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Stereoselective syntheses of γ-alkyl (aryl)-α,β-dihydroxy-γ-butyrolactones and naturally occurring lipid guggultetrol

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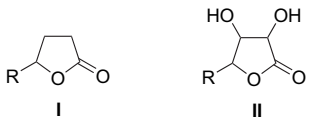
Abstract—γ-Oxo-butyramides derived from tartaric acid serve as excellent precursors for the synthesis of γ-alkyl (aryl)-α,β-dihydroxy-γ-butyrolactones and for the synthesis of tetrols containing three contiguous stereogenic centres. The methodology presented here is general for the synthesis of γ-alkyl (aryl)-α,β-dihydroxy-γ-butyrolactones. Utility of the chiral building block was demonstrated by the synthesis of naturally occurring lipid guggultetrol.

1. Introduction

Asymmetric synthesis of biologically active natural products from chiral pool precursors has always been an attractive method because of the rich source of chirality and abundance of the chiral pool compounds. Amongst these chiral pool compounds tartaric acid has attracted much attention in asymmetric synthesis over the decades and continues to stimulate its use as the starting point for the synthesis of varied chiral building blocks useful for the synthesis of natural products.[1] Our own interest in the use of tartaric acid as a chiral pool precursor resulted in the synthesis of bio-active natural products such as insect pheromones and styryllactones.[2] Herein, we report a general synthesis of γ-oxo-α,β-dihydroxybutyramides from tartaric acid and its application in an expeditious enantiospecific synthesis of γ-alkyl (aryl)-α,β-dihydroxy-γ-butyrolactones and 1,2,3,4-tetrols, demonstrated by the synthesis of naturally occurring lipid guggultetrol.

Optically pure γ-butyrolactones (**I**) are common structural motifs encountered in a number of naturally occurring compounds possessing therapeutic properties (Fig. 1). Consequently, syntheses of γ-alkylated-γ-butyrolactones have attracted much attention.[3] However, the synthesis of γ-alkyl-γ-butyrolactones containing α,β-hydroxy substitution (**II**) is scantily addressed in the literature.[4] These lactones are not only present in natural products but also serve as excellent precursors for the synthesis of a variety of other important bio-active compounds.[5]

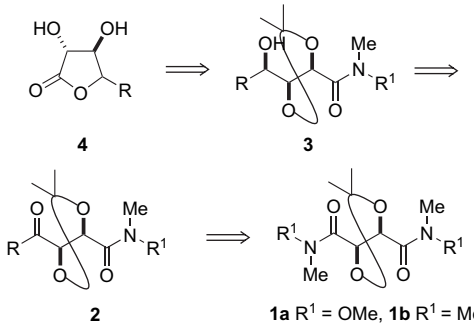


I II

Figure 1. γ-Butyrolactone (**I**) and α,β-dihydroxy-γ-butyrolactone (**II**).

2. Results and discussion

Our approach for a general method for the synthesis of γ-alkyl (aryl)-α,β-dihydroxybutyrolactones was based on the γ-hydroxy group assisted lactonization of the γ-hydroxybutyramides. It is well established in the literature that γ-hydroxybutyramides undergo acid mediated esterification/lactonization to yield γ-butyrolactones much faster than their analogues without the hydroxy group.[6] We anticipated that such a lactonization of γ-hydroxyamides **3** by an acid mediated cyclization should furnish the γ-alkyl-α,β-dihydroxy lactones **4** (Scheme 1). γ-Hydroxyamides **3** can be obtained by stereoselective reduction of the keto-amide



Scheme 1. Retrosynthesis of γ-alkyl (aryl)-α,β-dihydroxybutyrolactones.

Keywords: γ-Butyrolactone; Stereoselective reduction; L-(+)-Tartaric acid; Guggultetrol.
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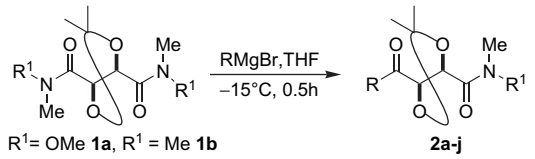
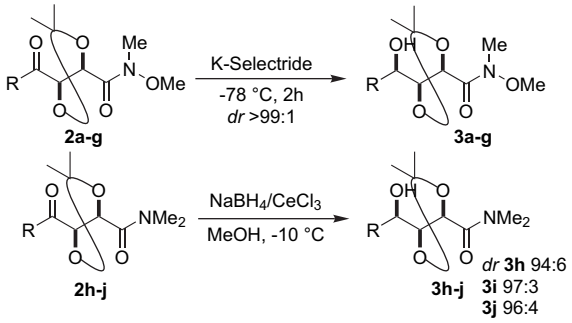
2, which is easily formed by Grignard reagent addition to the bis-amides **1a**,**b** derived from L-(+)-tartaric acid.

We commenced our synthetic sequence by the controlled addition of Grignard reagents to the bis-amides **1a**,**b**. It was observed that the bis-Weinreb amide **1a** is a suitable substrate for the addition of *alkyl* Grignard reagents, whereas, bis-dimethylamide **1b** is found to be the ideal substrate for the addition of *aryl* Grignard reagents for the generation of the keto-amides **2a–g** and **2h–j**, respectively (Scheme 2, Table 1).



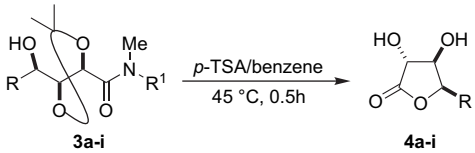
Scheme 2. Synthesis of γ-alkyl (aryl)-γ-oxo-butyramides from **1a**,**b**.

Reduction of the keto-amides **2a–g** possessing a γ-alkyl group was accomplished either with L-Selectride or with K-Selectride to yield the corresponding alcohols **3a–g** as single diastereomers. Reduction of keto-amides **2h–j** with $NaBH_4/CeCl_3$ proceeded with good diastereoselectivity (dr up to 97:3) affording the alcohols **3h–j**.[7] The minor isomer obtained from the reduction was removed by a single recrystallization (Scheme 3, Table 2).



Scheme 3. Stereoselective reduction of γ-oxo-butyramides **2a–j** to γ-hydroxy-butyramides **3a–j**.

After successfully obtaining the required γ-hydroxybutyramides **3a–j**, generation of the lactones **4a–j** was investigated. After optimization of the reaction conditions, it was found that the deprotection of the acetonide, with concomitant formation of the lactones **4a–j** could be achieved in a single pot by treating the amides **3a–i** with *p*-toluenesulfonic acid in benzene at 45 °C. γ-Hydroxybutyramides **3a–i** produced the product lactones **4a–i** in good yields (Scheme 4, Table 3).[8]



Scheme 4. Synthesis of γ-alkyl (aryl)-α,β-dihydroxybutyramides **4a–i**.

Table 3. Synthesis of γ-alkyl (aryl)-α,β-dihydroxybutyramides **4a–i** from **3a–i**[a]

No.	4a	4b	4c	4d	4e	4f	4g	4h	4i
R	Me	Et	^{n}Bu	^{n}octyl	^{i}Pr	$C_{14}H_{29}$	*c*-C_6H_{11}	Ph	*p*-tolyl
Yield[b] %	92	95	96	98	95	94	93	99	94

[a] All reactions were performed at 45 °C in benzene.
[b] Refers to isolated yields after chromatography.

Reaction of γ-hydroxybutyramide **3j**, to our surprise produced the lactone **4j**, epimerized at the C-4 position via the probable formation of a benzylic carbocation. The structure of lactone **4j** was confirmed by single crystal X-ray diffraction analysis.[9] Further support for the epimerization came from the following experiment. A diasteromeric mixture (dr **3j**:**3j′** 7:3) of alcohols obtained by the reduction of ketone **2j** with $NaBH_4$, on treatment with *p*-TSA in benzene at 45 °C afforded a single isomer of the lactone **4j**, clearly showing the epimerization under the conditions employed (Scheme 5).

After establishing a concise and efficient route for the synthesis of γ-alkyl (aryl)-α,β-dihydroxy-γ-butyrolactones, we turned our attention to the application of γ-hydroxy Weinreb amides **3a–g** for the synthesis of tetrols having contiguous stereogenic centres. Many of these tetrols are useful intermediates for the synthesis of a number of biologically active compounds[10] and represent a class of compounds closely related to phytosphingosines.[11] For example, D-*xylo*-octadecane-1,2,3,4-tetrol (guggultetrol) **6** is a naturally occurring lipid isolated from the gum-resin of the tree *Commiphoru mukul (guggulu)*, known in Ayurveda, the Indian traditional

Table 1. Synthesis of γ-alkyl (aryl)-γ-oxo-butyramides **2a–j**[a]

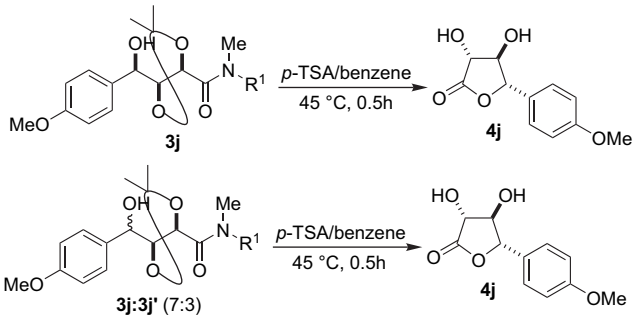
No.	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j
R^1	OMe	OMe	OMe	OMe	OMe	OMe	OMe	Me	Me	Me
R	Me	Et	^{n}Bu	^{n}octyl	^{i}Pr	*c*-C_6H_{11}	$C_{14}H_{29}$	Ph	*p*-tolyl	*p*-anisyl
Yield[b] %	60	90	92	91	71	94	94	92	91	85

[a] All reactions were performed at −15 °C in THF except for entries **2f** and **2g**, for which the reaction was carried out at 0 °C.
[b] Yield refers to the isolated yield after column chromatography.

Table 2. Synthesis of γ-alkyl (aryl)-γ-hydroxybutyramides **3a–j** by the reduction of keto-amides **2a–j**

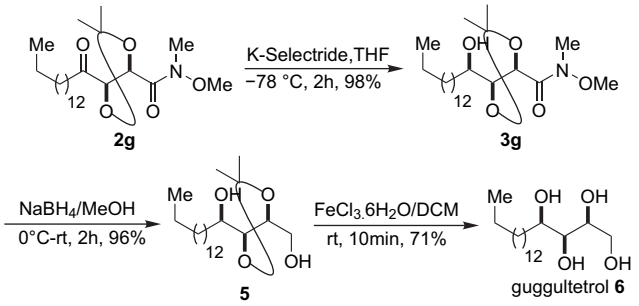
No.	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j
R^1	OMe	OMe	OMe	OMe	OMe	OMe	OMe	Me	Me	Me
R	Me	Et	^{n}Bu	^{n}octyl	^{i}Pr	*c*-C_6H_{11}	$C_{14}H_{29}$	Ph	*p*-tolyl	*p*-anisyl
Yield %	97[b]	95[b]	83[b]	93[b]	95[b]	95[b]	98[b]	86[a]	89[a]	87[a]

[a] Refers to the isolated yield of the major diastereomer after crystallization.
[b] Refers to the isolated yields after column chromatography.



Scheme 5. Synthesis of γ-(*p*-anisyl)-α,β-dihydroxybutyramide **4j**.

system of medicine, for the treatment of arthritis, inflammation, obesity and disorders of lipid metabolism.[12] Application of the methodology for the synthesis of guggultetrol **6** was undertaken (Scheme 6). Accordingly, reduction of the hydroxy-Weinreb amide **3g** with $NaBH_4$ produced the alcohol **5** in 96% yield. Deprotection of the acetonide in **5** using $FeCl_3 \cdot 6H_2O$ furnished guggultetrol **6** {$[\alpha]_D$ +13.6 (*c* 0.5, EtOH), lit.[12b,c] $[\alpha]_D$ +11.4 (*c* 0.34, EtOH)}, thus constituting a concise and efficient synthesis.



Scheme 6. Stereoselective synthesis of natural lipid guggultetrol **6**.

3. Conclusion

In summary, we have demonstrated the utility of keto-amides derived from L-(+)-tartaric acid as useful synthons for synthesis of γ-alkyl (aryl)-α,β-dihydroxy-γ-butyrolactones. The synthetic sequence described is operationally simple, general and is applicable for the synthesis of a number of analogues. Utility of these keto-amides is further exemplified by the synthesis of guggultetrol, a naturally occurring lipid possessing three contiguous stereogenic centres.

4. Experimental

4.1. General procedures

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, all the reactions were performed under argon atmosphere. Petroleum ether refers to the fraction boiling between 60 and 80 °C.

4.2. General procedure for the preparation of (4*R*,5*R*)-5-(alkanoyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (2a–g)

In an oven dried two neck 100 mL, round bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet was placed (4*R*,5*R*)-*N*,*N*′-dimethoxy-2,2,*N*,*N*′-tetramethyl-1,3-dioxolane-4,5-dicarboxamide (**1a**) (0.55 g, 2.0 mmol) dissolved in 10 mL of THF. The solution was cooled to −15 °C and a THF solution of RMgX (3 mmol) was added slowly and stirred for 0.5 h at the same temperature. After the reaction was complete (disappearance of starting diamide as indicated by TLC), it was cautiously quenched by addition of saturated ice cold solution of NH_4Cl (10 mL). It was then poured into water (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). After removal of the solvent, the residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as an eluent to yield (4*R*,5*R*)-5-(alkanoyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (**2a**–**g**).

4.2.1. (4*R*,5*R*)-5-Acetyl-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (2a). Yield 60%; colourless oil; R_f 0.4 (1:1 ethyl acetate/petroleum ether); $[\alpha]_D$ +5.5 (*c* 5.6, $CHCl_3$); IR (neat): 2990, 2941, 1722, 1668, 1383, 1087, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, 1H, *J*=5.1 Hz), 4.83 (d, 1H, *J*=5.1 Hz), 3.73 (s, 3H), 3.24 (s, 3H), 2.31 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.3, 169.6, 112.6, 82.5, 73.8, 61.6, 32.3, 26.6, 26.5, 26.1; HRMS for $C_{10}H_{17}NO_5$+Na calcd, 254.1004; found, 254.1005.

4.2.2. (4*R*,5*R*)-*N*-Methoxy-2,2,*N*-trimethyl-5-propionyl-1,3-dioxolane-4-carboxamide (2b). Yield 90%; colourless oil; R_f 0.5 (1:1 ethyl acetate/petroleum ether); $[\alpha]_D$ +8 (*c* 1.5, $CHCl_3$); IR (neat): 2984, 2941, 2852, 1721, 1672, 1462, 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, 1H, *J*=6.0 Hz), 4.83 (d, 1H, *J*=6.0 Hz), 3.72 (s, 3H), 3.24 (s, 3H), 2.84–2.54 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.09 (t, 3H, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 169.6, 112.5, 81.9, 73.8, 61.5, 32.4, 32.3, 26.5, 26.0, 6.9; HRMS for $C_{11}H_{19}NO_5$+Na calcd, 268.1161; found, 268.1155.

4.2.3. (4*R*,5*R*)-*N*-Methoxy-2,2,*N*-trimethyl-5-pentanoyl-1,3-dioxolane-4-carboxamide (2c). Yield 92%; colourless oil; R_f 0.5 (1:1 ethyl acetate/petroleum ether); $[\alpha]_D$ +7 (*c* 1, $CHCl_3$); IR (neat): 2987, 2874, 1718, 1672, 1463, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, 1H, *J*=5.7 Hz), 4.82 (d, 1H, *J*=5.7 Hz), 3.72 (s, 3H), 3.24 (s, 3H), 2.87–2.52 (m, 2H), 1.66–1.52 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.40–1.29 (m, 2H), 0.92 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 169.8, 112.7, 82.2, 73.9, 61.6, 38.9, 32.4, 26.6, 26.2, 25.1, 22.2, 13.8; HRMS for $C_{13}H_{23}NO_5$+Na calcd, 296.1474; found, 296.1474.

4.2.4. (4*R*,5*R*)-*N*-Methoxy-2,2,*N*-trimethyl-5-nonanoyl-1,3-dioxolane-4-carboxamide (2d). Yield 91%; colourless oil; R_f 0.5 (1:1 ethyl acetate/petroleum ether); $[\alpha]_D$ +7 (*c* 2, $CHCl_3$); IR (neat): 2929, 2856, 1720, 1674, 1465, 1381, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, 1H, *J*=5.7 Hz), 4.82 (d, 1H, *J*=5.7 Hz), 3.72 (s, 3H), 3.24

(s, 3H), 2.75–2.54 (m, 2H), 1.62–1.55 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.28 (br s, 10H), 0.88 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 169.7, 112.6, 82.2, 73.8, 61.6, 39.2, 32.3, 31.7, 29.2, 29.0, 26.6, 26.1, 23.0, 22.5, 14.0; HRMS for $C_{17}H_{31}NO_5$+Na calcd, 352.2100; found, 352.2103.

4.2.5. (4*R*,5*R*)-*N*-Methoxy-2,2,*N*-trimethyl-5-(2-methylpropionyl)-1,3-dioxolane-4-carboxamide (2e). Yield 71%; colourless oil; R_f 0.5 (1:1 ethyl acetate/petroleum ether); $[\alpha]_D$ +24 (c 1.4, $CHCl_3$); IR (neat): 2976, 2939, 1714, 1670, 1468, 1383, 1259, 987 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (d, 1H, J=6.9 Hz), 4.95 (d, 1H, J=6.9 Hz), 3.72 (s, 3H), 3.24 (s, 3H), 3.09 (sep, 1H, J=6.9 Hz), 1.50 (s, 3H), 1.43 (s, 3H), 1.16 (d, 3H, J=6.9 Hz), 1.12 (d, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 169.8, 112.5, 80.8, 74.0, 61.6, 37.3, 32.4, 26.6, 26.1, 18.3, 17.3; HRMS for $C_{12}H_{21}NO_5$+Na calcd, 282.1317; found, 282.1310.

4.2.6. (4*R*,5*R*)-*N*-Methoxy-2,2,*N*-trimethyl-5-(cyclohexylcarbonyl)-1,3-dioxolane-4-carboxamide (2f). Yield 94%; colourless oil; R_f 0.5 (1:1 ethyl acetate/petroleum ether); $[\alpha]_D$ +16 (c 1, $CHCl_3$); IR (neat): 2931, 1707, 1670, 1452, 1261, 1155, 985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, 1H, J=5.1 Hz), 4.92 (d, 1H, J=5.1 Hz), 3.70 (s, 3H), 3.23 (s, 3H), 2.86–2.76 (m, 1H), 1.96–1.15 (m, 11H), 1.50 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 170.0, 112.6, 80.9, 73.9, 61.6, 47.1, 32.5, 28.7, 27.5, 26.6, 26.2, 25.8, 25.7, 25.3; HRMS for $C_{15}H_{25}NO_5$+Na calcd, 322.1630; found, 322.1629.

4.2.7. (4*R*,5*R*)-*N*-Methoxy-2,2,*N*-trimethyl-5-pentadecanoyl-1,3-dioxolane-4-carboxamide (2g). Yield 94%; colourless oil; R_f 0.6 (1:1 ethyl acetate/petroleum ether); $[\alpha]_D$ +13.8 (c 1.3, $CHCl_3$); IR (neat): 2925, 2854, 1720, 1675, 1465, 1082 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, 1H, J=5.4 Hz), 4.82 (d, 1H, J=5.4 Hz), 3.72 (s, 3H), 3.24 (s, 3H), 2.75–2.53 (m, 2H), 1.62–1.55 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.26 (br s, 22H), 0.88 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 169.8, 112.7, 82.3, 73.9, 61.7, 39.3, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 26.7, 26.2, 23.1, 22.7, 14.1; HRMS for $C_{23}H_{43}NO_5$+Na calcd, 436.3039; found, 436.3058.

4.3. General procedure for the preparation of (4*R*,5*R*)-5-aroyl-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (2h–j)

In a two neck 100 mL, round bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet was placed diamide **1b** (0.49 g, 2 mmol). This was dissolved in 10 mL of THF and was cooled to −15 °C. A freshly prepared THF solution of ArMgBr (3 mL of 1 M solution in THF, 3 mmol) was added slowly and the reaction mixture was stirred at the same temperature. Progress of the reaction was monitored by TLC and after the reaction was complete (~0.5 h), it was cautiously quenched by addition of saturated ice cold solution of NH_4Cl (10 mL). It was then poured into water (10 mL) and extracted with EtOAc (3×10 mL). Combined ethyl acetate extracts were washed with brine (30 mL) and dried (Na_2SO_4). Evaporation of solvent and silica gel column chromatography of the residue using petroleum ether and ethyl acetate as eluent yielded (4*R*,5*R*)-5-aroyl-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (**2h–j**).

4.3.1. (4*R*,5*R*)-5-Benzoyl-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (2h). Yield 92%; pale yellow solid; mp 79–80.4 °C; R_f 0.5 (2:3 ethyl acetate/petroleum ether); $[\alpha]_D$ −23 (c 1, $CHCl_3$); IR (KBr): 2989, 2938, 1687, 1653, 1213, 1155, 1063 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 2H, J=7.2 Hz), 7.59 (t, 1H, J=7.5 Hz), 7.48 (dd, 2H, J=7.5, 7.2 Hz), 5.96 (d, 1H, J=5.7 Hz), 5.17 (d, 1H, J=5.7 Hz), 3.16 (s, 3H), 3.00 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 168.2, 134.8, 133.6, 129.3, 128.5, 112.5, 79.4, 75.0, 37.0, 35.9, 26.4, 26.3. Analysis calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.28; H, 7.02; N, 5.31.

4.3.2. (4*R*,5*R*)-5-(*p*-Methylbenzoyl)-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (2i). Yield 91%; pale yellow solid; mp 124.0–125.4 °C; R_f 0.5 (2:3 ethyl acetate/petroleum ether); $[\alpha]_D$ −11.2 (c 1.6, $CHCl_3$); IR (KBr): 2990, 2940, 1685, 1655, 1606, 1381, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 2H, J=8.1 Hz), 7.26 (d, 2H, J=8.1 Hz), 5.91 (d, 1H, J=5.7 Hz), 5.15 (d, 1H, J=5.7 Hz), 3.15 (s, 3H), 2.99 (s, 3H), 2.40 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 168.3, 144.5, 132.5, 129.5, 129.2, 112.5, 79.4, 75.0, 37.0, 35.9, 26.4, 26.3, 21.6. Analysis calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.93; H, 7.40; N, 4.89.

4.3.3. (4*R*,5*R*)-5-(*p*-Methoxybenzoyl)-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (2j). Yield 94%; pale yellow solid; mp 94.0–95.0 °C; R_f 0.5 (1:1 ethyl acetate/petroleum ether); $[\alpha]_D$ −18.9 (c 1.8, $CHCl_3$); IR (KBr): 2923, 1656, 1601, 1513, 1262, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 2H, J=9.3 Hz), 6.95 (d, 2H, J=9.3 Hz), 5.88 (d, 1H, J=5.7 Hz), 5.17 (d, 1H, J=5.7 Hz), 3.87 (s, 3H), 3.17 (s, 3H), 3.00 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 168.4, 163.9, 131.8, 128.0, 113.8, 112.4, 79.3, 75.0, 55.4, 37.1, 35.9, 26.4. Analysis calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.73; H, 6.95; N, 4.49.

4.4. General procedure for preparation of (4*R*,5*S*)-5-((*R*)-1-hydroxyalkyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (3a–g)

To a solution of (4*R*,5*R*)-5-(alkanoyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (**2a–g**) (1.5 mmol) in 10 mL of THF was added K-Selectride (3 mL, 3 M solution in THF) dropwise at −78 °C over 5 min, under argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature and quenched with water (15 mL) and extracted with EtOAc (3×15 mL). Combined extracts were washed with brine (15 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was exposed to open air for 24 h. It was then dissolved in CH_2Cl_2 (20 mL) and the undissolved solid residue (formed borates from Selectride) was filtered through a pad of Celite. The Celite pad was washed with CH_2Cl_2 (10 mL) and the combined organic layer was concentrated. The residue obtained was purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluent to afford (4*R*,5*S*)-5-((*R*)-1-hydroxyalkyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (**3a–g**).

4.4.1. (4*R*,5*S*)-5-((*R*)-1-Hydroxyethyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (3a). Yield 97%; colourless oil; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ −19 (*c* 1.2, $CHCl_3$); IR (neat): 3466, 2986, 1666, 1381, 1069, 881 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.72 (br s, 1H), 4.34 (br s, 1H), 3.86–3.83 (m, 1H), 3.76 (s, 3H), 3.24 (s, 3H), 2.47 (br s, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.24 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 110.9, 81.8, 73.6, 66.7, 61.6, 32.2, 26.9, 26.0, 19.7; HRMS for $C_{10}H_{19}NO_5$+Na calcd, 256.1161; found, 256.1158.

4.4.2. (4*R*,5*S*)-5-((*R*)-1-Hydroxypropyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (3b). Yield 95%; colourless oil; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ −16 (*c* 1.5, $CHCl_3$); IR (neat): 3477, 2938, 1670, 1382, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (br s, 1H), 4.41 (br s, 1H), 3.76 (s, 3H), 3.56–3.53 (m, 1H), 3.24 (s, 3H), 2.19 (d, 1H, *J*=7.2 Hz), 1.61–1.41 (m, 2H), 1.49 (s, 3H), 1.01 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 110.8, 80.4, 73.6, 71.5, 61.6, 32.2, 27.3, 26.9, 26.0, 10.1; HRMS for $C_{11}H_{21}NO_5$+Na calcd, 270.1317; found, 270.1306.

4.4.3. (4*R*,5*S*)-5-((*S*)-1-Hydroxypentyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (3c). Yield 83%, colourless oil; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ +6.1 (*c* 1.2, $CHCl_3$); IR (neat): 3478, 2933, 2861, 1670, 1450, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.76 (br s, 1H), 4.39 (br s, 1H), 3.75 (s, 3H), 3.61 (br s, 1H), 3.24 (s, 3H), 1.60–1.32 (m, 6H), 1.48 (s, 3H), 1.46 (s, 3H), 0.90 (t, 3H, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 110.9, 80.8, 73.7, 70.2, 61.6, 34.2, 27.9, 26.9, 26.0, 22.5, 13.9; HRMS for $C_{13}H_{25}NO_5$+Na calcd, 298.1630; found, 298.1638.

4.4.4. (4*R*,5*S*)-5-((*R*)-1-Hydroxynonyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (3d). Yield 93%; colourless oil; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ −4 (*c* 5.2, $CHCl_3$); IR (neat): 3469, 2927, 1668, 1381, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (br s, 1H), 4.39 (br s, 1H), 3.75 (s, 3H), 3.62 (br s, 1H), 3.24 (s, 3H), 2.05 (br s, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.49–1.17 (m, 14H), 0.88 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 110.9, 80.8, 73.7, 70.2, 61.6, 34.5, 32.3, 31.8, 29.5, 29.4, 29.2, 27.0, 26.0, 25.7, 22.6, 14.0; HRMS for $C_{17}H_{33}NO_5$+Na calcd, 354.2256; found, 354.2260.

4.4.5. (4*R*,5*S*)-5-((*R*)-1-Hydroxy-2-methylpropyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (3e). Yield 95%; colourless oil; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ −38 (*c* 1, $CHCl_3$); IR (neat): 3494, 2939, 1668, 1382, 1062, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (br s, 1H), 4.56 (br s, 1H), 3.75 (s, 3H), 3.24 (br s, 1H), 2.13 (d, 1H, *J*=9.9 Hz), 1.82–1.71 (m, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.02 (d, 3H, *J*=6.9 Hz), 0.98 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 110.8, 78.5, 74.7, 73.9, 61.6, 32.1, 26.8, 26.0, 19.1, 18.4; HRMS for $C_{12}H_{23}NO_5$+Na calcd, 284.1474; found, 284.1469.

4.4.6. (4*R*,5*S*)-5-((*R*)-1-Hydroxy(cyclohexyl)methyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (3f). Yield 95%; colourless oil; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ −8 (*c* 1.4, $CHCl_3$); IR (neat): 3480, 2925, 1668, 1381, 1213, 879 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.81 (br s, 1H), 4.56 (d, 1H, *J*=6.0 Hz), 3.75 (s, 3H), 3.29 (d, 1H, *J*=7.2 Hz), 3.24, (s, 3H), 2.01–1.64 (m, 6H), 1.49 (s, 3H), 1.46 (s, 3H), 1.32–0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 110.9, 78.3, 73.9, 61.6, 41.8, 32.3, 29.3, 28.9, 26.9, 26.3, 26.1, 26.0, 25.9; HRMS for $C_{15}H_{27}NO_5$+Na calcd, 324.1787; found, 324.1783.

4.4.7. (4*R*,5*S*)-5-((*R*)-1-Hydroxypentadecyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (3g). Yield 98%; colourless oil; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ −8 (*c* 1.5, $CHCl_3$); IR (neat): 3476, 2925, 2854, 1671, 1380, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (br s, 1H), 4.39 (br s, 1H), 3.75 (s, 3H), 3.61 (br s, 1H), 3.24 (s, 3H), 2.11 (br s, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.49–1.25 (m, 26H), 0.88 (t, 3H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 110.8, 80.8, 73.7, 70.2, 61.6, 34.5, 32.3, 31.8, 29.6, 29.5, 29.4, 29.3, 26.9, 26.0, 25.7, 22.6, 14.0; HRMS for $C_{23}H_{45}NO_5$+Na calcd, 438.3195; found, 438.3200.

4.5. General procedure for the preparation of (4*R*,5*S*)-5-((*R*)-hydroxy(aryl)methyl)-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (3h–j)

To a solution of (4*R*,5*R*)-5-aroyl-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (**2h–j**) (1.5 mmol) in methanol (10 mL) cooled to −15 °C was added $CeCl_3 \cdot 7H_2O$ (1.12 g, 3 mmol) and the reaction mixture was stirred for 15 min. $NaBH_4$ (0.11 g, 3 mmol) was then added portionwise and stirred at the same temperature for 1 h. After the reaction was complete (TLC), water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent followed by silica gel column chromatography of the crude residue with petroleum ether and ethyl acetate as an eluent afforded **3h–j** as white solid. Recrystallization from ethyl acetate/petroleum ether yielded the diastereomerically pure (4*R*,5*S*)-5-((*R*)-hydroxy(aryl)methyl)-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (**3h–j**).

4.5.1. (4*R*,5*S*)-5-((*R*)-Hydroxy(phenyl)methyl)-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (3h). Yield 86%; white needles; mp 154–156 °C; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ −31 (*c* 2, $CHCl_3$); IR (KBr): 3395, 2937, 1644, 1380, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.27 (m, 5H), 4.89–4.81 (m, 2H), 4.41 (d, 1H, *J*=6.9 Hz), 3.58 (d, 1H, *J*=6.9 Hz), 3.03 (s, 3H), 2.90 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 140.4, 128.1, 127.7, 126.7, 110.7, 81.1, 74.5, 72.4, 37.0, 35.8, 26.8, 26.2. Analysis calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.82; H, 7.67; N, 5.20.

4.5.2. (4*R*,5*S*)-5-((*R*)-Hydroxy(*p*-tolyl)methyl)-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (3i). Yield 89%; white needles; mp 126.4–128 °C; R_f 0.4 (3:2 ethyl acetate/petroleum ether); $[\alpha]_D$ −9.4 (*c* 1.6, $CHCl_3$); IR (KBr): 3425, 2987, 2937, 1649, 1381, 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, 2H, *J*=8.1 Hz), 7.14 (d, 2H,

J=8.1 Hz), 4.86 (dd, 1H, J=6.9, 3.9 Hz), 4.77 (dd, 1H, J=6.9, 3.9 Hz), 4.41 (d, 1H, J=6.9 Hz), 3.41 (d, 1H, J=6.9 Hz), 3.02 (s, 3H), 2.89 (s, 3H), 2.33 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 137.4, 137.3, 128.8, 126.6, 110.7, 81.2, 74.5, 72.3, 37.0, 35.8, 26.9, 26.2, 21.1. Analysis calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.47; H, 7.91; N, 4.70.

4.5.3. (4*R*,5*S*)-5-((*R*)-Hydroxy(*p*-anisyl)methyl)-2,2,*N*,*N*-tetramethyl-1,3-dioxolane-4-carboxamide (3j). Yield 87%; white needles; mp 147.3–147.7 °C; R_f (60% ethyl acetate/petroleum ether) 0.3; $[\alpha]_D$ −23.1 (c 1.6, $CHCl_3$); IR (KBr): 3423, 2938, 1647, 1514, 1250, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H, J=9.0 Hz), 6.88 (d, 2H, J=9.0 Hz), 4.86 (dd, 1H, J=6.9, 4.2 Hz), 4.76 (d, 1H, J=4.2 Hz), 4.39 (d, 1H, J=6.9 Hz), 3.80 (s, 3H), 3.38 (br s, 1H), 3.03 (s, 3H), 2.90 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 159.2, 132.5, 128.0, 113.6, 110.7, 81.2, 74.6, 72.3, 55.2, 37.0, 35.8, 26.9, 26.3. Analysis calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.04; H, 7.51; N, 4.50.

4.6. General procedure for preparation of (2*R*,3*S*,4*R*)-2,3-dihydroxy-4-alkyl (aryl) butyrolactone (4a–j)

To a solution of hydroxyamide **3a–j** (0.5 mmol) in dry benzene (5 mL) was added *p*-toluenesulfonic acid monohydrate (0.10 g, 0.55 mmol) and stirred for 0.5 h at 45 °C. The reaction mixture was cooled to room temperature and K_2CO_3 (0.08 g) was added and stirred for 10 min. The reaction mixture was filtered through a pad of Celite and the Celite pad was washed with EtOAc (20 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluent to afford (2*R*,3*S*,4*R*)-2,3-dihydroxy-4-alkyl (aryl) butyrolactone (**4a–j**).

4.6.1. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-methylbutyrolactone (4a). Yield 92%; colourless oil; R_f 0.4 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +77 (c 1, MeOH), lit.[4f] $[\alpha]_D$ +77.2 (c 2.4, MeOH); IR (neat): 3399, 2917, 1773, 1513, 1148, 1051, 952 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.72–4.67 (m, 1H), 4.20–4.18 (m, 2H), 1.34 (d, 3H, J=6.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 177.3, 79.3, 75.1, 74.2, 14.8. Analysis calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.20; H, 6.14.

4.6.2. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-ethylbutyrolactone (4b). Yield 95%; colourless oil; R_f 0.4 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +84 (c 1, MeOH), lit.[4f] $[\alpha]_D$ +84.6 (c 1.02, MeOH); IR (neat): 3402, 2974, 1773, 1147, 968 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.49–4.43 (m, 1H), 4.20 (t, 1H, J=5.4 Hz), 4.13 (d, 1H, J=5.4 Hz), 1.89–1.57 (m, 2H), 1.02 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 177.4, 84.8, 74.8, 74.6, 23.0, 10.3; HRMS for $C_6H_{10}O_4$+Na calcd, 169.0477; found, 169.0477.

4.6.3. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-*n*-butylbutyrolactone (4c). Yield 96%; white solid; mp 63.5–64.5 °C (lit.[4f] mp 74–76 °C); R_f 0.4 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +91 (c 1, $CHCl_3$), lit.[4f] $[\alpha]_D$ +91.5 (c 1, $CHCl_3$); IR (KBr): 3409, 2958, 1768, 1147, 982 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.56–4.50 (m, 1H), 4.18 (dd, 1H, J=5.4, 5.1 Hz), 4.13 (d, 1H, J=5.4 Hz), 1.83–1.39 (m, 6H), 0.94 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 177.4, 83.5, 74.9, 74.6, 29.5, 29.0, 23.6, 14.3. Analysis calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.92; H, 8.02.

4.6.4. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-octylbutyrolactone (4d). Yield 98%; white solid; mp 68–70 °C (lit.[5b] mp 68–70 °C); R_f 0.4 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +72 (c 1, $CHCl_3$), lit.[5b] $[\alpha]_D$ −71.9 (c 0.78, $CHCl_3$ for the other enantiomer); IR (KBr): 3433, 2924, 1777, 1466, 1152, 975 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.57–4.50 (m, 1H), 4.18 (dd, 1H, J=5.4, 4.8 Hz), 4.13 (d, 1H, J=5.4 Hz), 1.79–1.73 (m, 1H), 1.64–1.31 (m, 13H), 0.90 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 177.4, 83.5, 74.9, 74.6, 33.0, 30.6, 30.4, 29.8, 26.8, 23.7, 14.4. Analysis calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.50; H, 9.49.

4.6.5. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-isopropylbutyrolactone (4e). Yield 95%; colourless oil; R_f 0.4 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +86 (c 0.5, MeOH); IR (neat): 3452, 2954, 1770, 1471, 976 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.21 (dd, 1H, J=9.0, 3.9 Hz), 4.15 (dd, 1H, J=3.9, 2.4 Hz), 4.03 (d, 1H, J=2.4 Hz), 2.23–2.01 (m, 1H), 1.06 (d, 3H, J=6.9 Hz), 0.98 (d, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 177.8, 90.0, 76.0, 74.1, 28.2, 19.8, 18.2; HRMS for $C_7H_{12}O_4$+Na calcd, 183.0633; found, 183.0630.

4.6.6. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-tetradecylbutyrolactone (4f). Yield 94%; white solid; mp 87–89 °C; R_f 0.5 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +56.6 (c 1.2, MeOH); IR (KBr): 3408, 2918, 1774, 1469, 1155, 982 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.56–4.50 (m, 1H), 4.18 (dd, 1H, J=5.4, 5.1 Hz), 4.12 (d, 1H, J=5.4 Hz), 1.79–1.41 (m, 2H), 1.42–1.28 (m, 24H), 0.89 (t, 3H, J=6.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 177.4, 83.5, 74.9, 74.6, 33.1, 30.8, 30.7, 30.6, 30.5, 30.4, 29.8, 26.8, 23.7, 14.5. Analysis calcd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 68.81; H, 11.04.

4.6.7. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-cyclohexylbutyrolactone (4g). Yield 93%; white solid; mp 137–138 °C; R_f 0.4 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +12.8 (c 0.7, MeOH); IR (KBr): 3448, 2924, 1763, 1722, 1226, 1049, 977 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.26 (dd, 1H, J=9.3, 3.9 Hz), 4.14 (dd, 1H, J=3.9, 2.4 Hz), 4.01 (d, 1H, J=2.4 Hz), 1.98–1.68 (m, 6H), 1.39–1.00 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD) δ 177.8, 88.9, 75.8, 73.9, 37.5, 30.8, 29.0, 27.4, 26.7, 26.6. Analysis calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.04; H, 8.24.

4.6.8. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-phenylbutyrolactone (4h). Yield 99%; white solid; mp 93.5–95 °C; R_f 0.4 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +31.4 (c 0.7, MeOH); IR (KBr): 3419, 2925, 1763, 1454, 1115, 991 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.40–7.29 (m, 5H), 5.66 (d, 1H, J=5.4 Hz), 4.40 (t, 1H, J=5.4 Hz), 4.22 (d, 1H, J=5.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 177.3, 136.1, 129.2, 127.8, 84.0, 75.8, 74.3. Analysis calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.73; H, 5.51.

4.6.9. (2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-tolylbutyrolactone (4i). Yield 94%; white solid; mp 96.5–100.5 °C; R_f 0.4

(7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +40 (*c* 0.6, MeOH); IR (KBr): 3459, 2921, 1763, 1203, 1007 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.18 (s, 4H), 5.61 (d, 1H, *J*=5.4 Hz), 4.37 (dd, 1H, *J*=5.7, 5.4 Hz), 4.22 (d, 1H, *J*=5.7 Hz), 2.33 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 177.4, 139.2, 133.0, 129.9, 127.8, 84.0, 75.9, 74.3, 21.2. Analysis calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.16; H, 6.00.

4.6.10. (2*R*,3*S*,4*S*)-4-Anisyl-2,3-dihydroxybutyrolactone (4j). Yield 94%; cubic crystals; mp 176.5–178.5 °C; R_f 0.3 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ +30 (*c* 0.8, MeOH); IR (KBr): 3444, 2920, 1783, 1516, 1127, 994 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.34 (d, 2H, *J*=8.7 Hz), 6.96 (d, 2H, *J*=8.7 Hz), 4.95 (d, 1H, *J*=8.7 Hz), 4.45 (d, 1H, *J*=9.0 Hz), 4.10 (dd, 1H, *J*=9.0, 8.7 Hz), 3.80 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.1, 161.8, 129.9, 129.3, 115.1, 82.8, 81.3, 75.7, 55.8. Analysis calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.28; H, 5.50.

4.7. Preparation of (*R*)-1-((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentadecan-1-ol (5)

In a single neck round bottom flask equipped with magnetic stir bar and guard tube was placed a solution of (4*R*,5*S*)-5-((*R*)-1-hydroxypentadecyl)-*N*-methoxy-2,2,*N*-trimethyl-1,3-dioxolane-4-carboxamide (**3g**) (0.2 g, 0.56 mmol) in 10 mL of MeOH. $NaBH_4$ (0.05 g, 1.4 mmol) was added to the solution portionwise at 0 °C. The reaction mixture was slowly warmed up to room temperature and stirred for 2 h at the same temperature. After the reaction was complete (TLC), the reaction mixture was concentrated and water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent followed by silica gel column chromatography of the crude residue with petroleum ether and ethyl acetate as eluent gave (*R*)-1-((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentadecan-1-ol (**5**) as colourless oil: yield 96%; R_f 0.4 (7:3 ethyl acetate/petroleum ether); $[\alpha]_D$ −25 (*c* 0.6, $CHCl_3$); IR (neat): 3417, 2924, 2853, 1466, 1371, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05–4.00 (m, 1H), 3.81–3.51 (m, 4H), 2.39 (br s, 1H), 2.21 (br s, 1H), 1.46–1.37 (m, 2H), 1.39 (s, 6H), 1.29–1.22 (m, 24H), 0.84 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.2, 80.0, 77.6, 70.5, 62.1, 34.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.2, 27.1, 25.7, 22.6, 14.1; HRMS for $C_{21}H_{42}O_4$+Na calcd, 381.2981; found, 381.2986.

4.8. Preparation of (2*S*,3*S*,4*R*)-octadecane-1,2,3,4-tetraol (guggultetrol 6)

In a single neck round bottom flask equipped with magnetic stir bar and guard tube was placed a solution of (*R*)-1-((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-pentadecan-1-ol (**5**) (0.15 g, 0.47 mmol) in CH_2Cl_2 (10 mL). $FeCl_3 \cdot 6H_2O$ (0.44 g, 1.6 mmol) was introduced into the flask at room temperature. The resulting yellow coloured suspension was stirred for 15 min and after the reaction was complete (monitored by TLC), it was quenched by the addition of saturated solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the residue afforded (2*S*,3*S*,4*R*)-octadecane-1,2,3,4-tetraol (**6**) as white solid: yield 71%; mp 81–140 °C (lit.[12c] mp 87–135 °C); R_f 0.5 (4:1 ethyl acetate/petroleum ether); $[\alpha]_D$ +13.6 (*c* 0.5, EtOH), lit.[11b] $[\alpha]_D$ +11.4 (*c* 0.34, EtOH); IR (KBr): 3367, 2920, 2850, 1469, 1074 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.70–3.56 (m, 4H), 3.42 (dd, 1H, *J*=3.9, 3.6 Hz), 1.53–1.21 (m, 26H), 0.89 (t, 3H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 74.4, 74.1, 64.4, 34.5, 33.1, 30.8, 30.5, 26.9, 23.8, 14.5; HRMS for $C_{18}H_{38}O_4$+Na calcd, 341.2668; found, 341.2660.

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