanol under reduced pressure followed by column chromatography (ether–petroleum ether 1:9) gave the lactone **22** (90 mg, 81%) as colorless oil. IR 1778.2 cm^{-1}; $[\alpha]_D^{25}$ +14.56 (*c* 1.6, $CHCl_3$); ^1H NMR δ 0.05 (3H, br s), 0.07 (3H, br s), 0.87 (12H, br s), 1.30–1.51 (8H, m), 1.56 (4H, br s), 1.60 (4H, br s), 2.46 (1H, dd, *J*=3.8, 17.7 Hz), 2.61 (1H, dd, *J*=9.8, 17.7 Hz), 2.75 (1H, m), 3.54 (1H, t, *J*=7.5 Hz), 3.89 (1H, m), 4.04 (1H, t, *J*=7.3 Hz), 4.16 (1H, dd, *J*=4.5, 6.4 Hz), 4.36 (1H, t, *J*=2.6 Hz); ^{13}C NMR δ −4.6, −4.5, 14.1, 18.1, 23.0, 23.9, 24.0, 25.2, 26.0 ($3CH_3$), 27.6, 30.4, 33.6, 34.5, 36.2, 36.5, 66.8, 73.4, 76.2, 83.9, 110.3, 176.7; HRMS (ESI) calcd for $C_{23}H_{42}O_5SiNa$ $(M+Na)^+$, 449.2699; found, 449.2684.

4.1.12. Deprotection of silyl group from the lactone ***22***

Deprotection of TBDMS group from the lactone **22** (70 mg, 0.16 mmol) in tetrahydrofuran (5 mL) was accomplished with tetrabutylammonium fluoride (68 mg, 0.24 mmol). After stirring the reaction mixture at rt for 4 h, it was worked up to afford after column chromatography (ethyl acetate–petroleum ether 1:3) the hydroxy-lactone **12** (41 mg, 80%). $[\alpha]_D^{26}$ +7.6 (*c* 0.71, $CHCl_3$).

4.1.13. (4S,5S)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-pentanoyldihydrofuran-2(3H)-one ***23***

Following the procedure for oxidation of the alcohol **5** the hydroxy-lactone **12** (150 mg, 0.48 mmol) in dichloromethane (10 mL) was carried out with Dess–Martin periodinane (244 mg, 0.58 mmol) to afford after column chromatography (ether–petroleum ether 1:4) the keto-lactone **23** (146 mg, 98%) as white crystalline solid. Mp 71–72 °C; IR 1780.2, 1714.6 cm^{-1}; $[\alpha]_D^{25}$ +39.3 (*c* 1.8, $CHCl_3$); ^1H NMR δ 0.90 (3H, t, *J*=7.3 Hz), 1.29–1.63 (14H, m), 2.59–2.66 (2H, m), 2.69–2.79 (2H, m), 2.89 (1H, m), 3.53 (1H, dd, *J*=6.3, 8.3 Hz), 4.04 (1H, t, *J*=7.8 Hz), 4.24 (1H, t, *J*=6.2 Hz), 4.81 (1H, d, *J*=8.0 Hz); ^{13}C NMR δ 14.0, 22.3, 23.8, 24.1, 24.6, 25.2, 29.0, 33.8, 35.6, 40.0, 40.6, 67.0, 72.1, 84.0, 111.0, 175.5, 209.8; HRMS (ESI) calcd for $C_{17}H_{26}O_5Na$ $(M+Na)^+$, 333.1678; found, 333.1672.

4.1.14. General procedure for the reduction of the keto-lactones with $NaBH_4$–MeOH at 0 °C (Condition A): (4S,5S)-4-[(2S)-1,4-dioxaspiro[4.5]dec-2-yl]-5-[(1S)-1-hydroxypentyl]dihydrofuran-2(3H)-one ***24***

To a magnetically stirred solution of the keto-lactone **23** (150 mg, 0.48 mmol) in methanol (12 mL) at 0 °C was added $NaBH_4$ (22 mg, 0.56 mmol) portion-wise. After stirring for 20 min at that temperature the reaction mixture was quenched by addition of AcOH. Usual workup of the reaction mixture afforded after column chromatography (ethyl acetate–petroleum ether 1: 3) a 1:1 diastereomeric mixture of hydroxyl-lactones **12** (60 mg, 40%) and **24** (41 mg, 41%) as light yellow viscous liquid. IR 3489.0, 1772.5 cm^{-1}; $[\alpha]_D^{25}$ +8.24 (*c* 0.93, $CHCl_3$); ^1H NMR δ 0.89 (3H, t, *J*=6.7 Hz), 1.31–1.45 (6H, m), 1.46–1.68 (10H, m), 2.43 (1H, dd, *J*=7.8, 13.4 Hz), 2.77 (1H, dd, *J*=9.8, 13.2 Hz), 2.82 (1H, m), 3.22 (1H, br s), 3.58 (1H, t, *J*=7.8 Hz), 3.78 (1H, t, *J*=3.9 Hz), 4.12 (1H, t, *J*=7.3 Hz), 4.37–4.43 (2H, m); ^{13}C NMR δ 14.1, 22.7, 23.9, 24.0, 25.0, 28.2, 29.1, 32.8, 34.8, 35.8, 40.4, 67.9, 71.0, 72.3, 82.8, 111.1, 176.2; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $(M+Na)^+$, 335.1834; found, 335.1828.

4.1.15. (4S,5R)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-pentanoyldihydrofuran-2(3H)-one ***25***

Following the procedure for oxidation of the hydroxy-acetone **12**, the hydroxy-lactone **13** (500 mg, 1.6 mmol) was oxidized with Dess–Martin periodinane to afford the keto-lactone **25** (480 mg, 97%) as a crystalline white solid. Mp 68–69 °C; IR 1789.8, 1716.5 cm^{-1}; $[\alpha]_D^{25}$ −93.9 (*c* 1.41, $CHCl_3$); ^1H NMR δ 0.90 (3H, t, *J*=7.3 Hz), 1.24–1.40 (4H, m), 1.52–1.62 (10H, m), 2.52–2.73 (5H, m), 3.58 (1H, dd, *J*=6.4, 8.5 Hz), 4.10 (1H, dd, *J*=6.9, 8.3 Hz), 4.33 (1H, dt, *J*=3.4, 6.4 Hz), 4.68 (1H, d, *J*=5.4 Hz); ^{13}C NMR δ 13.9, 22.3, 23.8, 24.0, 25.0, 25.2, 28.5, 34.4, 36.0, 39.0, 40.7, 67.0, 74.8, 83.8, 110.6, 175.2, 208.1; HRMS (ESI) calcd for $C_{17}H_{26}O_5Na$ $(M+Na)^+$, 333.1678; found, 333.1674.

4.1.16. (4S,5R)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-[(1R)-1-hydroxypentyl]dihydrofuran-2(3H)-one ***26***

Following the reduction condition A, the keto-lactone **25** (120 mg, 1.3 mmol) was reduced to a 1:1 diastereomeric mixture of separable hydroxyl-lactones **13** (49 mg, 38%) and **26** (48 mg, 37%). IR 3444.6, 1778.2 cm^{-1}; $[\alpha]_D^{25}$ −5.4 (*c* 0.8, $CHCl_3$); ^1H NMR δ 0.94 (3H, t, *J*=6.7 Hz), 1.44 (6H, m), 1.59 (4H, br s), 1.63 (6H, br s), 2.64 (2H, dd, *J*=3.6, 7.7 Hz), 2.75 (1H, m), 3.60 (2H, m), 4.08 (1H, t, *J*=7.4 Hz), 4.22 (1H, dt, *J*=5.2, 6.4 Hz), 4.34 (1H, dd, *J*=1.5, 5.0 Hz); ^{13}C NMR δ 14.1, 22.6, 23.8, 24.0, 25.2, 28.0, 29.7, 33.7, 34.6, 36.0, 39.4, 67.0, 72.3, 74.8, 84.2, 110.4, 176.8; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $(M+Na)^+$, 335.1834; found, 335.1838.

4.1.17. (4R,5R)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-pentanoyldihydrofuran-2(3H)-one ***27***

Following the procedure for oxidation of the hydroxy-acetone **12**, the hydroxy-acetone **16** (200 mg, 0.64 mmol) was oxidized with Dess–Martin periodinane to afford the keto-lactone **27** (188 mg, 95%) as a crystalline white solid. Mp 72–73 °C; IR 1793.7, 1714.6 cm^{-1}; ^1H NMR δ 0.90 (3H, t, *J*=7.2 Hz), 1.25–1.37 (4H, m), 1.54–1.60 (10H, m), 2.32 (1H, m), 2.49–2.71 (4H, m), 3.70 (1H, dd, *J*=4.7, 8.3 Hz), 4.06–4.16 (2H, m), 4.88 (1H, d, *J*=2.8 Hz); ^{13}C NMR δ 13.9, 22.3, 23.8, 24.1, 25.0, 25.1, 30.4, 34.3, 36.4, 39.2, 40.8, 61.5, 75.9, 82.8, 110.7, 175.2, 207.7; HRMS (ESI) calcd for $C_{17}H_{26}O_5Na$ $(M+Na)^+$, 333.1678; found, 333.1693.

4.1.18. (4R,5S)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-pentanoyldihydrofuran-2(3H)-one ***28***

Following the procedure for oxidation of the hydroxy-acetone **12**, the hydroxy-acetone **17** (200 mg, 0.64 mmol) was oxidized with Dess–Martin periodinane to afford the keto-lactone **28** (190 mg, 96%) as a crystalline white solid. Mp 69–71 °C; IR 1784.2, 1714.2 cm^{-1}; ^1H NMR δ 0.91 (3H, t, *J*=7.3 Hz), 1.30–1.40 (4H, m), 1.52–1.60 (10H, m), 2.39 (2H, m), 2.60 (1H, m), 2.80–2.90 (2H, m), 3.53 (1H, dd,

J=6.1, 8.0 Hz), 3.90 (1H, m), 4.04 (1H, dd, J=6.0, 8.0 Hz), 5.04 (1H, d, J=7.6 Hz); ^{13}C NMR δ 14.0, 22.3, 23.9, 24.1, 25.0, 25.1, 30.0, 34.9, 36.6, 42.0, 43.9, 68.1, 74.4, 81.4, 111.0, 175.0, 207.4; HRMS (ESI) calcd for $C_{17}H_{26}O_5Na$ $(M+Na)^+$, 333.1678; found, 333.1676.

*4.1.19. General procedure for the reduction of the keto-lactones with $NaBH_4$–$CeCl_3\cdot 7H_2O$–MeOH at −20 °C (Condition B): (4S,5S)-4-[(2S)-1,4-dioxaspiro[4.5]dec-2-yl]-5-[(1S)-1-hydroxypentyl]dihydrofuran-2(3H)-one **24***

To a magnetically stirred solution of the keto-lactone **23** (200 mg, 0.64 mmol) in methanol (15 mL) was added $CeCl_3\cdot H_2O$ (169 mg, 0.64 mmol) and stirred for 5 min at rt. The reaction mixture was then cooled to −20 °C (ice–salt bath) and to it $NaBH_4$ (30 mg, 0.77 mmol) was added portion-wise. After stirring for 30 min at −20 °C the reaction mixture was quenched by addition of AcOH. Usual workup of the reaction mixture afforded after column chromatography (ethyl acetate–petroleum ether 1:3) the hydroxyl-lactone **24** (172 mg, 85%) as a light yellow viscous liquid.

*4.1.20. (4S,5R)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-[(1R)-1-hydroxypentyl]dihydrofuran-2(3H)-one **26***

Following the reduction condition B, the keto-lactone **25** (400 mg, 1.3 mmol) was reduced to a 2:3 diastereomeric mixture of alcohols **13** and **26**. Separation of the major diastereomer by flash chromatography on silica gel with 3:1 petroleum ether–EtOAc for elution gave hydroxyl-lactone **26** (200 mg, 50%) as a colorless viscous liquid.

*4.1.21. (4R,5S)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-[(1S)-1-hydroxypentyl]dihydrofuran-2(3H)-one **29***

Following the reduction condition B, the keto-lactone **28** (100 mg, 0.32 mmol) was reduced to afford exclusively the hydroxyl-lactone **29** (85 mg, 86%). IR 3440.8, 1779.2 cm^{-1}; ^{1}H NMR δ 0.90 (3H, t, J=6.8 Hz), 1.27–1.40 (6H, m), 1.44–1.63 (10H, m), 1.93–2.20 (2H, m), 2.59–2.67 (1H, m), 3.61–3.70 (2H, m), 4.00–4.12 (3H, m); ^{13}C NMR δ 14.0, 22.7, 23.8, 24.1, 25.0, 26.6, 30.5, 31.5, 34.9, 36.2, 42.0, 67.5, 71.2, 79.2, 82.3, 111.2, 176.4; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $(M+Na)^+$, 335.1834; found, 335.1836.

*4.1.22. (3aR,4R,6S,6aS)-6-Butyl-4-hydroxytetrahydrofuro[3,4-b]furan-2(3H)-one **34***

Following the procedure for conversion of the hydroxy-lactone **12** to the lactol **14**, the hydroxy-lactone **24** (100 mg, 0.32 mmol) was converted to the hemiacetal **34** (52 mg, 80%) as colorless sticky liquid. IR 3471.6, 1774.4 cm^{-1}; $[\alpha]_D^{26}$ +9.8 (c 1.64, $CHCl_3$); ^{1}H NMR δ 0.91 (3H, t, J=6.9 Hz), 1.33–1.45 (4H, m), 1.68 (2H, m), 2.50 (1H, dd J=3.5, 18.6 Hz), 2.83 (1H, dd, J=11.2, 18.6 Hz), 3.07 (1H, ddd, J=3.5, 7.0, 11.0 Hz), 4.24 (1H, dt, J=3.6, 6.9 Hz), 4.99 (1H, dd, J=3.6, 6.9 Hz), 5.32 (1H, s); ^{13}C NMR δ 14.1, 22.8, 28.3, 28.5, 32.2, 46.3, 80.2, 83.7, 103.1, 176.3; HRMS (ESI) calcd for $C_{10}H_{16}O_4Na$ $(M+Na)^+$, 223.0946; found, 223.0944.

*4.1.23. (3aR,6S,6aS)-6-Butyltetrahydrofuro[3,4-b]furan-2,4-dione **35***

Following the procedure described for oxidation of the lactol **14**, the lactol **34** (35 mg, 0.18 mmol) in acetone (1 mL) was oxidized with Jones reagent to afford after column chromatography bis-lactone **35** (32 mg, 92%) as a white crystalline solid. Mp 84–86 °C (lit. 85–85.5 °C); IR 1770.5 cm^{-1}; $[\alpha]_D^{26}$ +24.50 (c 1.3, $CHCl_3$), [lit. $[\alpha]_D^{23}$ +26.20 (c 0.50, $CHCl_3$)]; ^{1}H NMR δ 0.93 (3H, t, J=7.0 Hz), 1.36–1.51 (4H, m), 1.81–1.92 (2H, m), 2.91–2.95 (2H, m), 3.49 (1H, ddd, J=3.8, 6.1, 7.9 Hz), 4.58 (1H, ddd, J=3.9, 6.5, 7.7 Hz), 5.10 (1H, dd, J=3.9, 6.1 Hz); ^{13}C NMR δ 13.9, 22.5, 27.5, 28.6, 31.2, 41.9, 79.9, 82.5, 173.5, 175.3; HRMS (ESI) calcd for $C_{10}H_{14}O_4Na$ $(M+Na)^+$, 221.0790; found, 221.0780.

*4.1.24. 5-[1(R)-1-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-(4S,5R)-4-[(2S)-1,4-dioxa-spiro[4.5]dec-2-yl]dihydrofuran-2-one **36***

Following the procedure for the protection of the hydroxy-lactone **17**, the secondary alcohol **26** (160 mg, 0.51 mmol) was protected as TBDMS ether using TBDMSOTf (0.14 mL, 0.61 mmol) and 2,6-lutidine (0.12 mL, 1.02 mmol) to afford after column chromatography the lactone **36** (180 mg, 97%) as a colorless liquid. IR 1778.6 cm^{-1}; $[\alpha]_D^{27}$ −4.82 (c 1.1, $CHCl_3$); ^{1}H NMR δ 0.08 (3H, s), 0.09 (3H, s), 0.88 (12H, br s), 1.25–1.33 (6H, m), 1.40 (2H, br s), 1.56 (4H, br s), 1.61 (4H, br s), 2.49–2.63 (3H, m), 3.56 (1H, dd, J=6.7, 8.2 Hz), 3.72 (1H, dt, J=2.6, 6.6 Hz), 4.05 (1H, dd, J=6.7, 8.1 Hz), 4.20 (1H, dt, J=3.5, 6.2 Hz), 4.39 (1H, t, J=2.5 Hz); ^{13}C NMR δ −4.3, −4.2, 14.1, 18.1, 22.9, 23.8, 24.0, 25.2, 25.9 ($3CH_3$), 27.8, 30.0, 32.7, 34.6, 36.2, 39.0, 66.9, 73.7, 75.8, 82.8, 110.3, 176.6; HRMS (ESI) calcd for $C_{23}H_{42}O_5SiNa$ $(M+Na)^+$, 449.2699; found, 449.2694.

*4.1.25. 5-[1(R)-1-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-(4S,5R)-4-[(2S)-1,4-dioxa-spiro[4.5]dec-2-yl]-3-phenyl-selanyl-dihydro-furan-2-one **37***

Following the procedure for the alkylation of the lactone **19** the lithium enolate of the lactone **36** (150 mg, 0.35 mmol) generated with LDA was alkylated with PhSeBr to afford the lactone **37** (150 mg, 73%) as a light yellow liquid. ^{1}H NMR (of diastereomeric mixture) δ 0.10 (6H, br s), 0.98 (12H, br s), 1.28 (12H, m), 1.57 (4H, br s), 2.70 (1H, m), 3.68 (1H, d, J=5.8 Hz), 3.94–4.08 (3H, m), 4.18–4.33 (2H, m), 7.28–7.40 (3H, m), 7.58–7.75 (2H, m); ^{13}C NMR δ −4.3, −3.9, 14.1, 14.3, 18.1, 22.8, 23.0, 23.8, 24.0, 25.2, 26.0 ($3CH_3$), 26.1 ($3CH_3$), 29.5, 29.8, 29.9 (grease), 32.1, 33.5, 34.6, 36.2, 37.5, 44.3, 46.0, 65.8, 66.1, 72.6, 73.2, 74.7, 75.7, 81.9, 82.1, 110.3, 110.4, 127.9, 128.6, 129.0 (2CH), 129.6 (2CH), 131.7, 134.9, 135.3 (2CH), 136.2 (2CH), 176.4; HRMS (ESI) calcd for $C_{29}H_{46}O_5SeSiNa$ $(M+Na)^+$, 605.2180; found, 605.2177.

*4.1.26. 5-[1(R)-1-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-(5R)-4-[(2S)-1,4-dioxa-spiro[4.5]dec-2-yl]-5H-furan-2-one **38***

Following the procedure described above for the conversion of lactone **20** to unsaturated lactone **21** the lactone **37** (150 mg,

0.35 mmol) was converted to unsaturated lactone **38** (109 mg, 100%). IR 1764.7 cm^{-1}; $[\alpha]_D^{25}$ +63.4 (*c* 0.65, $CHCl_3$); ^1H NMR δ 0.07 (3H, br s), 0.09 (3H, br s), 0.84–0.91 (12H, m), 1.25–1.49 (8H, m), 1.61 (8H, br s), 3.85 (1H, t, *J*=7.6 Hz), 4.16 (1H, m), 4.31 (1H, dd, *J*=6.6, 8.0 Hz), 4.88 (1H, t, *J*=6.5 Hz), 5.05 (1H, s), 6.00 (1H, s); ^{13}C NMR δ −4.6, −4.5, 14.1, 18.1, 22.7, 23.9, 24.0, 25.1, 25.9 ($3CH_3$), 28.4, 32.7, 35.1, 36.0, 68.4, 71.8, 72.6, 86.6, 111.1, 117.6, 167.8, 176.4; HRMS (ESI) calcd for $C_{23}H_{40}O_5SiNa$ $(M+Na)^+$, 447.2543; found, 447.2542.

*4.1.27. 5-[1(R)-1-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-(4R,5R)-4-[(2S)-1,4-dioxa-spiro[4.5]dec-2-yl]dihydro-furan-2-one **39***

A solution of the unsaturated lactone **38** (100 mg, 0.24 mmol) in EtOH (6 mL) was hydrogenated using PtO_2 as catalyst to afford after column chromatography (ether–petroleum ether 1:9) the lactone **39** (70 mg, 70%) as colorless oil. IR 1780.2 cm^{-1}; $[\alpha]_D^{27}$ +31.63 (*c* 0.43, $CHCl_3$); ^1H NMR δ 0.07 (3H, br s), 0.10 (3H, br s), 0.87 (12H, br s), 1.24–1.47 (8H, m), 1.55 (4H, br s), 1.59 (4H, br s), 2.15 (1H, dd, *J*=3.7, 17.7 Hz), 2.51 (1H, m), 2.68 (1H, dd, *J*=10.0, 17.7 Hz), 3.54 (1H, t, *J*=4.4 Hz), 3.68 (1H, m), 4.06 (2H, m), 4.54 (1H, br s); ^{13}C NMR δ −4.4, −4.0, 14.1, 18.1, 22.8, 23.9, 24.1, 25.2, 25.9 ($3CH_3$), 27.6, 31.6, 33.4, 34.7, 36.6, 40.2, 67.4, 74.4, 77.2, 82.8, 110.4, 176.5; HRMS (ESI) calcd for $C_{23}H_{42}O_5SiNa$ $(M+Na)^+$, 449.2699; found, 449.2689.

*4.1.28. (4R,5R)-4-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-5-[(1R)-1-hydroxypentyl]dihydrofuran-2(3H)-one **40***

Following the procedure of deprotection of the silyl group of the lactone **22**, the protected lactone **39** (70 mg, 0.16 mmol) in tetrahydrofuran (5 mL) at 0 °C was deprotected using tetrabutylammonium fluoride (68 mg, 0.24 mmol) to afford after column chromatography (ethyl acetate–petroleum ether 1:3) the hydroxy-lactone **40** (42 mg, 82%) as a colorless liquid. IR 3458.1, 1770.5 cm^{-1}; $[\alpha]_D^{26}$ +8.93 (*c* 2.06, $CHCl_3$); ^1H NMR δ 0.91 (3H, t, *J*=6.8 Hz), 1.38 (6H, m), 1.55 (6H, br s), 1.60 (4H, br s), 2.21 (1H, m), 2.60–2.76 (2H, m), 3.56–3.67 (2H, m), 4.07 (2H, m), 4.45 (1H, t, *J*=2.2); ^{13}C NMR δ 14.1, 22.6, 23.9, 24.1, 25.1, 28.0, 31.7, 33.7, 34.8, 36.5, 40.4, 67.5, 72.9, 77.2, 84.6, 110.6, 176.4; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $(M+Na)^+$, 335.1834; found, 335.1830.

*4.1.29. (3aS,4S,6R,6aR)-6-Butyl-4-hydroxytetrahydrofuro [3,4-b]furan-2(3H)-one **41***

Following the similar protocol as used for the conversion of the hydroxy-lactone **12** to lactols **14**, the hydroxy-lactone **40** (40 mg, 0.13 mmol) was converted to the lactol **41** (20 mg, 78%). IR 3471.6, 1770.5 cm^{-1}; $[\alpha]_D^{25}$ −10.0 (*c* 0.2, $CHCl_3$) [lit. (mixture of lactols) $[\alpha]_D$ −14.9 (*c* 1.0, $CHCl_3$)]; HRMS (ESI) calcd for $C_{10}H_{16}O_4Na$ $(M+Na)^+$, 223.0946; found, 223.0942.

*4.1.30. (3aS,6R,6aR)-6-Butyltetrahydrofuro[3,4-b]furan-2,4-dione (−)-**35***

Jones oxidation of lactol **41** (20 mg, 0.1 mmol) in acetone following the usual procedure afforded the bis-lactone (−)-**35** (18 mg, 91%) as white crystal. Mp 83–85 °C [(lit. 85–85.5 °C)]; IR 1770.5 cm^{-1}; $[\alpha]_D^{26}$ −21.5 (*c* 1.09, $CHCl_3$) [lit. $[\alpha]_D^{23}$ −18.9 (*c* 4.79, $CHCl_3$)]; HRMS (ESI) calcd for $C_{10}H_{14}O_4Na$ $(M+Na)^+$, 221.0790; found, 221.0778.

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References and notes

1. McCorkindale, N. J.; Wright, J. L. C.; Brian, P. W.; Clarke, S. M.; Hutchinson, S. A. *Tetrahedron Lett.* **1968**, *6*, 727.
2. Krohn, K.; Ludewig, K.; Aust, H. J.; Draeger, S.; Schulz, B. *J. Antibiot.* **1994**, *47*, 113.
3. Abate, D.; Abraham, W.-R.; Meyer, H. *Phytochemistry* **1997**, *44*, 1443.
4. Al-Abed, Y.; Naz, N.; Mootoo, D.; Voelter, W. *Tetrahedron Lett.* **1996**, *37*, 8641.
5. Honda, T.; Kobayashi, Y.; Tsubuki, M. *Tetrahedron* **1993**, *49*, 1211.
6. Nubbemeyer, U. *Synthesis* **1993**, 1120.
7. Sharma, G. V. M.; Vepachedu, S. R. *Tetrahedron Lett.* **1991**, *47*, 519.
8. Honda, T.; Kobayashi, Y.; Tsubuki, M. *Tetrahedron Lett.* **1990**, *31*, 4891.
9. Tochtermann, W.; Schroeder, G. R.; Snatzke, G.; Peters, E. M.; Peters, K.; Von Schnering, H. G. *Chem. Ber.* **1988**, *121*, 1625.
10. Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4786.
11. Sakai, T.; Yoshida, M.; Kohmoto, S.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1982**, *23*, 5185.
12. Ohrui, H.; Sueda, N.; Kuzuhara, H. *Nippon Kagaku Kaishi* **1981**, 769.
13. Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1978**, *35*, 3233.
14. Tsuboi, S.; Muranaka, K.; Sakai, T.; Takeda, A. *J. Org. Chem.* **1986**, *51*, 4944.
15. Tsuboi, S.; Fujita, H.; Muranaka, K.; Seko, K.; Takeda, A. *Chem. Lett.* **1982**, 1909.
16. Kosugi, H.; Sekiguchi, S.; Sekita, R.; Uda, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 520.
17. Carlson, R. M.; Oyler, A. R. *J. Org. Chem.* **1976**, *41*, 4065.
18. Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932.
19. Kato, M.; Tanaka, R.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1971**, 1561.
20. Sharma, G. V. M.; Krishnudu, K. *Tetrahedron Lett.* **1995**, *36*, 2661.
21. Yu, M.; Lynch, V.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 2563.
22. Ghosh, S.; Sinha, S.; Drew, M. G. B. *Org. Lett.* **2006**, *8*, 3781.
23. Banerjee, S.; Ghosh, S.; Sinha, S.; Ghosh, S. *J. Org. Chem.* **2005**, *70*, 4199.
24. Dess, D. B.; Martin, J. C. J. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
25. Panda, J.; Ghosh, S. *Tetrahedron Lett.* **1999**, *40*, 6693.
26. AM1 calculations were performed by using Hyper Chem (version 6.0).
27. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 3902.