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Enantiodivergent synthesis of (+)- and (-)-isolaurepan

Gonzalo Pazos, Manuel Pérez, Zoila Gándara, Generosa Gómez*, Yagamare Fall*

Departamento de Química Orgánica, Facultad de Química, Universidad de Vigo, 36200 Vigo, Spain

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ABSTRACT

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1. Introduction

A large number of marine natural products contain a medium ring ether in their structures and present a wide range of biological activities.¹ The synthesis of these unique structures constitutes a considerable challenge for organic chemists.² (+)-Iso-laurepinnacin (**1**)³ and (+)-neoisoprelaurefucin (**2**),⁴ which were both isolated from species of the genus *Laurencia* and contain a 2,7-disubstituted oxepane core (Fig. 1), have received much attention as





(+)-Isolaurepinnacin (1)







Fig. 1. Structures of representative Laurencia acetogenin metabolites.

synthetic targets. (+)-Isolaurepan (**3**) and (–)-isolaurepan (**4**) are fully saturated analogues of **1** and **2**, respectively, and of other chiral oxepene and oxepane derivatives.⁵

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Several reports of the stereoselective construction of racemic *cis*-2,7-disubstituted oxepanes have appeared,^{2e,6} but there are very few syntheses of nonracemic species such as (+)-isolaurepan⁷ and only one for the synthesis of (-)-isolaurepan.⁸

The work proposed in this paper is part of the overall objective of our research group directed toward the synthesis of ether rings as components of a large number of natural products.⁹ In a preliminary communication we reported an enantioselective synthesis of (+)-isolaurepan.¹⁰

2. Results and discussion

The enantiodivergent synthesis of (+)-and (-)-isolaurepan was achieved from a common chiral template

easily available from tri-O-acetyl-p-glucal, using as key step a diastereoselective thermal Claisen re-

arrangement, combined with a ring expansion reaction using trimethylsilyldiazomethane.

In this paper, we describe the enantioselective synthesis of (+)-isolaurepan and (-)-isolaurepan, both obtained from commercially available tri-O-acetyl-D-glucal (**5**) (Scheme 1). Our synthetic strategy is based in the intermediate 2,6-*cis*-disubstituted tetrahydropyran **6**, obtained through a thermal Claisen rearrangement.¹¹ From this compound and following analogues synthetic route were afforded oxepanes **7** and **8** by ring expansion with trimethylsilyldiazomethane.¹² A subsequent Wolf–Kishner reaction and side chain manipulation afforded (+)-isolaurepan (**3**) and (-)-isolaurepan (**4**).

2.1. Synthesis of (+)-isolaurepan

The procedure started with the synthesis of compound **9**, following the procedure described by Mori and Hayashi,¹³ in two steps



^{*} Corresponding author. Fax: +34 986 81 22 62; e-mail addresses: ggomez@ uvigo.es (G. Gómez), yagamare@uvigo.es (Y. Fall).

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Scheme 1. Retrosynthetic analysis.

from **5**¹⁴ in 85% yield (Scheme 2). This compound presents a latent allylic alcohol, which underwent a thermal Claisen rearrangement. The preparation of aldehyde **6** from allylic alcohol **9** via ester **11** was at first frustrated, by the yield of **11** being only 30% when obtained by Johnson rearrangement.¹⁵ The Eschenmoser [3,3]-sigmatropic rearrangement of alcohol **9** to amide **10**¹⁶ was also unsuccessful, recovering only part of the starting material without conversion.

As the Johnson orthoester rearrangement and the Eschenmoser variant involve the in situ generation of an allyl vinyl ether, we decided to change our strategy and use the classical Claisen rearrangement, by previous preparation of allyl vinyl ether **12**. This compound was successfully obtained by two alternative routes, which differed in the catalyst used. Thus, the reaction of allylic alcohol **9** with ethyl vinyl ether gave enolether **12** in 80% and 72% yields by catalysis with $Hg(OAc)_2^{17}$ or $Pd(OAc)_2$,¹⁸ respectively. Following purification by column chromatography, compound **12** underwent a Claisen rearrangement when heated in toluene at 185 °C, giving aldehyde **6** in 95% yield.

NMR spectroscopy confirmed the presence of single diastereoisomer as a reaction product. The high stereoselectivity obtained can be explained by conformational effects of the ring substituents in equatorial position. The stereochemistry of **6** was confirmed by NOE experiments (Scheme 3).



Scheme 3. NOE-NMR of aldehyde 6.

With aldehyde **6** in hand, we addressed the transformation of its side chains and the expansion of its ring (Scheme 4).

Wittig reaction over **6** afforded an 80% yield of diene **13**, which upon hydrogenation on Pd/C gave **14** in nearly quantitative yield. Removal of the silyl protecting group of **14**, followed by selective protection of the primary alcohol provided alcohol **15**, which was converted into ketone **16** in 80% yield. The crucial oxepane formation was accomplished by reaction of **16** with trimethylsilyldiazomethane in the presence of BF₃ ·OEt₂ in CH₂Cl₂ at -78 °C, which gave the seven-membered ketone **7** in 60%. In this reaction was also isolated 8% of its isomeric ketone after acidic hydrolysis of the intermediary trimethylsilyl enolether. Wolf–Kishner reaction of **7** afforded oxepane **17** in 58% yield.¹⁹ Removal of the silyl protecting group of **17** with TBAF gave the known alcohol **18**,^{7a,c} which was transformed into alkyne **19** by alkylation of the corresponding triflate. Finally, alkyne **19** was uneventfully converted into the



Scheme 2. Reagents and conditions: (a) i. K₂CO₃, MeOH; ii. ¹Bu₂Si(OTf)₂, DMF, Py; (b) MeC(OMe)₃, TMBA, 160 °C; (c) MeC(OMe)₂NMe₂, toluene, 120 °C; (d) ethyl vinyl ether, Hg(OAc)₂, 65 °C; (e) ethyl vinyl ether, Pd(OAc)₂, Bipy, CF₃CO₂H, Et₃N, 80 °C; (f) toluene, 185 °C, 5 h.



Scheme 4. Reagents and conditions: (a) *n*-BuPPh₃Br, *n*-BuLi, THF, 0 °C; (b) H₂, Pd/C (10%), MeOH; (c) i. TBAF, THF, rt; ii. TBDPSCI, imidazole, DMAP, DMF; (d) TAPP, NMO, CH₂Cl₂, molecular sieves; (e) (i) TMSCHN₂, BF₃·OEt₂, CH₂Cl₂, -78 °C; ii. PPTS, MeOH; (f) i. NH₂NHTs, MeOH, 70 °C, molecular sieves; ii. NaBH₃CN, DMF, 130 °C; (g) TBAF, THF; (h) j. Tf₂O, CH₂Cl₂, Py, -15 °C; ii. TMSCCH, *n*-BuLi, THF/DMPU, 0 °C; (i) i. TBAF, THF; ii. H₂, Pd/C (10%), MeOH.

target (+)-isolaurepan **3** in 79% yield. All attempts to obtain **3** directly from alcohol **18** by the method described in the literature^{7a} were unsuccessful.

2.2. Synthesis of (-)-isolaurepan

(-)-Isolaurepan was obtained from aldehyde **6** by a synthetic sequence similar to that used for the synthesis of (+)-isolaurepan (Scheme 5).

Wittig reaction of **6** followed by hydrogenation on Pd/C gave **21** in very good yields. Deprotection of silyl ether group of **21**, followed by selective protection of the primary alcohol provided compound **22** in 82% overall yield. The free secondary alcohol was converted into ketone **23** in 82% yield by treatment with TPAP. With the same procedure used by (+)-isolaurepan, the reaction of **23** with trimethylsilyldiazomethane at -78 °C, furnished the seven-membered ketone **8** in 66% and 7% yield of its isomeric ketone. The oxepane **24** was obtained by Wolf–Kishner reaction of **8** in 55% yield,¹⁹ and removal of the silyl protecting group of **24** with TBAF gave the known alcohol **25**.⁸ Swern oxidation of alcohol **25**, followed by Wittig reaction gave the alkene **26** in 64% yield. Finally, hydrogenation of **26** on Pd/C afforded the desired (–)-isolaurepan **4** in nearly quantitative yield.

3. Conclusions

In conclusion, we have developed an efficient and enantioselective synthesis of (+)-isolaurepan and (-)-isolaurepan from



Scheme 5. Reagents and conditions: (a) *n*-MePPh₃Br, *n*-BuLi, THF, 0 °C; (b) H₂, Pd/C (10%), MeOH; (c) i. TBAF, THF, rt; ii. TBDPSCI, imidazole, DMAP, DMF; (d) TPAP, NMO, CH₂Cl₂, molecular sieves; (e) i. TMSCHN₂, BF₃·OEt₂, CH₂Cl₂, -78 °C; ii. PPTS, MeOH; (f) i. NH₂NHTs, MeOH, 70 °C, molecular sieves; ii. NaBH₃CN, DMF, 130 °C; (g) TBAF, THF; (h) i. (COCl)₂, DMSO, Et₃N, CH₂Cl₂; ii. *n*-C₅H₁₁PPh₃I, *n*-BuLi, THF, 0 °C; (i) H₂, Pd/C (10%), MeOH.

commercially available tri-O-acetyl-D-glucal (**5**). Furthermore, intermediate **6** is a valuable building block that will allow us to extend our work on racemic polyoxacyclic compounds²⁰ to the enantioselective synthesis of polyoxacycles with trans–cis–trans stereochemistry, present in several natural products.

4. Experimental

4.1. General methods

Solvents were purified and dried by standard procedures before use. Melting points uncorrected.¹H and ¹³C NMR spectra were recorded in a Bruker ARX-400 spectrometer (400 MHz ¹H, 100.61 MHz ¹³C) using TMS as internal standard (chemical shifts in δ values, *J* in hertz). Mass spectrometry was carried out with a Hewlett Packard 5988A spectrometer. Flash chromatography (FC) was performed on silica gel (Merck 60, 230–400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F₂₅₄, 0.25 mm).

4.2. Methyl 2-((4aR,65,8aS)-2,2-di-*tert*-butyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl)acetate (11)

To a solution of alcohol **9** (50 mg, 0.18 mmol) and CH₃C(OCH₃)₃ (2 mL) was added a catalytic amount of 2,4,6-trimethylbenzoic acid (TMBA) and the mixture was heated in a sealed tube at 160 °C for 48 h. The solvent was rotatory evaporated to give a residue, which was chromatographed on silica gel using 4% EtOAc/hexane as eluent, affording **11** (18 mg, 30%) as a colorless liquid, R_{f} : 0.37 (10%)

EtOAc/hexane); $[\alpha]_D^{20}$ +27.41 (*c* 1.82, MeOH); IR (film), cm⁻¹: 2938.98, 2861.84, 1743.33, 1126.22, 1095.37, 860.09; H NMR (CDCl₃, δ): 5.82 (1H, d, *J*=10.3 Hz, H-8), 5.58 (1H, d, *J*=10.3 Hz, H-7), 4.59–4.54 (1H, m, H-6), 4.32 (1H, dd, *J*=8.3, 1.2 Hz, H-8a), 4.09 (1H, dd, *J*=9.96, 5.03 Hz, H-4), 3.78 (1H, t, *J*=10.24 Hz, H-4), 3.63 (3H, s, OCH₃), 3.45 (1H, ddd, *J*=10.4, 8.5, 5.1 Hz, H-4a), 2.46–2.41 (2H, m, CH₂–C=O), 1.03 (9H, s, CH₃–^tBu), 0.97 (9H, s, CH₃–^tBu); C NMR (CDCl₃, δ): 171.0 (C=O), 130.8 (CH-8), 128.2 (CH-7), 74.7 (CH-4a), 72.1 (CH-6), 69.9 (CH-8a), 67.1 (CH₂-4), 51.8 (OCH₃), 40.1 (CH₂–C=O), 27.5 (CH₃–^tBu), 27.1 (CH₃–^tBu), 22.7 (C–^tBu), 20.1 (C–^tBu); MS (FAB⁺) [*m*/*z*, (%)]: 343 (M⁺+1, 46), 342 (M⁺, 20), 341 (M⁺-1, 55), 286 (19), 285 (M⁺–^tBu, 86), 270 (21), 269 (M⁺–CH₂CO₂Me, 100), 239 (10), 219 (19), 211 (14), 201 (36), 167 (16); HRMS (FAB⁺): 343.1863 calculated for C₁₇H₃₁O₅Si, found 343.1859.

4.3. (4a*R*,8*R*,8a*S*)-2,2-Di-*tert*-butyl-8-(vinyloxy)-4,4a,8,8a-tet-rahydropyrano[3,2-*d*][1,3,2]dioxasiline (12)

Method A: A solution of allylic alcohol **9** (5.2 g, 18.2 mmol) and $Hg(OAc)_2$ (1.74 g, 5.46 mmol) in ethyl vinyl ether (40 mL) in a sealed tube was heated at 65 °C for 4 days, adding $Hg(OAc)_2$ (1.74 g, 5.46 mmol) every 24 h. The mixture was washed with water (3×35 mL) and brine (3×35 mL) and the solvent removed under vacuum to afford a residue, which was chromatographed on silica gel using 2% EtOAc/hexane as eluent, affording **12** (4.5 g, 80%) as a colorless liquid; 0.5 g (10%) of the starting allylic alcohol was recovered.

Method B: To a solution of 9 (1.95 g. 6.81 mmol). Pd(OAc)₂ (46 mg, 0.2 mmol) and bipyridine (32 mg, 0.2 mmol) in ethyl vinyl ether (30 mL) was added Et₃N (1.9 mL, 13.62 mmol). The resulting suspension was stirred at room temperature for 5 min. Trifluoroacetic acid (52 µL, 0.68 mmol) was added and the mixture heated in a sealed tube at 80 °C for 3 days. The solvent was removed under vacuum to afford a residue, which was chromatographed on silica gel using 5% EtOAc/hexane as eluent, affording 12 (1.5 g, 72%) as a colorless liquid; Rf: 0.63 (30% EtOAc/hexane); 0.34 g (17%) of the starting allylic alcohol was recovered; $[\alpha]_D^{20}$ –77.39 (*c* 2.88, MeOH); IR (film), cm⁻¹: 2938.98, 2982.71, 2865.47, 1639.27, 1473.35, 1095.37, 1122.37; H NMR (CDCl₃, δ): 6.53 (1H, dd, *J*=14.00, 6.44 Hz, H-1'), 6.32 (1H, dd, J=6.03, 1.24 Hz, H-6), 4.78 (1H, dd, J=6.03, 1.88 Hz, H-7), 4.43–4.36 (2H, m, H-10, H-2'), 4.18 (1H, dd, J=10.30, 4.94 Hz, H-4), 4.13 (1H, dd, J=10.30, 7.08 Hz, H-8a), 4.03 (1H, dd, J=6.44, 1.35 Hz, H-2'), 3.98 (1H, t, J=10.30 Hz, H-4), 3.90-3.81 (1H, m, H-4a), 1.06 (9H, s, CH₃-^tBu), 1.00 (9H, s, CH₃-^tBu); C NMR (CDCl₃, δ): 151.2 (CH-1'), 144.7 (CH-6), 100.6 (CH-7), 88.9 (CH₂-2'), 77.4 (CH-8), 75.2 (CH-8a), 72.5 (CH-4a), 65.9 (CH₂-4), 27.3 (C-CH₃-^tBu), 26.9 (C-CH₃-^tBu), 22.7 (C-^tBu), 19.8 (C-^tBu); MS (FAB^+) [m/z, (%)]: 313 $(M^++1, 4)$, 312 $(M^+, 3)$, 311 $(M^+-1, 9)$, 270 (23), 269 (M^+ –OCHCH₂, 100), 268 (8), 255 (M^+ –^tBu, 7), 213 (8), 201 (5); HRMS (FAB⁺): 313.1757 calculated for $C_{16}H_{29}O_4Si$, found 313.1790.

4.4. 2-((4a*R*,6*S*,8a*S*)-2,2-Di-*tert*-butyl-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)acetaldehyde (6)

A solution of **12** (4.2 g, 13.46 mmol) in toluene (40 mL) was heated to 185 °C in a sealed tube for 5 h. The solvent was removed under vacuum to afford a residue, which was chromatographed on silica gel using 2% EtOAc/hexane as eluent, affording aldehyde **6** (4 g, 95%) as a white solid; mp=68–69 °C, *R*_f: 0.6 (30% EtOAc/hexane); $[\alpha]_{D}^{20}$ +21.44 (*c* 1.73, MeOH); IR (film, cm⁻¹): 2938.98, 2861.34, 1727.91, 1473.35, 1130.08, 1091.51, 860.09; H NMR (CDCl₃, δ): 9.75 (1H, t, *J*=2.06 Hz, CHO), 5.93 (1H, d, *J*=10.34 Hz, H-8), 5.68–5.61 (1H, m, H-7), 4.77–4.67 (1H, m, H-6), 4.43–4.36 (1H, m, H-8a), 4.16 (1H, dd, *J*=9.97, 5.05 Hz, H-4), 3.84 (1H, t, *J*=10.24 Hz,

H-4), 3.54 (1H, ddd, *J*=10.34, 8.52, 5.08 Hz, H-4a), 2.57 (2H, dd, *J*=6.05, 2.06 Hz, *CH*₂-CHO), 1.05 (9H, s, *CH*₃-^{*t*}Bu), 0.99 (9H, s, *CH*₃-^{*t*}Bu); C NMR (CDCl₃, δ): 200.4 (C=O), 131.2 (CH-8), 127.8 (CH-7), 74.7 (CH-4a), 70.9 (CH-6), 70.0 (CH-8a), 67.0 (CH₂-4), 48.3 (CH₂-CHO), 27.5 (CH₃-^{*t*}Bu), 27.0 (CH₃-^{*t*}Bu), 22.7 (C-^{*t*}Bu), 20.0 (C-^{*t*}Bu); MS (FAB⁺) [*m*/*z*, (%)]: 313 (M⁺+1, 6), 312 (M⁺, 7), 311 (M⁺-1, 21), 283 (M⁺-CHO, 11), 270 (23), 269 (M⁺-CH₂CHO, 100), 268 (13), 267 (15), 255 (M⁺-^{*t*}Bu, 17), 239 (20), 213 (21), 211 (19), 201 (27); HRMS (FAB⁺): 313.1757 calculated for C₁₆H₂₉O₄Si, found 313.1790.

4.5. (4a*R*,6*S*,8a*S*)-2,2-Di-*tert*-butyl-6-(hex-2'-enyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (13)

To a suspension of butyltriphenylphosphonium bromide (5.73 g, 14.35 mmol) in THF (30 mL) at 0 °C was added *n*-BuLi (5.7 mL of a 2.5 M solution in hexane, 14.35 mmol) and stirring was continued for 20 min whereupon the color of the mixture turned to orange. A solution of aldehyde 6 (3.2 g, 10.25 mmol) in THF (30 mL) was added via cannula and the mixture stirred for 20 min then quenched with an aqueous saturated solution of NH₄Cl (50 mL) and the product extracted with EtOAc (3×60 mL). The combined organic phases were dried, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 2% EtOAc/hexane as eluent, affording diene 13 (2.7 g, 80%) as a colorless liquid; Rf: 0.62 (30% EtOAc/hexane); [α]²⁰_D +52.31 (*c* 1.67, MeOH); IR (film, cm⁻¹): 2954.28, 2935.13, 2865.48, 1650.77, 1469,49, 1126.22; H NMR $(CDCl_3, \delta)$: 5.85 (1H, d, I=10.34 Hz, H-8), 5.63 (1H, m, H-7), 5.54-5.46 (1H. m. H-2'), 5.45-5.33 (1H. m. H-3'), 4.43-4.35 (1H. m. H-8a), 4.23–4.19 (1H, m, H-6), 4.17 (1H, dd, J=9.98, 4.94 Hz, H-4), 3.87 (1H, t, *J*=10.22, H-4), 3.50 (1H, ddd, *J*=10.49, 8.52, 5.06 Hz, H-4a), 2.27 (1H, dd, *J*=8.49, 5.87 Hz, H-1'), 2.05–1.94 (1H, m, H-4'), 1.37 (1H, dt, *J*=22.05, 7.34 Hz, H-5'), 1.05 (9H, s, CH₃-^{*t*}Bu), 0.99 (9H, s, CH₃-^{*t*}Bu), 0.89 (3H, t, *J*=7.34 Hz, H-6'); C NMR (CDCl₃, δ): 132.5 (CH-2'), 129.9 (CH-8), 129.2 (CH-7), 124.2 (CH-3'), 75.3 (CH-6), 74.7 (CH-4a), 70.3 (CH-8a), 67.3 (CH₂-4), 33.2 (CH₂-1'), 29.5 (CH₂-4'), 27.5 (CH₃-^tBu), 27.1 (CH₃-^tBu), 22.7 (C-^tBu), 22.5 (CH₂-5'), 20.0 $(C-^{t}Bu)$, 13.8 $(CH_{3}-6')$; MS (FAB^{+}) [m/z, (%)]: 353 $(M^{+}+1, 26)$, 352 $(M^+, 26), 351 (M^+-1, 67), 296 (30), 295 (M^+-{}^tBu, 100), 285 (23),$ 269 (M⁺-CH₂CHCHCH₂CH₂CH₃, 46), 267 (27), 239 (28), 213 (45), 211 (29), 201 (33), 183 (22), 171 (21), 169 (21), 167 (24), 165 (28), 163 (22), 161 (23); HRMS (FAB⁺): 352.2434 calculated for C₂₀H₃₆O₃Si, found 353.2434.

4.6. (4aR,6S,8aS)-2,2-Di-*tert*-butyl-6-hexylhexahydropyrano [3,2-d][1,3,2]dioxasiline (14)

A suspension of **13** (2.68 g, 10.42 mmol) and Pd/C (10%) (1.6 g, 0.2 mmol) in MeOH (40 mL) was stirred under H₂ atmosphere for 10 h. The mixture was filtered through Celite[®] and the filtrate concentrated under vacuum to give pure 14 (2.68 g, 99%) as a colorless liquid; R_f : 0.62 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –17.03 (c 2.20, MeOH); IR (film, cm⁻¹): 2954.78, 2865.09, 2935.17, 1468,79, 1125.99, 1047.28; H NMR (CDCl₃, δ): 4.07 (1H, dd, *J*=10.15, 4.89 Hz, H-4), 3.81 (1H, t, J=10.15 Hz, H-4), 3.71 (1H, ddd, J=10.63, 9.15, 4.56 Hz, H-6), 3.36-3.24 (2H, m, H-8a, H-4a), 2.13-2.06 (1H, m, H-8), 1.76–1.67 (1H, m, H-7), 1.54–1.41 (2H, m, H-1', H-8), 1.41–1.32 (3H, m, H-1', H-2', H-7), 1.31–1.20 (7H, m, H-2', 2H-3', 2H-4', 2H-5'), 1.03 (9H, s, CH₃—^{*t*}Bu), 0.98 (9H, s, CH₃–^{*t*}Bu), 0.87 (3H, t, *J*=6.81 Hz, 3H-6'); C NMR (CDCl₃, δ): 77.9 (CH-8a or CH-4a), 77.6 (CH-8a or CH-4a), 74.10 (CH-6), 67.25 (CH2-4), 35.76 (CH2-1'), 32.67 (CH2-8), 31.77 (CH₂-4'), 30.98 (CH₂-7), 29.31 (CH₂-3'), 27.49 (CH₃-^tBu), 27.13 $(CH_3 - {}^tBu)$, 25.68 $(CH_2 - 2')$, 22.63 $(C - {}^tBu)$, 22.59 $(CH_2 - 5')$, 19.92 (C^{-*t*}Bu), 14.06 (CH₃-6'); MS (FAB⁺) [*m*/*z*, (%)]: 357 (M⁺+1, 28), 356 (M⁺, 18), 355 (M⁺-1, 61), 339 (10), 300 (23), 299 (M⁺-^tBu, 100), 297 (12), 227 (14), 201 (15); HRMS (FAB⁺): 357.2747 calculated for $C_{20}H_{41}O_3Si$, found 357.2845.

4.7. (2*R*,3*S*,6*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-6-hexyltetrahydro-2*H*-pyran-3-ol (15)

To a solution of 14 (2.55 g. 7.14 mmol) in THF (35 mL) was added TBAF (21.4 mL of a 1 M solution in THF. 21.4 mmol) and the mixture was stirred at room temperature for 20 h. The solvent was evaporated to afford a residue, which was chromatographed on silica gel using 50% EtOAc/hexane as eluent, affording diol 14' (1.5 g, 96%) as a white solid; mp=62–63 °C, R_{f} : 0.1 (30% EtOAc/hexane); $[\alpha]_{D}^{20}$ +22.66 (*c* 1.56, MeOH); IR (film, cm⁻¹): 3301.54, 2927.29, 2854.13, 1060.66, 771.38; H NMR (CDCl₃, δ): 3.82 (1H, dd, *J*=11.43, 3.99 Hz, CH₂-OH), 3.75 (1H, dd, *J*=11.43, 4.90 Hz, CH₂-OH), 3.52 (1H, td, J=10.68, 10.56, 4.74 Hz, H-3), 3.34–3.25 (1H, m, H-6), 3.16 (1H, td, J=8.95, 4.35, 4.35 Hz, H-2), 2.69 (2H, br s, 2OH), 2.12–2.03 (1H, m, H-4), 1.75-1.67 (1H, m, H-5), 1.55-1.43 (2H, m, H-1', H-4), 1.42-1.31 (3H, m, H-1', H-2', H-5), 1.33-1.21 (7H, m, H-2', 2H-3', 2H-4', 2H-5'), 0.88 (3H, t, J=5.92 Hz, H-6'); C NMR (CDCl₃, δ): 81.1 (CH-2), 77.5 (CH-6), 67.7 (CH-3), 63.4 (CH2-OH), 35.7 (CH2-1'), 32.5 (CH2-4), 31.7 (CH2-4'), 30.8 (CH2-5), 29.3 (CH2-3'), 25.7 (CH2-2'), 22.6 (CH2-5'), 14.0 (CH₃-6'); MS (FAB⁺) [*m*/*z*, (%)]: 217 (M⁺+1, 50), 216 (M⁺, 14), 215 (M⁺-1, 83), 213 (11), 200 (10), 199 (M⁺-OH, 56), 198 (11), 197 (12), 186 (21), 181 (27), 163 (19); HRMS (FAB+): 217.1725 calculated for C₁₂H₂₅O₃, found 217.1759.

The selective protection of the primary alcohol of diol 14' was carried out as follows: to a solution of 14' (1.55 g, 7.14 mmol) in DMF (30 mL) were added imidazole (0.58 g, 8.57 mmol), TBDPSCl (2.22 mL, 8.57 mmol), and a catalytic amount of DMAP. The mixture was stirred at room temperature for 30 min and diluted with EtOAc (50 mL). The resulting organic phase was washed with water $(3 \times 40 \text{ mL})$ and brine $(3 \times 40 \text{ mL})$, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 5% EtOAc/hexane as eluent, affording alcohol 15 (3.15 g, 96%) as a colorless liquid; R_f : 0.5 (30% EtOAc/hexane); $[\alpha]_D^{20}$ 6.16 (*c* 2.27, MeOH); IR (film, cm⁻¹): 3451.96, 2931.27, 2857.99, 1461.78, 1106.94, 701.96; H NMR (CDCl₃, δ): 7.72–7.67 (4H, m, Ph–H₀), 7.47–7.36 (6H, m, Ph_{p,m}), 3.90 (1H, dd, J=10.11, 4.69 Hz, CH₂-OTBDPS), 3.78 (1H, dd, J=10.11, 7.66 Hz, CH₂-OTBDPS), 3.68-3.60 (1H, m, H-2), 3.54 (1H, s, OH), 3.34-3.20 (2H, m, H-3, H-6), 2.16-2.07 (1H, m, H-4), 1.72-1.63 (1H, m, H-5), 1.54-1.41 (2H, m, H-1', H-4), 1.40-1.28 (3H, m, H-1', H-2', H-5), 1.28-1.20 (7H, m, H-2', 2H-3', 2H-4', 2H-5'), 1.06 (9H, s, CH_3 - tBu), 0.86 (3H, t, *J*=6.81 Hz, H-6'); C NMR (CDCl₃, δ): 135.6 and 135.6 (CH_o-Ph), 132.6 and 132.6 (C-Ph), 129.9 (CH_p-Ph), 127.79 and 127.8 (CH_m-Ph), 79.2 (CH-2), 77.3 (CH-6), 70.9 (CH-3), 67.3 (CH2-OTBDPS), 35.8 (CH2-1'), 31.8 (CH2-4), 31.8 (CH2-4'), 30.4 (CH2-5), 29.3 (CH2-3'), 26.8 (CH3-tBu), 25.6 (CH2-2'), 22.6 (CH2-5'), 19.1 (C t Bu), 14.0 (CH₃-6'); MS (FAB⁺) [*m*/*z*, (%)]: 454 (M⁺, 4), 453 (M⁺-1, 9), 398 (15), 397 (M⁺-^{*t*}Bu, 44), 379 (11), 377 (M⁺-Ph, 26), 359 (16), 319 (14), 299 (12), 241 (20), 221 (15), 200 (19), 199 (100), 198 (11), 197 (48), 183 (19), 181 (37), 167 (11), 165 (18), 163 (41), 161 (24); HRMS (FAB⁺): 454.2903 calculated for C₂₈H₄₂O₃Si, found 454.2903.

4.8. (2*R*,6*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-6hexyldihydro-2*H*-pyran-3(4*H*)-one (16)

To a solution of alcohol **15** (3.05 g, 6.71 mmol) in CH₂Cl₂ (50 mL) were added 4 Å molecular sieves (2 g), NMO (2.35 g, 20.14 mmol), and a catalytic amount of TPAP. The resulting greenish solution was stirred at room temperature for 18 h. The solvent was evaporated to afford a residue, which was chromatographed on silica gel using 5% EtOAc/hexane as eluent, affording ketone **16** (2.4 g, 80%) as a colorless liquid; *R*_f: 0.62 (30% EtOAc/hexane); $[\alpha]_{D}^{20}$ +1.59 (*c* 1, MeOH); IR (film, cm⁻¹): 2931.27, 2861.84, 1724.05, 1280.65, 1114.65; H NMR

(CDCl₃, δ): 7.78-7.69 (4H, m, Ph-H_o), 7.45-7.35 (6H, m, Ph_{p,m}), 4.06-3.93 (3H, m, H-6, CH2-OTBDPS), 3.67 (1H, m, H-2), 2.68-2.58 (1H, m, H-4), 2.48-2.38 (1H, m, H-4), 2.08-1.88 (2H, m, H-5), 1.73-1.61 (1H, m, H-1'), 1.61-1.48 (2H, m, H-1', H-2'), 1.45-1.24 (7H, m, H-2', 2H-3', 2H-4', 2H-5'), 1.04 (9H, s, CH₃-tBu), 0.91 (3H, t, *I*=6.60 Hz, 3H-6'); C NMR (CDCl₃, δ): 209.7 (C=O), 135.7 and 135.6 (CH₀-Ph), 133.5 and 133.4 (C-Ph), 129.5 (CH_n-Ph), 127.6 and 127.5 (CH_m-Ph), 83.8 (CH-6), 75.41 (CH-2), 63.6 (CH₂-OTBDPS), 37.5 (CH2-4), 35.9 (CH2-1'), 31.8 (CH2-5), 30.4 (CH2-4'), 29.3 (CH2-3'), 26.6 (CH₃-^tBu), 25.6 (CH₂-2'), 22.6 (CH₂-5'), 19.2 (C-^tBu), 14.1 (CH₃-6'); MS (FAB⁺) [*m*/*z*, (%)]: 453 (M⁺+1, 5), 452 (M⁺, 9), 451 (M⁺-1, 20), 435 (18), 395 (M⁺-^tBu, 24), 375 (M⁺-Ph, 16), 374 (22), 373 (43), 297 (21), 257 (28), 241 (51), 239 (24), 237 (30), 223 (18), 221 (34), 213 (M⁺–TBDPS,13), 200 (19), 199 (100), 198 (18), 199 (84), 183 (23), 180 (26),171 (36), 167 (16), 165 (29), 163 (49); HRMS (FAB⁺): 452.2747 calculated for C₂₈H₄₀O₃Si, found 452.2747.

4.9. (2*R*,7*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-7hexyloxepan-3-one (7) and (2*S*,7*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)-7-hexyloxepan-4-one (7')

To a solution of ketone **16** (2.32 g, 5.12 mmol) in CH_2Cl_2 (40 mL) at -78 °C were added BF₃·OEt₂ (0.77 mL, 6.14 mmol) and TMSCHN₂ (2.68 mL of a 2 M solution in hexane, 5.37 mmol). The mixture was stirred at -78 °C for 30 min before adding an aqueous saturated solution of NaHCO₃ (30 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (3×30 mL). The combined organic phases were washed with water $(3 \times 30 \text{ mL})$, brine $(3 \times 30 \text{ mL})$, dried, filtered, and evaporated to give a residue, which was dissolved in MeOH (40 mL). PPTS (1.92 g, 7.68 mmol) was added and the mixture stirred at room temperature for 1 h. The product was extracted with EtOAc (3×30 mL) and the combined organic phases washed with an aqueous saturated solution of NaHCO₃ (3×30 mL) and brine (3×30 mL). Drying, filtration, and solvent evaporation afforded a residue, which was chromatographed on silica gel using 1% EtOAc/hexane as eluent, affording ketone 7 (1.45 g, 60%) along with its isomeric ketone 7' (0.14 g, 8%).

4.9.1. Compound 7. Colorless liquid; Rf: 0.48 (20% EtOAc/hexane); $[\alpha]_{D}^{20}$ +41.47 (c 1.51, MeOH); IR (film, cm⁻¹): 2931.27, 2857.99, 1716.34, 1110.82, 701.96; H NMR (CDCl₃, δ): 7.79-7.65 (4H, m, Ph-H_o), 7.45-7.34 (6H, m, Ph_{p,m}), 3.96 (1H, dd, J=10.65, 4.41 Hz, CH₂-OTBDPS), 3.89 (1H, dd, J=10.65, 2.06 Hz, CH₂-OTBDPS), 3.81-3.78 (1H, m, H-2), 3.25-3.16 (1H, m, H-7), 3.08-2.96 (1H, m, H-4), 2.44 (1H, dd, J=11.20, 6.63 Hz, H-4), 2.04–1.93 (1H, m, H-5), 1.86-1.78 (1H, m, H-1'), 1.73-1.57 (2H, m, H-6, H-1'), 1.55-1.40 (3H, m, H-2', H-5, H-6), 1.40-1.18 (7H, m, H-2', 2H-3', 2H-4', 2H-5'), 1.03 (9H, s, CH₃-^{*t*}Bu), 0.87 (3H, t, *J*=6.36 Hz, 3H-6'); C NMR (CDCl₃, δ): 216.6 (C=O), 135.8 and 135.6 (CH₀-Ph), 133.2 and 133.1 (C-Ph), 129.6 and 129.6 (CH_n-Ph), 127.6 and 127.5 (CH_m-Ph), 87.6 (CH-2), 83.7 (CH-7), 66.2 (CH2-OTBDPS), 43.2 (CH2-4), 37.3 (CH2-6), 36.3 (CH₂-1'), 31.8 (CH₂-4'), 29.3 (CH₂-3'), 26.6 (CH₃-^tBu), 25.6 (CH₂-2'), 23.7 (CH₂-5), 22.6 (CH₂-5'), 19.2 (C^{-t}Bu), 14.1 (CH₃-6'); MS (FAB⁺) [m/z, (%)]: 467 (M⁺+1, 4), 466 (M⁺, 3), 465 (M⁺-1, 6), 449 (24), 411 (12), 410 (34), 409 (M^+ –^{*t*}Bu, 100), 390 (15), 389 (M^+ –Ph, 29), 331 (25), 311 (15), 242 (17), 241 (68), 239 (14), 227 (M⁺–TBDPS, 7), 223 (20), 221 (37); HRMS (FAB⁺): 467.2903 calculated for C₂₉H₄₃O₃Si, found 467.2981.

4.9.2. Compound **7**'. Colorless liquid; R_f : 0.40 (20% EtOAc/hexane); $[\alpha]_D^{20}$ –39.7 (*c* 1.59, MeOH); IR (film, cm⁻¹): 2931.27, 2857.99, 1708.62, 1110.82, 701.96; H NMR (CDCl₃, δ): 7.70–7.64 (4H, m, Ph–H_o), 7.46–7.35 (6H, m, Ph_{p,m}), 3.91–3.83 (1H, m, H-2), 3.73 (1H, dd, *J*=10.15, 6.06 Hz, *CH*₂–OTBDPS), 3.50 (1H, dd, *J*=10.10, 5.82 Hz, *CH*₂–OTBDPS), 3.47–3.44 (1H, m, H-7), 2.79–2.68 (2H, m, H-3, H-5), 2.58–2.49 (2H, m, H-3, H-5), 1.86–1.78 (1H, m, H-6),

1.66–1.54 (1H, m, H-6), 1.52–1.35 (3H, m, 2H-1', H-2'), 1.35–1.17 (7H, m, H-2', 2H-3', 2H-4', 2H-5'), 1.05 (9H, s, CH₃–^tBu), 0.85 (3H, t, *J*=6.54, 6.54 Hz, 3H-6'); C NMR (CDCl₃, δ): 211.6 (C=O), 135.6 and 135.5 (CH₀–Ph), 133.3 and 133.19 (C–Ph), 129.7 and 129.6 (CH_p–Ph), 127.7 and 127.6 (CH_m–Ph), 83.4 (CH-7), 76.9 (CH-2), 66.5 (CH₂–OTBDPS), 48.5 (CH₂-3), 42.2 (CH₂-5), 36.6 (CH₂-1'), 32.4 (CH₂-6), 31.7 (CH₂-4'), 29.2 (CH₂-3'), 26.7 (CH₃–^tBu), 25.9 (CH₂-2'), 22.6 (CH₂-5'), 19.1 (C–^tBu), 14.1 (CH₃-6'); MS (FAB⁺) [*m*/*z*, (%)]: 467 (M⁺+1, 4), 466 (M⁺, 4), 465 (M⁺–1, 7), 409 (M⁺–^tBu, 100), 389 (M⁺–Ph, 29), 331 (27), 311 (16), 241 (30), 227 (M⁺–TBDPS, 8), 221 (17), 200 (15), 199 (76), 197 (48), 193 (23), 181 (25), 200 (19), 163 (26); HRMS (FAB⁺): 467.2903 calculated for C₂₉H₄₃O₃Si, found 467.2981.

4.10. *tert*-Butyl(((2*S*,7*S*)-7-hexyloxepan-2-yl)methoxy)diphenylsilane (17)

To a solution of ketone **7** (380 mg, 0.81 mmol) in MeOH (20 mL) were added NH₂NHTs (167 mg, 0.89 mmol), PTSA (9 mg, 48 μ mol), and 4 Å molecular sieves (300 mg). The mixture was stirred at 70 °C for 33 h. The organic solvent was removed under vacuum and the residue was dissolved in CH₂Cl₂, washed with water (3×15 mL) and brine (3×15 mL), dried, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 5% EtOAc/hexane as eluent, affording hydrazones **7a** (400 mg, 78%) and **7b** (90 mg, 17%).

4.10.1. Compound 7a. Colorless liquid; Rf: 0.27 (20% EtOAc/hexane); $[\alpha]_{D}^{20}$ +60.04 (c 1.53, MeOH); IR (film, cm⁻¹): 3220.54, 2929.34, 2857.99, 1342.21, 1168.65, 1112.73, 703.89; H NMR (CDCl₃, δ): 7.72–7.67 (4H, m, Ph–H₀), 7.67–7.61 (2H, m, Ts–H₀), 7.46–7.32 (6H, m, Ph_{p,m}), 7.09 (2H, d, J=8.14 Hz, Ts-H_m), 4.12 (1H, dd, J=6.46, 3.52 Hz, H-2), 3.74 (1H, dd, J=10.86, 3.52 Hz, CH₂-OTBDPS), 3.65 (1H, dd, J=10.86, 6.46 Hz, CH₂-OTBDPS), 3.18-3.10 (1H, m, H-7), 2.33 (3H, s, CH₃-Ph), 2.24-2.15 (1H, m, H-4), 1.85-1.77 (1H, m, H-4), 1.68–1.61 (2H, m, H-1', H-5), 1.58–1.33 (5H, m, H-1', H-2', 2H-6, H-5), 1.33-1.17 (7H, m, H-2', 2H-3', 2H-4', 2H-5'), 0.99 (9H, s, CH_3 -^tBu), 0.86 (3H, t, J=6.97 Hz, 3H-6'); C NMR (CDCl₃, δ): 161.8 (C=N), 143.8 (C-Ts), 135.6 and 135.6 (CH_o-Ph), 134.9 (CH_p-Ts), 133.5 and 133.4 (C-Ph), 129.6 and 129.5 (CH_p-Ph), 129.3 (CH_o-Ts), 127.8 (CH_m-Ts), 127.5 and 127.51 (CH_m-Ph), 83.1 (CH-7), 81.1 (CH-2), 66.3 (CH₂-OTBDPS), 37.2 (CH₂-6), 35.9 (CH₂-1'), 31.7 (CH₂-4'), 29.3 (CH₂-3'), 26.7 (CH₃-^tBu), 25.6 (CH₂-2'), 23.7 (CH₂-4), 22.6 (CH₂-5'), 21.5 (CH₂-5), 19.1 (C^{-t}Bu), 14.1 (CH₃-6'); MS (FAB⁺) [*m*/*z*, (%)]: 637 (M⁺+3, 19), 636 (M⁺+2, 47), 635 (M⁺+1, 100), 633 (M⁺-1, 5), 578 (13), 577 (M⁺-^tBu, 30), 213 (11), 199 (33), 197 (22), 163 (11); HRMS (FAB⁺): 635.3261 calculated for C₃₆H₅₁N₂O₄SSi, found 635.3294.

4.10.2. Compound **7b**. Colorless liquid; R_f : 0.35 (20% EtOAc/hexane); H NMR (CDCl₃, δ): 8.47 (1H, s, NH), 7.51–7.43 (6H, m, Ph–H_o, Ts–H_o), 7.42–7.31 (6H, m, Ph_{p,m}), 7.04 (2H, d, *J*=8.12 Hz, Ts–H_m), 4.73 (1H, dd, *J*=6.25, 4.59 Hz, H-2), 3.90 (dd, *J*=9.56, 4.59 Hz, CH₂–OTBDPS), 3.49 (1H, m, CH₂–OTBDPS), 3.11–3.02 (1H, m, H-7), 2.30 (3H, s, CH₃–Ph), 2.14 (1H, t, *J*=11.87 Hz, H-7), 1.90–1.80 (1H, m, H-4), 1.64–1.56 (2H, m, H-1', H-5), 1.54–1.37 (5H, m, H-1', H-2', 2H-6, H-5), 1.37–1.19 (7H, m, H-2', 2H-3', 2H-4', 2H-5'), 1.02 (9H, s, CH₃–^tBu), 0.89 (3H, t, *J*=6.88 Hz, 3H-6'); MS (FAB⁺) [*m*/*z*, (%)]: 637 (M⁺+3, 20), 636 (M⁺+2, 47), 635 (M⁺+1, 100), 633 (M⁺-1, 4), 578 (11), 577 (M⁺–^tBu, 26), 213 (9), 199 (28), 197 (18), 163 (9); HRMS (FAB⁺): 635.3261 calculated for C₃₆H₅₀N₂O₄SSi, found 635.3281.

To a solution of **7a** (400 mg, 0.63 mmol) in DMF (20 mL) were added NaBH₃CN (158 mg, 2.52 mmol) and PTSA (33 mg, 0.176 mmol) and the mixture was stirred at 130 °C for 2 h. NaBH₃CN (158 mg, 2.52 mmol) and PTSA (33 mg, 0.176 mmol) were again added to the mixture and stirring was continued for 3 h. The mixture was allowed to reach room temperature. EtOAc (20 mL)

was added and the organic phase washed with water $(3 \times 20 \text{ mL})$ and brine (3×20 mL), dried, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 1% EtOAc/ hexane as eluent, affording oxepane 17 (175 mg, 61%) as a gray liquid; R_{f} : 0.63 (20% EtOAc/hexane); $[\alpha]_{D}^{20}$ –8.08 (*c* 0.91, MeOH); IR (film, cm⁻¹): 2927.41, 2857.99, 1457.92, 1106.94, 1002.23; H NMR (CDCl₃, δ): 7.73-7.67 (4H, m, Ph-H_o), 7.45-7.35 (6H, m, Ph_{p,m}), 3.69 (1H, dd, *J*=9.92, 6.32 Hz, CH₂-OTBDPS), 3.64-3.57 (1H, m, H-7), 3.47 (1H, dd, J=9.92, 5.69 Hz, CH2-OTBDPS), 3.44-3.38 (1H, m, H-2), 1.81-1.59 (4H, m, H-1', H-2', H-3, H-6), 1.58-1.39 (6H, m, H-3, 2H-4, 2H-5, H-6), 1.38-1.18 (8H, m, H-1' H-2', 2H-3', 2H-4', 2H-5'), 1.06 (9H, s, CH₃-^tBu), 0.87 (3H, t, *J*=6.80 Hz, 3H-6'); C NMR (CDCl₃, δ): 135.6 (CH₀-Ph), 133.8 and 133.8 (C-Ph), 129.5 and 129.5 (CH_n-Ph), 127.5 and 127.5 (CH_m-Ph), 80.5 (CH-7), 80.4 (CH-2), 67.2 (CH₂-OTBDPS), 37.3 (CH₂-6), 36.8 (CH₂-1'), 32.3 (CH₂-3), 31.8 (CH₂-4'), 29.4 (CH₂-3'), 26.8 (CH₃-^tBu), 26.2 (CH₂-5), 25.5 (CH₂-2'), 24.8 (CH₂-4), 22.6 (CH₂-5'), 19.2 (C-^tBu), 14.1 (CH₃-6'); MS (FAB⁺) [m/z, (%)]: 452 (M⁺, 4), 465 (M⁺-1, 6), 396 (14), 395 (M⁺-^tBu, 100), 375 (M⁺–Ph, 13), 241 (12), 239 (11), 229 (11), 223 (11), 200 (22), 199 (100), 198 (13), 197 (45); HRMS (FAB⁺): 453.3111 calculated for C₂₉H₄₅O₂Si, found 453.3189.

4.11. ((2S,7S)-7-Hexyloxepan-2-yl)methanol (18)

To a solution of 17 (50 mg, 0.11 mmol) in THF (2 mL) was added TBAF (110 µL of a 1 M solution in THF, 0.11 mmol) and the mixture stirred at room temperature for 4 h. The solvent was evaporated to give a residue, which was chromatographed on silica gel using 1% EtOAc/hexane as eluent, affording alcohol 18 (22 mg, 95%) as a colorless liquid; R_f : 0.36 (20% EtOAc/hexane); $[\alpha]_D^{20} = -2.07$ (c 1, MeOH); IR (film, cm⁻¹): 3448.15, 2927.37, 2858.09, 1457.91, 1106.94, 1002.28; H NMR (CDCl₃, δ): 3.64–3.55 (1H, m, H-2), 3.51–3.40 (3H, m, CH₂-OH, H-7), 2.24-2.17 (1H, s, OH), 1.79-1.38 (12H, m, 2H-1', 2H-2", 2H-3, 2H-4, 2H-5, 2H-6), 1.36-1.22 (6H, m, 2H-3', 2H-4', 2H-5'), 0.87 (3H, t, J=6.59 Hz, 3H-6'); C NMR (CDCl₃, δ): 81.1 (CH-7), 80.3 (CH-2), 66.5 (CH₂-OH), 37.2 (CH₂-6), 36.7 (CH₂-1'), 32.0 (CH₂-3), 31.8 (CH₂-4'), 29.3 (CH₂-3'), 26.3 (CH₂-5), 25.4 (CH₂-2'), 25.1 (CH_2-4) , 22.6 (CH_2-5') , 14.1 (CH_3-6') ; MS (FAB^+) [m/z, (%)]: 215 (M⁺+1, 7), 214 (M⁺, 6), 213 (M⁺-1, 15), 183 (100), 165 (67); HRMS (FAB⁺): 215.1933 calculated for C₁₃H₂₇O₂, found 215.1903.

4.12. (3-((2*S*,7*S*)-7-Hexyloxepan-2-yl)prop-1-ynyl)trimethylsilane (19)

To a solution of alcohol **18** (33 mg, 0.15 mmol) in pyridine (40 μ L) and CH_2Cl_2 (4 mL) at -15 °C was added dropwise Tf_2O (42 μ L). The mixture was stirred for 30 min at $-15\ ^\circ C$, then diluted with CH_2Cl_2 (15 mL), washed with water $(3 \times 10 \text{ mL})$ and brine $(3 \times 10 \text{ mL})$, dried, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 2% EtOAc/hexane as eluent, affording triflate 18' (45 mg, 85%) as a colorless liquid; Rf: 0.42 (20% EtOAc/ hexane); $[\alpha]_D^{20}$ –7.14 (*c* 0.91, MeOH); IR (film, cm⁻¹): 2929.34, 2857.99, 1373.68, 1249.65, 1176.36, 1031.73; H NMR (CDCl₃, δ): 4.39 (1H, dd, J=10.21, 7.79 Hz, CH₂-OTf), 4.34 (dd, J=10.21, 3.79 Hz, CH₂-OTf), 3.86-3.78 (1H, m, H-2), 3.48-3.41 (1H, m, H-7), 1.81–1.60 (4H, m, H-1', H-2', H-3, H-6), 1.58–1.41 (6H, m, H-3, 2H-4, 2H-5, H-6), 1.39–1.21 (8H, m, H-1' H-2', 2H-3', 2H-4', 2H-5'), 0.88 (3H, t, J=6.80 Hz, 3H-6'); C NMR (CDCl₃, δ): 123.4, 120.2 and 117.0 (CF₃), 81.7 (CH-7), 78.5 (CH₂-OTf), 76.8 (CH-2), 36.9 (CH₂-6), 36.6 (CH₂-1'), 31.8 (CH₂-3), 31.4 (CH₂-4'), 29.3 (CH₂-3'), 25.9 (CH₂-5), 24.9 (CH₂-2'), 24.8 (CH₂-4), 22.6 (CH₂-5'), 14.0 (CH₃-6'); MS (FAB⁺) [*m*/*z*, (%)]: 347 (M⁺+1, 52), 346 (M⁺, 19), 345 (M⁺-1, 99), 343 (12), 289 (12), 271 (15), 261 (47), 259 (13), 213 (M⁺-SO₂CF₃, 14), 209 (26), 198 (19), 197 (M⁺-OTf, 100), 195 (25), 193 (19), 183 (20), 179 (16), 177 (18), 169 (36), 165 (15); HRMS (FAB⁺): 347.1406 calculated for C₁₄H₂₆F₃O₄S, found 347.1504.

To a solution of trimethylsilyl acetylene (105 µL, 0.75 mmol) and DMPU (0.5 mL) in THF (1 mL) at 0 °C was added *n*-BuLi (300 µL of a 2.5 M solution in hexanes, 0.75 mmol) and the mixture stirred for 20 min affording a bright yellow solution. Triflate 18' (53 mg, 0.15 mmol) in THF (1 mL) was added via cannula and the mixture stirred at 0 °C for 30 min. After quenching with an aqueous saturated solution of NH₄Cl (10 mL), the product was extracted with EtOAc (3×10 mL). The combined organic phases were dried, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 1% EtOAc/hexane as eluent, affording alkyne 19 (40 mg, 88%) as a colorless liquid; Rf: 0.66 (20% EtOAc/ hexane); $[\alpha]_D^{20}$ +8.16 (c 1, MeOH); IR (film, cm⁻¹): 2927.41, 2857.99, 1457.92, 1106.94, 1002.23; H NMR (CDCl₃, δ): 3.66-3.57 (1H, m, H-2), 3.46-3.37 (1H, m, H-7), 2.47 (1H, dd, J=16.72, 6.58 Hz, H-1"), 2.29 (1H, dd, J=16.72, 7.01 Hz, H-1"), 1.93-1.83 (1H, m, H-6), 1.78-1.42 (9H, m, H-1', H-2', 2H-3, 2H-4, 2H-5, H-6), 1.40-1.20 (8H, m, H-1' H-2', 2H-3', 2H-4', 2H-5'), 0.87 (3H, t, J=6.16 Hz, 3H-6'), 0.14 (9H, s, CH₃-Si); C NMR (CDCl₃, δ): 104.9 (C-3"), 85.3 (C-2"), 80.4 (CH-7), 78.6 (CH-2), 37.2 (CH₂-6), 36.6 (CH₂-1'), 35.5 (CH₂-3), 31.8 (CH2-4'), 29.3 (CH2-3'), 28.0 (CH2-1"), 26.2 (CH2-5), 25.5 (CH2-2'), 24.7 (CH₂-4), 22.7 (CH₂-5'), 14.1 (CH₃-6'), 0.07 (Si-CH₃); MS (FAB⁺) [m/z, (%)]: 295 (M⁺+1, 100), 294 (M⁺, 25), 293 (M⁺-1, 93), 279 (12), 227 (12), 226 (43), 209 (16), 195 (8), 184 (12), 183 (88), 181 (15), 167 (11), 166 (11), 165 (51), 163 (13); HRMS (FAB⁺): 295.2379 calculated for C₁₈H₃₅OSi, found 295.2457.

4.13. (2S,7R)-2-Hexyl-7-propyloxepane (3) [(+)-isolaurepan]

To a solution of **19** (30 mg, 0.1 mmol) in THF (3 mL) was added TBAF (100 µL of a 1 M solution in THF, 0.1 mmol) and the mixture stirred at room temperature for 9 h. The solvent was evaporated to give a residue, which was chromatographed on silica gel using 1% EtOAc/hexane as eluent, affording alkyne 19/(18 mg, 81%) as a colorless liquid; R_f : 0.61 (20% EtOAc/hexane); $[\alpha]_D^{20}$ -3.53 (c 0.71, MeOH); IR (film, cm⁻¹): 3298.14, 2927.41, 2857.99, 1457.82, 1106.95, 1002.23; H NMR (CDCl₃, δ): 3.66–3.57 (1H, m, H-7), 3.47–3.38 (1H, m, H-2), 2.42 (1H, ddd, *J*=16.56, 6.11, 2.04 Hz, H-1"), 2.27 (1H, ddd, J=16.56, 6.65, 1.95 Hz, H-1"), 1.95 (1H, s, H-3"), 1.93-1.83 (1H, m, H-3), 1.76-1.41 (9H, m, H-1', H-2', H-3, 2H-4, 2H-5, 2H-6), 1.39-1.21 (8H, m, H-1' H-2', 2H-3', 2H-4', 2H-5'), 0.87 (3H, t, J=6.16 Hz, 3H-6'); C NMR (CDCl₃, δ): 82.1 (C-2"), 80.5 (CH-2), 78.4 (CH-7), 69.1 (C-3"), 37.2 (CH₂-3), 36.6 (CH₂-1'), 35.4 (CH₂-6), 31.9 (CH₂-4'), 29.3 (CH2-3'), 26.6 (CH2-1"), 26.2 (CH2-4), 25.4 (CH2-2'), 24.7 (CH2-5), 22.6 (CH₂-5'), 14.1 (CH₃-6'); MS (FAB⁺) [*m*/*z*, (%)]: 223 (M⁺+1, 18), 222 (M⁺, 5), 221 (M⁺-1, 18), 219 (18), 207 (7), 191 (5), 183 (7), 176 (6); HRMS (FAB⁺): 222.1984 calculated for C₁₅H₂₇O, found 222.2062.

A suspension of alkyne 19'(18 mg, 81 µmol) and Pd/C (10%) (17 mg, 1.62 µmol) in MeOH (2 mL) was stirred under H₂ atmosphere for 24 h. The catalyst was removed by filtration over Celite[®] and the filtrate was concentrated under vacuum to give a residue, which was chromatographed on silica gel using 1% EtOAc/hexane as eluent, affording oxepane 3 (18 mg, 98%) as a colorless liquid; Rf. 0.64 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +1.72 (c 0.94, CHCl₃); lit.^{7a} $[\alpha]_D^{20}$ +1.5 (c 0.97, CHCl₃); IR (film, cm⁻¹): 2950.43, 2920.25, 2851.33, 1464.99, 1375.89, 1142.79; H NMR (CDCl₃, δ): 3.42–3.32 (2H, m, H2, H-7), 1.75–1.59 (4H, m, H-1', H-2', H-3, H-6), 1.58–1.39 (8H, m, H-1", H-2", H-3, 2H-4, 2H-5, H-6), 1.38-1.21 (10H, m, H-1' H-2', H-1", H-2" 2H-3', 2H-4', 2H-5'), 0.92-0.84 (6H, m, 3H-3", 3H-6'); C NMR (CDCl₃, δ): 80.30 (C-2 or C-7), 80.03 (C-2 or C-7), 39.59 (CH₂-1"), 37.40 (CH2-3), 36.89 (CH2-1'), 36.84 (CH2-6), 31.87 (CH2-4'), 29.30 (CH2-3'), 26.25 (CH2-4), 25.30 (CH2-5), 25.26 (CH2-2'), 22.63 (CH2-5'), 19.45 (CH2-5), 14.08 (CH3-3" or CH3-6'), 14.04 (CH3-3" or CH3-6'); MS (FAB⁺) [*m*/*z*, (%)]: 227 (M⁺+1, 5), 226 (M⁺, 6), 225 (M⁺-1, 7), 183 (26), 179 (10), 167 (13), 166 (11), 165 (29), 163 (12); HRMS (FAB⁺): 226.2297 calculated for C₁₅H₃₀O, found 226.2292.

4.14. (4aR,65,8aS)-6-Allyl-2,2-di-*tert*-butyl-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (20)

To a suspension of methyltriphenylphosphonium bromide (5.08 g, 14.22 mmol) in THF (35 mL) at 0 °C was added n-BuLi (5.68 mL of a 2.5 M solution in hexane, 14.22 mmol) and stirring was continued for 20 min whereupon the color of the mixture turned to orange. A solution of aldehvde 6 (3.17 g. 10.16 mmol) in THF (35 mL) was added via cannula and the mixture stirred for 25 min. Then the reaction was guenched with an aqueous saturated solution of NH₄Cl (20 mL) and the product extracted with EtOAc (3×50 mL). The combined organic phases were dried, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 2% EtOAc/hexane as eluent, affording diene 20 (2.62 g, 83%) as a white solid; mp=61 °C, R_f : 0.69 (20% EtOAc/hexane); $[\alpha]_{D}^{22}$ +6.66 (*c* 1.25, CHCl₃); IR (NaCl, cm⁻¹): 2938.98, 2865.79, 1735.62, 1643.02, 1473.35, 1126.22, 1095.37; H NMR (CDCl₃, δ): 5.85 (1H, m, H-8), 5.78 (1H, m, H-2'), 5.64 (1H, m, H-7), 5.09 (1H, m, H-3'), 4.38 (1H, m, H-8a), 4.26 (1H, m, H-6), 4.17 (1H, dd, J=9.9, 5.0 Hz, H-4), 3.87 (1H, t, *J*=10.2 Hz, H-4), 3.50 (1H, ddd, *J*=10.5, 8.5, 5.1 Hz, H-4a), 2.28 (1H, m, H-1'), 1.05 (9H, s, CH₃-^{*t*}Bu), 0.99 (9H, s, CH₃-^{*t*}Bu); C NMR (CDCl₃, δ): 133.7 (CH-2'), 130.0 (CH-8), 129.1 (CH-7), 117.4 (CH2-3'), 74.9 (CH-6), 74.7 (CH-4a), 70.3 (CH-8a), 67.2 (CH2-4), 39.6 (CH₂-1'), 27.5 (CH₃-^tBu), 27.1 (CH₃-^tBu), 22.6 (C-^tBu), 20.0 (C^{-*t*}Bu); MS (FAB⁺) [*m*/*z*, (%)]: 311 (M⁺+1, 18), 310 (M⁺, 29), 310 (M⁺-1, 11), 253 (M⁺-^tBu, 100), 269 (M⁺-CH₂CHCH₂, 31), 196 (19), 170 (33); HRMS (FAB⁺): 310.2004 calculated for C₁₇H₃₀O₃Si, found 310.2014.

4.15. (4aR,6S,8aS)-2,2-Di-*tert*-butyl-6-propylhexahydropyrano [3,2-d][1,3,2]dioxasiline (21)

A suspension of 20 (2.5 g, 8.06 mmol) and Pd/C (10%) (241 mg) in MeOH (35 mL) was stirred under H₂ atmosphere for 10 h. The mixture was filtered through Celite[®] and the filtered solution was concentrated under vacuum to give pure 21 (2.45 g, 97%) as a white solid; mp=64 °C, Rf: 0.7 (20% EtOAc/hexane); IR (NaCl, cm⁻¹): 2954.63, 2865.35, 2935.18, 1469.02, 1125.99, 1047.33; $[\alpha]_{D}^{22}$ -42.21 (*c* 1.18, CHCl₃); H NMR (CDCl₃, δ): 4.07 (1H, dd, *J*=10.08, 4.86 Hz, H-4), 3.81 (1H, t, *J*=10.22 Hz, H-4), 3.73–3.68 (1H, m, H-6), 3.39–3.23 (2H, m, H-4a,H-8a), 2.13-2.07 (1H, m, H-8), 1.76-1.68 (1H, m, H-7), 1.53–1.23 (6H, m, H-7, H-8, 2H-1', 2H-2'), 1.03 (9H, s, CH₃–^tBu), 0.98 (9H, s, CH₃-^{*t*}Bu), 0.89 (3H, s, *J*=6.91 Hz, 3H-3'); C NMR (CDCl₃, δ): 77.5 (CH-4a or CH-8a), 77.5 (CH-4a or CH-8a), 74.1 (CH-6), 67.2 (CH₂-4), 37.8 (CH₂-1'), 32.6 (CH₂-8), 30.9 (CH₂-7), 27.4 (CH₃-^tBu), 27.1 (CH₃-^tBu), 22.6 (C-^tBu), 19.9 (C-^tBu), 18.9 (CH₂-2'), 14.1 (CH₃-3'); MS (FAB⁺) [*m*/*z*, (%)]: 315 (M⁺+1, 31), 314 (M⁺, 24), 313 (M⁺-1, 46), 257 (M⁺-^tBu, 100), 184 (16), 171 (14); HRMS (FAB⁺): 315.2277 calculated for C₁₇H₃₅O₃Si, found 315.2269.

4.16. (2*R*,3*S*,6*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-6propyltetrahydro-2*H*-pyran-3-ol (22)

To a solution of **21** (1.8 g, 5.73 mmol) in THF (30 mL) was added TBAF (17.2 mL of a 1 M solution in THF, 17.2 mmol) and the mixture was stirred at room temperature for 20 h. The solvent was evaporated to afford a residue, which was chromatographed on silica gel using 50% EtOAc/hexane as eluent, affording diol **21**′ (0.98 g, 99%) as a white solid; mp=64 °C, *Rf*. 0.4 (50% EtOAc/hexane); IR (NaCl, cm⁻¹): 3305.56, 2927.32, 2853.99, 1060.64, 772.26; $[\alpha]_D^{23}$ –11.25 (*c* 1, CHCl₃); H NMR (CDCl₃, δ): 3.82 (1H, dd, *J*=11.41, 4.09 Hz, *CH*₂OH), 3.75 (1H, dd, *J*=11.43, 4.99 Hz, *CH*₂OH), 3.52 (1H, m, H-3), 3.32 (1H, m, H-6), 3.16 (1H, td, *J*=9.12, 4.53, 4.52 Hz, H-2), 2.59 (2H, s, 2OH), 2.08 (1H, m, H-4), 1.70 (1H, m, H-5), 1.54–1.23 (6H, m, H-4, H-5, 2H-1′, 2H-2′), 0.89 (3H, t, *J*=6.98 Hz, 3H-3′); C NMR (CDCl₃, δ): 81.1 (CH-2), 77.3 (CH-6), 67.7 (CH-3), 63.4 (CH₂–OH), 37.8 (CH₂–1′), 32.5

(CH₂-4), 30.8 (CH₂-5), 18.9 (CH₂-2'), 14.1 (CH₃-3'); MS (FAB⁺) [m/z, (%)]: 175 (M⁺+1, 28), 174 (M⁺, 18), 173 (M⁺-1, 49), 162 (12), 157 (M⁺-OH, 61); HRMS (FAB⁺): 174.1256 calculated for C₉H₁₈O₃, found 174.1251.

To a solution of 21' (0.98 g, 5.6 mmol) in DMF (25 mL) were added imidazole (0.45 g, 6.72 mmol), TBDPSCl (1.75 mL, 6.72 mmol), and a catalytic amount of DMAP. The mixture was stirred at room temperature for 30 min and diluted with EtOAc (40 mL). The resulting organic phase was washed with water (3×15 mL) and brine (3×15 mL), filtered, and evaporated to give a residue, which was chromatographed on silica gel using 5% EtOAc/hexane as eluent, affording alcohol 22 (2.28 g, 98%) as a colorless liquid; R_f : 0.5 (30% EtOAc/hexane); IR (NaCl, cm⁻¹): 3423.63, 2931.02, 2857.35, 1461.79, 1106.89, 701.91; $[\alpha]_D^{24}$ +28.92 (*c* 1.66, CHCl₃); H NMR (CDCl₃, δ): 7.76–7.69 (4H, m, H₀–Ph), 7.49–7.37 (6H, m, H_{n.m}–Ph), 3.92 (1H, dd, J=10.09, 4.67 Hz, CH₂-OTBDPS), 3.79 (1H, dd, J=10.06, 7.70 Hz, CH₂-OTBDPS), 3.70-3.58 (2H, m, H-3, OH), 3.36-3.24 (2H, m, H-2, H-6), 2.17-2.09 (1H, m, H-4), 1.75-1.66 (1H, m, H-5), 1.56-1.23 (6H, m, H-4, H-5, 2H-1', 2H-2'), 1.08 (9H, s, CH₃-^tBu), 0.88 (3H, t, J=6.79 Hz, 3H-3'); C NMR (CDCl₃, δ): 135.66 and 135.62 (CH₀-Ph), 132.7 and 132.6 (C-Ph), 129.9 and 129.6 (CHp-Ph), 127.8 and 127.7 (CHm-Ph), 79.2 (CH-2), 77.0 (CH-6), 70.9 (CH-3), 67.3 (CH₂-OTBDPS), 37.9 (CH₂-1'), 31.8 (CH₂-4), 30.4 (CH₂-5), 26.8 (CH₃- ${}^{t}Bu$), 26.6 (CH₃- ${}^{t}Bu$), 19.1 (C-^{*t*}Bu), 18.8 (CH₂-2'), 14.1 (CH₃-3'); MS (FAB⁺) [*m*/*z*, (%)]: 412 (M⁺, 16), 411 (M^+ -1, 18), 355 (M^+ - ${}^{t}Bu$, 52), 324 (18), 289 (19), 252 (21), 251 (18), 197 (15), 181 (14); HRMS (FAB⁺): 412.2434 calculated for C₂₅H₃₆O₃Si, found 412.2433.

4.17. (2*R*,6*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-6propyldihydro-2*H*-pyran-3(4*H*)-one (23)

To a solution of alcohol 22 (2.2 g, 5.33 mmol) in CH₂Cl₂ (40 mL) were added 4 Å molecular sieves (1 g), NMO (1.87 g, 16.01 mmol), and a catalytic amount of TPAP. The resulting greenish solution was stirred at room temperature for 18 h. The solvent was evaporated to afford a residue, which was chromatographed on silica gel using 5% EtOAc/hexane as eluent, affording ketone 23 (1.8 g, 82%) as a colorless liquid; Rf: 0.71 (30% EtOAc/hexane); IR (NaCl, cm⁻¹): 2930.17, 2861.02, 1729.76, 1280.64, 1114.79; [α]_D²³ -8.95 (*c* 1.12, CHCl₃); H NMR (CDCl₃, δ): 7.75 (4H, m, H₀-Ph), 7.41 (6H, m, H_{p.m}-Ph), 4.01 (3H, m, H-6, CH₂-OTBDPS), 3.69 (1H, ddd, J=11.28, 7.73, 3.97 Hz, H-2), 2.63 (1H, m, H-4), 2.44 (1H, m, H-4), 2.03 (1H, m, H-5), 1.94 (1H, m, H-5), 1.68 (2H, m, 2H-1'), 1.61-1.42 (2H, m, 2H-2'), 1.05 (9H, s, CH₃-^{*t*}Bu), 0.99 (3H, t, *J*=7.11 Hz, 3H-3'); C NMR (CDCl₃, δ): 209.8 (C=O), 135.8 and 135.7 (CH₀-Ph), 133.6 and 133.5 (C-Ph), 129.65 and 129.61 (CHp-Ph), 127.7 and 127.6 (CHm-Ph), 83.1 (CH-6), 75.2 (CH-2), 63.7 (CH₂-OTBDPS), 38.1 (CH₂-4), 37.5 (CH₂-1'), 30.4 (CH₂-5), 26.7 (CH₃-^tBu), 26.6 (CH₃-^tBu), 19.3 (C-^tBu), 18.9 (CH₂-2'), 14.1 (CH_3-3') ; MS (FAB^+) [m/z, (%)]: 411 $(M^++1, 9)$, 410 $(M^+, 14)$, 353 $(M^+-{}^tBu, 39), 322 (21), 287 (18), 225 (28), 224 (17), 195 (13), 181$ (19), 169 (21), 165 (31), 164 (19); HRMS (FAB⁺): 411.2277 calculated for C₂₅H₃₅O₃Si, found 411.2262.

4.18. (2*R*,7*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-7propyloxepan-3-one (8) and (2*S*,7*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)-7-propyloxepan-4-one (8')

To a solution of ketone **23** (0.71 g, 1.74 mmol) in CH₂Cl₂ (15 mL) at -78 °C were added BF₃·OEt₂ (0.26 mL, 2.09 mmol) and TMSCHN₂ (0.91 mL of a 2 M solution in hexane, 1.82 mmol). An aqueous saturated solution of NaHCO₃ (15 mL) was added and the mixture was stirred at -78 °C for 30 min. The organic phase was separated and the aqueous phase extracted with EtOAc (3×15 mL). The combined organic phases were washed with water (3×30 mL), brine (3×30 mL), dried, filtered, and evaporated to give a residue,

which was dissolved in MeOH (15 mL). PPTS (0.65 g, 2.61 mmol) was added and the mixture stirred at room temperature for 1 h. The product was extracted with EtOAc (3×15 mL) and the combined organic phases were washed with an aqueous saturated solution of NaHCO₃ (3×50 mL) and brine (3×50 mL). Drying, filtration, and solvent evaporation afforded a residue, which was chromatographed on silica gel using 1% EtOAc/hexane as eluent, affording ketone **8** (0.49 g, 66%) along with its isomeric ketone **8**' (51 mg, 7%).

4.18.1. Compound 8. Colorless liquid; Rf: 0.52 (20% EtOAc/hexane); IR (NaCl, cm⁻¹): 2931.29, 2857.09, 1715.14, 1110.64, 700.99; $[\alpha]_D^{27}$ +21.25 (*c* 1.07, CHCl₃); H NMR (CDCl₃, δ): 7.76 (2H, m, H₀-Ph), 7.68 (2H, m, H_{p,m}-Ph), 7.40 (6H, m, Ph-H_{p,m}), 3.96 (1H, dd, J=10.70, 4.51 Hz, CH₂-OTBDPS), 3.89 (1H, dd, J=10.68, 2.72 Hz, CH2-OTBDPS), 3.79 (1H, dd, J=4.47, 2.75 Hz, H-2), 3.27-3.19 (1H, m, H-7), 3.04 (1H, m, H-4), 2.44 (1H, dd, *J*=11.35, 6.66 Hz, H-4), 1.98 (1H, m, H-5), 1.82 (1H, m, H-1'), 1.65 (2H, m, H-1', H-5), 1.58–1.27 (4H, m, 2H-2', 2H-6), 1.03 (9H, s, CH₃–^tBu), 0.91 (3H, t, *J*=7.19 Hz, 3H-3'); C NMR (CDCl₃, δ): 216.6 (C=O), 135.8 and 135.6 (CH_o-Ph), 133.3 and 133.2 (C-Ph), 129.6 and 129.6 (CH_p-Ph), 127.6 and 127.5 (CH_m-Ph), 87.6 (CH-2), 83.4 (CH-7), 66.2 (CH₂-OTBDPS), 43.2 (CH₂-4), 39.4 (CH₂-6), 36.4 (CH₂-1'), 26.7 (CH₃-^tBu), 23.7 (CH₂-5), 19.2 (C^{-t}Bu), 18.8 (CH₂-2'), 14.1 (CH₃-3'); MS (FAB⁺) [m/z, (%)]: 425 (M⁺+1, 7), 424 (M⁺, 12), 423 (M⁺-1, 8), 406 (22), 382 (M⁺-^tBu, 100), 347 (M⁺-Ph, 31), 199 (62), 185 (M⁺-TBDPS, 11); HRMS (FAB⁺): 424.2434 calculated for C₂₆H₃₆O₃Si, found 424.2433.

4.18.2. Compound $\mathbf{8}'$. Colorless liquid: R_f : 0.43 (20% EtOAc/hexane): IR (NaCl, cm⁻¹): 2931.32, 2856.98, 1716.25, 1109.85, 701.87; $[\alpha]_D^{27}$ -2.32 (c 0.85, CHCl₃); H NMR (CDCl₃, δ): 7.62 (4H, m, H₀-Ph), 7.41 (6H, m, H_{n,m}-Ph), 3.86 (1H, m, H-2), 3.73 (1H, dd, J=10.29, 6.02 Hz, CH₂-OTBDPS), 3.51 (1H, dd, J=10.25, 5.96 Hz, CH₂-OTBDPS), 3.47 (1H, m, H-7), 2.74 (2H, m, H-3, H-5), 2.55 (2H, m, H-3, H-5), 2.01 (1H, m, H-6), 1.85 (1H, m, H-6), 1.73–1.23 (4H, m, 2H-1', 2H-2'), 1.06 (9H, s, $CH_3 - {}^tBu$), 0.88 (3H, t, J=7.09 Hz, 3H-3'); C NMR (CDCl₃, δ): 211.7 (C=O), 135.6 and 135.5 (CH₀-Ph), 133.4 (C-Ph), 129.77 and 129.73 (CH_n-Ph), 127.8 and 127.7 (CH_m-Ph), 83.1 (CH-7), 76.9 (CH-2), 66.6 (CH2-OTBDPS), 48.6 (CH2-3), 42.2 (CH2-5), 38.7 (CH2-1'), 32.4 (CH₂-6), 26.8 (CH₃-^tBu), 20.2 (C-^tBu), 19.1 (CH₂-2'), 14.0 (CH₃-3'); MS (FAB⁺) [m/z, (%)]: 425 (M⁺+1, 11), 424 (M⁺, 14), 423 (M⁺-1, 9), 406 (25), 382 (M⁺-^tBu, 100), 348 (32), 347 (M⁺-Ph, 28), 201 (15), 199 (26), 197 (12); HRMS (FAB⁺): 424.2433 calculated for C₂₆H₃₆O₃Si, found 424.2429.

4.19. *tert*-Butyldiphenyl(((2*S*,7*S*)-7-propyloxepan-2-yl)methoxy)silane (24)

To a solution of ketone 8 (0.52 g, 1.22 mmol) in MeOH (15 mL) were added NH₂NHTs (0.27 g, 1.47 mmol), PTSA (14 mg, 0.073 mmol), and 4 Å molecular sieves (300 mg). The mixture was stirred at 70 °C for 12 h. The organic solvent was removed under vacuum and the residue was dissolved in CH₂Cl₂, washed with water (3×15 mL) and brine (3×15 mL), dried, filtered, and evaporated under reduced pressure. The residue obtained was diluted in DMF (12 mL) whereupon NaBH₃CN (0.25 g, 4.04 mmol) and PTSA (38 mg, 0.2 mmol) were added and the mixture was stirred at 130 °C for 6 h. The mixture was allowed to reach room temperature. EtOAc (20 mL) was added and the organic phase washed with water (3×20 mL) and brine (20 mL), dried, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 3% EtOAc/hexane as eluent, affording oxepane 24 (0.27 g, 55%) as a gray liquid; R_f : 0.63 (20% EtOAc/hexane); IR (NaCl, cm⁻¹): 2927.25, 2857.98, 1457.69, 1107.01, 1002.24; $[\alpha]_D^{26}$ –13.40 (c 1, $CHCl_3$); H NMR (CDCl₃, δ): 7.83–7.76 (4H, m, H_o–Ph), 7.44–7.34 (6H, m, H_{p,m}–Ph), 3.69 (1H, dd, J=9.36, 6.31 Hz, CH2-OTBDPS), 3.63-3.56 (1H, m, H-

7), 3.47 (1H, dd, J=9.96, 5.67 Hz, $CH_2-OTBDPS$), 3.44–3.39 (1H, m, H-2), 1.82–1.41 (9H, m, 2H-1', 2H-3, 2H-4, H-5, 2H-6), 1.39–1.20 (3H, m, 2H-2', H-5), 1.06 (9H, s, $CH_3-{}^{t}Bu$), 0.88 (3H, t, J=7.11 Hz, 3H-3'); C NMR (CDCl₃, δ): 135.6 (CH_o-Ph), 133.8 (C–Ph), 129.5 (CH_p-Ph), 127.55 and 127.52 (CH_m-Ph), 80.5 (CH-7), 80.2 (CH-2), 67.2 ($CH_2-OTBDPS$), 39.4 (CH_2-1'), 36.8 (CH_2-6), 32.4 (CH_2-3), 26.8 ($CH_3-{}^{t}Bu$), 25.5 (CH_2-5), 24.8 (CH_2-4), 19.3 (CH_2-2'), 19.2 ($C-{}^{t}Bu$), 14.1 (CH_3-3'); MS (FAB⁺) [m/z, (%)]: 410 (M⁺, 9), 409 (M⁺-1, 7), 354 (18), 353 (M⁺- ${}^{t}Bu$, 100), 333 (M⁺-Ph, 17), 199 (15), 197 (12), 187 (10), 181 (14), 161 (19); HRMS (FAB⁺): 410.2631 calculated for C₂₆H₃₈O₂Si, found 410.2629.

4.20. ((2S,7S)-7-Propyloxepan-2-yl)methanol (25)

To a solution of **24** (0.23 g, 0.56 mmol) in THF (10 mL) was added TBAF (0.84 mL of a 1 M solution in THF, 0.84 mmol) and the mixture stirred at room temperature for 12 h. The solvent was evaporated to give a residue, which was chromatographed on silica gel using 10% EtOAc/hexane as eluent, affording alcohol **25** (92 mg, 96%) as a colorless liquid; R_f : 0.31 (20% EtOAc/hexane); IR (NaCl, cm⁻¹): 3449.46, 2927.68, 2857.36, 1457.81, 1106.90, 1001.36; $[\alpha]_D^{26} - 8.33$ (c 0.92, CHCl₃); H NMR (CDCl₃, δ): 3.64 (1H, m, H-2), 3.48 (3H, m, H-2, CH₂-OH), 1.85–1.20 (12H, m, 2H-1', 2H-2', 2H-3, 2H-4, 2H-5, 2H-6), 0.92 (3H, t, *J*=7.10 Hz, 3H-3'); C NMR (CDCl₃, δ): 80.7 (CH-7), 80.3 (CH-2), 66.4 (CH₂-OH), 39.3 (CH₂-6), 36.6 (CH₂-1'), 31.9 (CH₂-3), 25.3 (CH₂-5), 25.0 (CH₂-4), 19.5 (CH₂-2'), 14.0 (CH₃-3'); MS (ESI) [*m*/*z*, (%)]: 173 (M⁺+1, 25), 172 (M⁺, 19), 171 (M⁺-1, 132), 155 (M⁺-OH, 33), 154 (12); HRMS (ESI): 173.1473 calculated for C₁₀H₂₁O₂, found 173.1469.

4.21. (25,75)-2-(Hex-1-enyl)-7-propyloxepane (26)

To a solution of $(COCl)_2$ (260 µL, 0.52 mmol) in CH₂Cl₂ (1 mL) at 0 °C was added DMSO (48 µL, 0.68 mmol) and the stirring was continued for 30 min. Then, a solution of alcohol **25** (30 mg, 0.17 mmol) in CH₂Cl₂ (1 mL) was added and the mixture stirred for 1 h. After that NEt₃ (119 µL, 0.85 mmol) was added and the resulted mixture was stirred for 2 h till room temperature. Then, was added CH₂Cl₂ (5 mL) and the organic layer was washed with H₂O (2×10 mL) and a saturated solution of brine (10 mL). The organic phase was dried over Na₂SO₄ and the solvent evaporated under reduced pressure.

To a suspension of triphenylpentylphosphonium iodine (114 mg, 0.25 mmol) in THF (1 mL) at 0 $^\circ\text{C}$ was added <code>n-BuLi</code> (100 μL of a 2.5 M solution in hexane, 0.25 mmol) and stirring was continued for 20 min whereupon the color of the mixture turned to orange. A solution of the residue obtained previously in Swern's reaction in THF (1 mL) was added via cannula and the mixture stirred for 30 min then guenched with an aqueous saturated solution of NH₄Cl (4 mL) and the product extracted with EtOAc (3×4 mL). The combined organic phases were dried, filtered, and evaporated to give a residue, which was chromatographed on silica gel using 2% EtOAc/hexane as eluent, affording compound 26 (25 mg, 64%) as a colorless liquid; R_f : 0.8 (20% EtOAc/hexane); IR (NaCl, cm⁻¹): 2927.36, 2857.98, 1659.36, 1459.87, 1106.08; $[\alpha]_D^{23}$ -4.82 (c 0.78, CHCl₃); H NMR (CDCl₃, δ): 5.45 (1H, m, H-1'), 5.38 (1H, m, H-2'), 4.23 (1H, m, H-2), 3.47 (1H, m, H-7), 2.14-1.97 (2H, m, H-3"), 1.80-1.21 (16H, m, 2H-3, 2H-4, 2H-5, 2H-6, 2H-1', 2H-2', 2H-4", 2H-5"), 0.95–0.86 (6H, m, 3H-3', 3H-6"); C NMR (CDCl₃, δ): 132.1 (CH-2"), 130.3 (CH-1"), 79.5 (CH-2), 75.9 (CH-7), 39.4 (CH₂-1'), 37.1 (CH2-6), 36.6 (CH2-3), 31.8 (CH2-3"), 27.6 (CH2-4"), 25.7 (CH2-5), 25.0 (CH2-4), 22.3 (CH2-5"), 19.4 (CH2-2'), 14.1 (CH3-3' or CH3-6"), 13.1 (CH₃-3' or CH₃-6"); MS (ESI) [m/z, (%)]: 224 (M⁺, 28), 223 (M⁺-1, 11), 167 (21), 166 (19); HRMS (ESI): 224.2140 calculated for C₁₅H₂₈O, found 224.2138.

4.22. (2R,7S)-2-Hexyl-7-propyloxepane (4) [(-)-isolaurepan]

A suspension of alkene 26 (25 mg, 0.11 mmol) and Pd/C (10%) (4 mg) in MeOH (2 mL) was stirred under H₂ atmosphere for 12 h. The catalyst was removed by filtration over Celite[®] and the filtrate concentrated under vacuum to give (-)-isolaurepan (24 mg, 96%) as a colorless liquid; Rf: 0.64 (20% EtOAc/hexane); IR (NaCl. cm⁻¹ 1): 2950.40, 2920.20, 2850.98, 1464.28, 1375.88, 1142.82; $[\alpha]_D^{25} - 1.86$ (c 0.94, CHCl₃); H NMR (CDCl₃, δ): 3.36 (2H, m, H2, H-6), 1.75–1.61 (4H, m, H-1', H-2', H-3, H-6), 1.59-1.40 (8H, m, H-1", H-2", H-3, 2H-4, 2H-5, H-6), 1.39-1.19 (10H, m, H-1' H-2', H-1", H-2" 2H-3', 2H-4", 2H-5"), 0.92–0.85 (6H, m, 3H3', 3H-6"); C NMR (CDCl₃, δ): 80.3 (CH-2 or CH-7), 80.1 (CH-2 or CH-7), 39.6 (CH2-1'), 37.4 (CH2-3), 36.9 (CH₂-1"), 36.8 (CH₂-6), 31.9 (CH₂-4'), 29.3 (CH₂-3"), 26.2 (CH₂-4), 25.3 (CH₂-5), 25.3 (CH₂-2"), 22.6 (CH₂-5'), 19.1 (CH₂-2'), 14.0 (CH₃-3' or CH₃-6"), 13.1 (CH₃-3' or CH₃-6"); MS (ESI) [*m*/*z*, (%)]: 227 (M⁺+1, 8), 226 (M⁺, 11), 225 (M⁺-1, 10), 183 (31), 167 (17); HRMS (ESI): 226.2297 calculated for C₁₅H₃₀O, found 226.2294.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.08.094.

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