Enantioselective Total Synthesis of (+)- and (–)-Vittatalactone

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Abstract: The asymmetric total synthesis of both enantiomers of (+)- and (–)-vittatalactone has been achieved using a desymmetrization strategy to create three methyl chiral centers. The key steps in these total syntheses are Myers asymmetric alkylation, copper-catalyzed alkylation, 2,2,6,6-tetramethyl-1-piperidinyloxyl–(diacetoxyiodo)benzene [TEMPO–PhI(OAc_2)] promoted oxidation and *p*-toluenesulfonyl chloride mediated lactonization. The products are obtained in good overall yields employing linear synthetic sequences.

Key words: vittatalactone, desymmetrization, Myers asymmetric alkylation, copper-catalyzed alkylation, lactonization

Polydeoxypropionates are an important class of biologically active molecules and the development of methods for their synthesis has led to the discovery of new strategies. The use and application of pheromones is expected to grow more rapidly and widely in the coming years because of increasing concerns of consumers about residual chemicals from agricultural products. The chemical syntheses of such compounds will ensure ample supplies and facilitate their practical use in agriculture and forestry. Vittatalactone, a structurally unique pheromone, was isolated from the striped cucumber beetle, *Acalymma vittatum* by Francke[1] and coworkers in 2005. It contains a novel *trans*-configured β-lactone moiety and an all *syn*-configured tetramethyl substituted alkyl chain as structural features. Breit et al.[2] have assigned the relative and absolute configurations of natural (+)-**1a** and unnatural (–)-**1b**[3] vittatalactones through total synthesis.

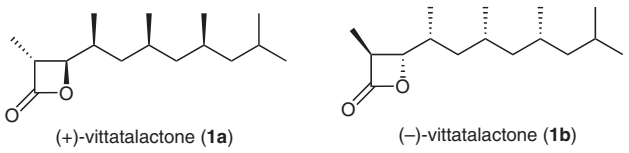

Figure 1 Structures of (+)- and (–)-vittatalactone

In continuation of our research on synthetic pheromones,[4,5] and our ongoing studies on the synthesis of biologically active molecules by exploiting desymmetrization strategies, the interesting structural features and biological activity of vittatalactone have attracted our attention toward its synthesis. Two total syntheses of vittatalactone have been reported: as key steps, the method of Breit and coworkers involved an *o*-diphenylphosphinobenzoic acid (*o*-DPPB) directed allylic substitution,[2] whilst that of Schneider et al. utilized an iridium-catalyzed hydrogenation.[6] Our group previously accomplished the total synthesis of (+)-vittatalactone by using an enzymatic desymmetrization approach.[7] We herein report the total synthesis of both enantiomers of vittatalactone, (+)-**1a** and (–)-**1b**, by exploiting our previously developed desymmetrization strategy.

Our retrosynthetic strategy is shown in Scheme 1 in which both enantiomers could be easily obtained from the common intermediate **5** by utilizing the appropriate chiral boron reagent.

The synthesis of (+)-vittatalactone started from the known triol **3a**[8] which was readily obtained from **5** using a desymmetrization approach. Protection of the 1,3-diol moiety was accomplished using 2,2-dimethoxypropane [$Me_2C(OMe)_2$][9] and a catalytic amount of *p*-toluenesulfonic acid in dichloromethane at 0 °C to afford **6a** in 85% yield. The primary hydroxy group in **6a** was converted into the corresponding iodide to give **7a**[10] in 94% yield using triphenylphosphine, imidazole and iodine in toluene at room temperature. Next, iodide **7a** was treated with the enolate derived from the *N*-propionyl-(*S*,*S*)-pseudoephedrine, according to the protocol described by Myers,[11] to give compound **2a** in a good 82% yield as a single diastereomer. Reductive cleavage of the chiral auxiliary using lithium amidotrihydroborate (LAB), prepared in situ from lithium diisopropylamide and borane monoammoniate ($BH_3{\cdot}NH_3$), furnished alcohol **8a** in 92% yield. The hydroxy group in **8a** was converted into the corresponding iodide as described above, and then treated with isopropylmagnesium chloride[12] in the presence of copper(I) cyanide to give the desired intermediate **9a** (Scheme 2).

Debenzylation of compound **9a** was achieved by using palladium hydroxide[13] to afford the secondary alcohol **10a** in 92% yield. This was converted into the corresponding xanthate[14] **11a** using lithium hexamethyldisilazide, carbon disulfide and methyl iodide in THF (86%) and then subjected to Barton–McCombie conditions[15] [tributylstannane (Bu_3SnH), catalytic 2,2′-azobis(isobutyronitrile)] to afford the deoxygenated product **12a** in 89% yield. Acetonide deprotection[16] of **12a** was carried out under acidic conditions to give the required diol **13a** in 86% yield. The 1,3-diol functionality of **13a** was selectively oxidized using 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and (diacetoxyiodo)benzene [$PhI(OAc)_2$][17] in

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acetonitrile–water to give the corresponding β-hydroxy acid which was used directly in the next step without purification. Lactonization[2] of the β-hydroxy acid was carried out with *p*-toluenesulfonyl chloride in pyridine to afford (+)-vittatalactone (**1a**) in 61% yield over the two steps. The ^{1}H and ^{13}C NMR spectra and optical rotation ($[\alpha]_D^{25}$ +3.0) were in good agreement with the literature.

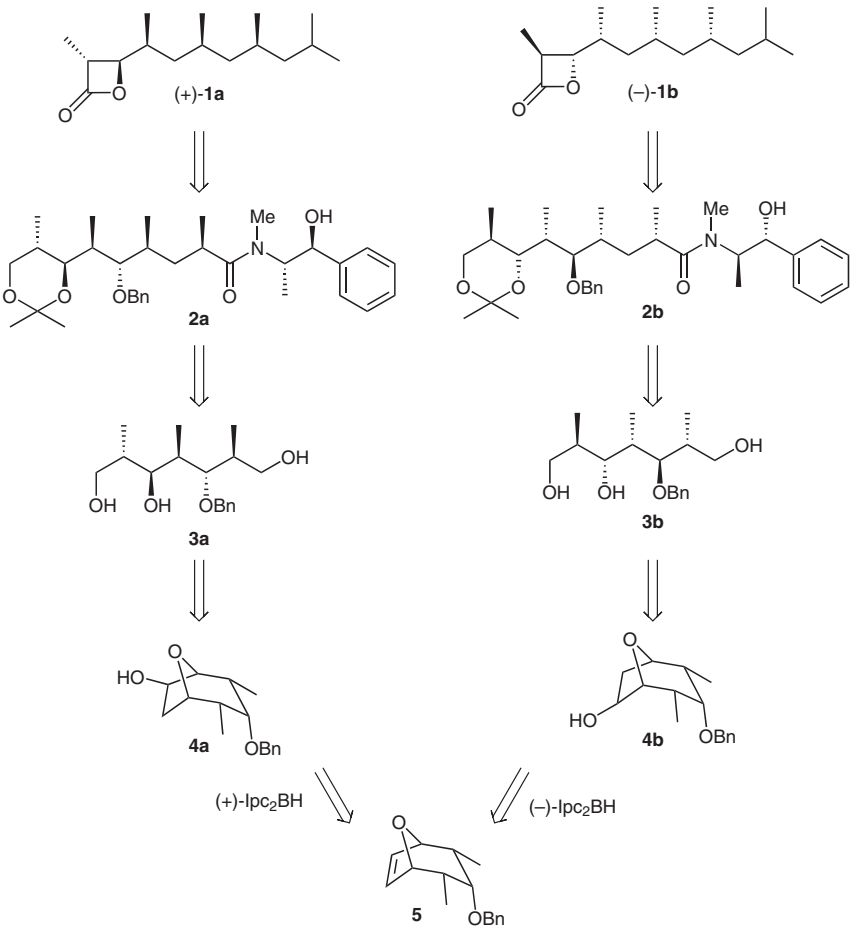
Similarly, the enantiomer (–)-**1b** was prepared from known triol **3b** as depicted in Scheme 3, by following the same series of reactions as described for the synthesis of (+)-vittatalactone (**1a**). Unnatural (–)-vittatalactone (**1b**) was obtained in good yield and the optical rotation ($[\alpha]_D^{25}$ –2.5) was in agreement with that reported.

In conclusion, we have demonstrated the application of our previously developed desymmetrization strategy for the synthesis of both enantiomers of vittatalactone. The approach adopted here demonstrates a synthetic application for the construction of polyketide motifs. The key steps in the synthesis are Myers asymmetric alkylation, copper-catalyzed alkylation, selective oxidation and *p*-toluenesulfonyl chloride mediated lactonization which were utilized successfully to complete the total synthesis of (+)- and (–)-vittatalactone in linear synthetic sequences with overall yields of 18.4% and 18.1%, respectively.

Unless otherwise mentioned, all the reactions were carried out under an inert atmosphere of Ar or N_2 using standard syringe, septa and cannula techniques. Commercial reagents were used without further purification. All solvents were purified by standard techniques. Optical rotations were obtained with a Jasco DIP-360 digital polarimeter. Infrared (IR) spectra were recorded with a Perkin-Elmer 683 spectrometer with NaCl optics. Samples were scanned neat, as KBr discs or in $CHCl_3$ as thin films. NMR spectra were recorded in $CDCl_3$ using Bruker 300 or Varian Unity 500 NMR spectrometers. Column chromatographic separations were carried out on silica gel (ACME, 60–120 mesh). Mass spectra were obtained on Finnigan MAT1020B or Micromass VG 70-70H spectrometers operating at 70 eV using a direct inlet system. Analytical data for the compounds shown in Scheme 2 are provided below. The optical rotations for the series of compounds listed in Scheme 3 are included for comparison. Melting points were determined using a Barnstead electrothermal melting point apparatus and are uncorrected.

(2*S*,3*S*,4*S*)-3-(Benzyloxy)-2-methyl-4-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]pentan-1-ol (6a)

To a stirred soln of triol **3a** (4.0 g, 13.51 mmol) in anhyd CH_2Cl_2 were added 2,2-dimethoxypropane [$Me_2C(OMe)_2$] (2.5 mL, 20.26 mmol) and recrystallized PTSA (cat.) at 0 °C. The mixture was stirred at r.t. for 5 h. After complete consumption of the starting material (as monitored by TLC), the mixture was quenched with sat. aq $NaHCO_3$ soln. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was dried over anhyd Na_2SO_4, evaporated and the residue purified by silica gel column chromatography (10% EtOAc–hexane) to afford the protected triol **6a** (3.9 g, 85%) as a white crystalline solid.



Scheme 1 Retrosynthesis of (+)- and (–)-vittatalactone

6a: $[\alpha]_D^{25}$ +28.2 (*c* 2, $CHCl_3$); mp 96–97 °C. **6b**: $[\alpha]_D^{25}$ –32.5 (*c* 1, $CHCl_3$); mp 96–97 °C.

IR (KBr): 3483, 2926, 2878, 1460, 1381, 1064, 755, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.73 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 1.20 (d, *J* = 7.1 Hz, 3 H), 1.34 (s, 6 H), 1.79–2.05 (m, 3 H), 2.60 (s, 1 H), 3.41–3.50 (m, 2 H), 3.53 (dd, *J* = 7.1, 11.1 Hz, 1 H), 3.65 (dd, *J* = 6.2, 11.3 Hz, 1 H), 3.86 (d, *J* = 10.5 Hz, 2 H), 4.64 (q, *J* = 14.9 Hz, 2 H), 7.23–7.35 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8, 12.4, 16.3, 19.4, 29.7, 30.2, 36.0, 37.4, 64.2, 66.1, 73.3, 75.4, 85.5, 97.9, 126.9, 127.5, 128.4, 138.3.

MS (ESI): *m*/*z* = 337 $[M + H]^+$.

HRMS (ESI-MS): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{32}O_4Na$: 359.2198; found: 359.2201.

(4*S*,5*S*)-4-[(2*S*,3*R*,4*R*)-3-(Benzyloxy)-5-iodo-4-methylpentan-2-yl]-2,2,5-trimethyl-1,3-dioxane (7a)

To a stirred soln of alcohol **6a** (3.0 g, 8.92 mmol) in anhyd toluene (25 mL) was added Ph_3P (3.04 g, 11.6 mmol) followed by I_2 (4.53 g, 17.8 mmol) and imidazole (1.21 g, 17.8 mmol) at 0 °C. The mixture was allowed to warm to r.t., stirred for 3 h, then quenched with sat. aq $Na_2S_2O_3$ soln and diluted with EtOAc (20 mL). The aq layer was extracted with EtOAc (2 × 30 mL) and the combined organic layer washed with brine (20 mL), dried over anhyd Na_2SO_4 and filtered. Evaporation of the solvent under vacuum gave a crude residue which was purified by silica gel column chromatography (5% EtOAc–hexane) to afford **7a** (3.7 g, 94%) as a yellow solid.

7a: $[\alpha]_D^{25}$ –1.9 (*c* 1.05, $CHCl_3$); **7b**: $[\alpha]_D^{25}$ +2.0 (*c* 1, $CHCl_3$); mp 52–53 °C.

IR (KBr): 2970, 2877, 1459, 1379, 1064, 732, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): d = 0.71 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 1.24 (d, *J* = 6.6 Hz, 3 H), 1.33 (d, *J* = 5.6 Hz, 6 H), 1.78–1.96 (m, 2 H), 2.00–2.13 (m, 1 H), 3.04 (t, *J* = 10.0 Hz, 1 H), 3.41 (dd, *J* = 7.1, 11.1 Hz, 3 H), 3.64 (dd, *J* = 5.0, 11.5 Hz, 1 H), 3.80 (d, *J* = 10.3 Hz, 1 H), 4.61 (q, *J* = 12.8 Hz, 2 H), 7.20–7.33 (m, 5 H).

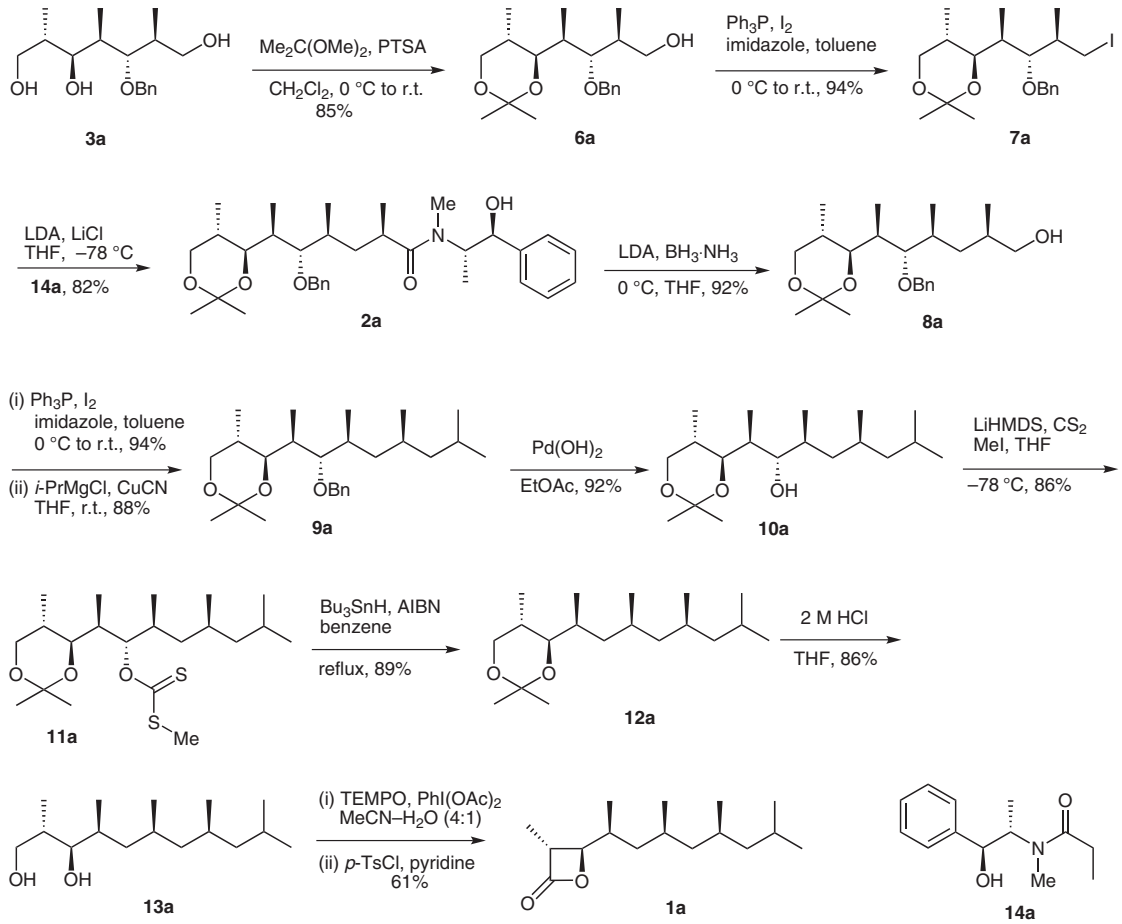
^{13}C NMR (75 MHz, $CDCl_3$): d = 9.8, 10.3, 12.4, 19.4, 29.7, 30.2, 36.9, 39.3, 66.1, 73.3, 74.8, 83.3, 97.9, 126.8, 127.3, 128.2.

MS (ESI): *m*/*z* = 469 $[M + Na]^+$.

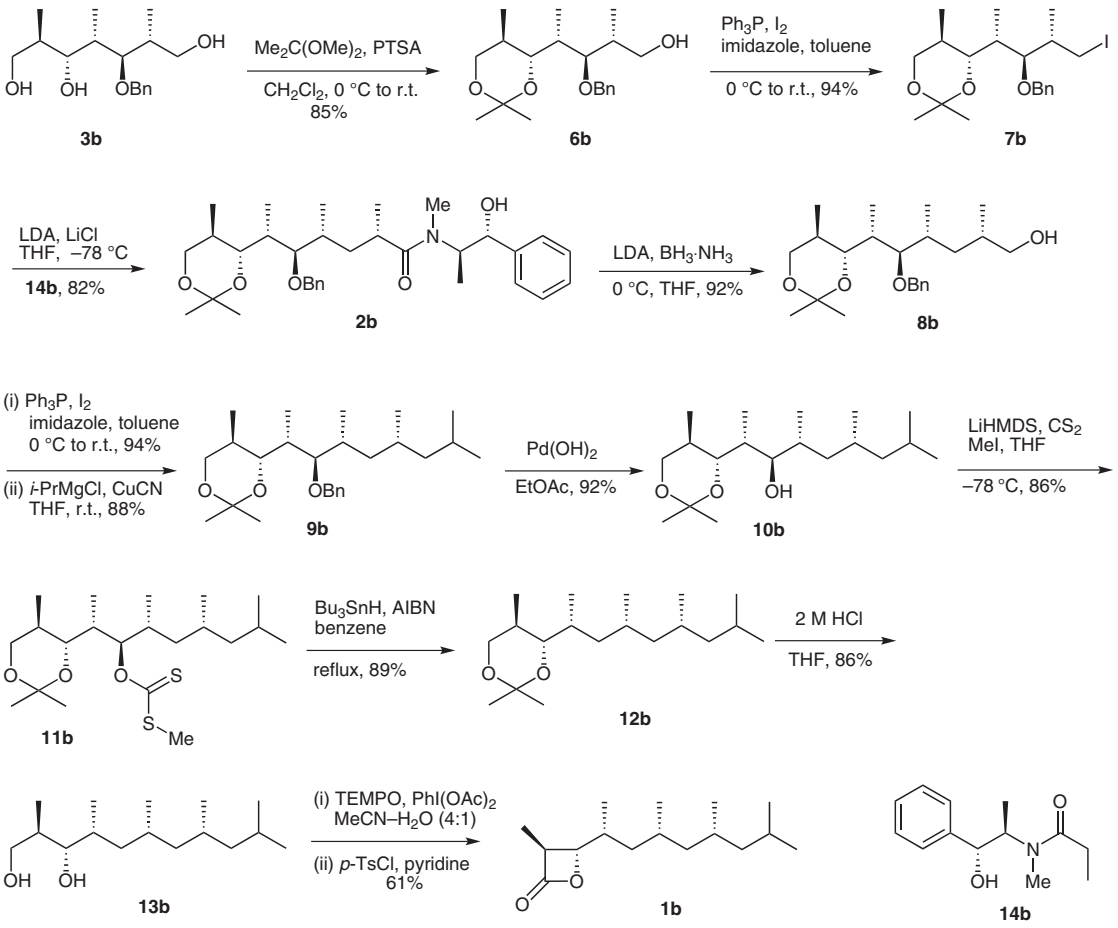
HRMS (ESI-MS): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{31}O_3INa$: 469.1215; found: 469.1201.

(2*R*,4*S*,5*S*,6*S*)-5-(Benzyloxy)-*N*-[(1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-*N*,2,4-trimethyl-6-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]heptanamide (2a)

LiCl (2.16 g, 50.4 mmol) was placed in a round-bottomed flask and flame-dried for 30 min under high vacuum and then allowed to cool to r.t. under an Ar atm. THF (18 mL) was added and the mixture cooled to –78 °C, then diisopropylamine (4.05 mL, 28.9 mmol) was added followed by *n*-BuLi (16.8 mL, 26.9 mmol, 1.6 M in hexanes) and the resulting soln stirred for 10 min. The mixture was warmed to 0 °C for 10 min before again being cooled to –78 °C. Next, a soln of *N*-propionyl-(*S*,*S*)–pseudoephedrine (**14a**) (3.12 g, 14.12 mmol) in THF (20 mL) was added and the mixture stirred at –78 °C for 1 h, warmed to 0 °C for 10 min and then to r.t. for a further 10 min.



Scheme 2 Synthesis of (+)-vittatalactone



Scheme 3 Synthesis of (–)-vittatalactone

After cooling to 0 °C, a soln of iodide **7a** (1.5 g, 3.36 mmol) in THF (15 mL) was added and the mixture stirred overnight. Sat. aq NH_4Cl soln was added to quench the reaction, the organic layer separated and the aq layer extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (30 mL), dried over anhyd Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (30% EtOAc–hexane) to afford the title compound **2a** (1.5 g, 82%) as a yellow liquid.

2a: $[\alpha]_D^{25}$ +50.0 (*c* 0.75, $CHCl_3$); **2b**: $[\alpha]_D^{25}$ –47.5 (*c* 0.4, $CHCl_3$).

IR (KBr): 3419, 2925, 2856, 1756, 1455, 1381, 1017, 757, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.0 Hz, 3 H), 0.87 (s, 3 H), 1.07 (d, *J* = 6.0 Hz, 4 H), 1.13 (d, *J* = 6.0 Hz, 3 H), 1.25 (t, *J* = 15.1 Hz, 4 H), 1.33 (d, *J* = 9.0 Hz, 6 H), 1.64 (s, 1 H), 1.82–1.99 (m, 3 H), 2.68 (s, 1 H), 2.85 (d, *J* = 6.0 Hz, 3 H), 3.28 (q, *J* = 9.0 Hz, 1 H), 3.39–3.50 (m, 1 H), 3.64 (dd, *J* = 6.0, 12.0 Hz, 1 H), 3.83 (d, *J* = 12.0 Hz, 1 H), 4.08 (t, *J* = 6.0 Hz, 1 H), 4.54–4.63 (m, 2 H), 7.21–7.35 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): d = 9.0, 12.2, 14.1, 15.3, 18.0, 18.5, 19.3, 26.8, 29.7, 30.0, 32.6, 33.5, 36.5, 57.8, 60.1, 66.0, 73.3, 74.7, 75.8, 84.2, 84.5, 97.7, 125.9, 126.6, 126.9, 127.2, 128.0, 128.4, 139.2, 142.3, 178.3.

MS (ESI): *m*/*z* = 540 $[M + H]^+$.

HRMS (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{50}O_5N$: 540.3688; found: 540.3703.

(2*R*,4*S*,5*S*,6*S*)-5-(Benzyloxy)-2,4-dimethyl-6-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]heptan-1-ol (8a)

To a stirred soln of diisopropylamine (5.1 mL, 36.27 mmol) in anhyd THF (25 mL) at –78 °C was added *n*-BuLi (21.3 mL, 34.14 mmol, 1.6 M in hexanes) and the resulting soln stirred for 5 min at –78 °C. The soln was warmed to 0 °C for 10 min, and then r.t. for 5 min and cooled to 0 °C. Solid $BH_3{\cdot}NH_3$ complex (1.16 g, 37.55 mmol) was added to the soln which resulted in vigorous gas evolution. After 10 min at 0 °C, the soln was warmed to r.t. and stirred for an additional 10 min and then again cooled to 0 °C. A soln of amide **2a** (2.3 g, 4.26 mmol) in THF (20 mL) was added and the mixture allowed to warm to r.t. overnight. Sat. aq NH_4Cl soln was added to quench the reaction and the aq layer was extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (30 mL), dried over anhyd Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (15% EtOAc–hexane) to afford **8a** (1.49 g, 92%) as a colourless liquid.

8a: $[\alpha]_D^{25}$ +30.2 (*c* 0.9, $CHCl_3$); **8b**: $[\alpha]_D^{25}$ –29.0 (*c* 1, $CHCl_3$).

IR (KBr): 3449, 2926, 2875, 1459, 1379, 1061, 735, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.71 (d, *J* = 6.7 Hz, 3 H), 0.83 (d, *J* = 6.7 Hz, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 1.12–1.20 (m, 1 H), 1.33 (d, *J* = 5.2 Hz, 7 H), 1.38–1.48 (m, 1 H), 1.64–1.73 (m, 1 H), 1.78–1.91 (m, 3 H), 3.29 (dd, *J* = 9.8, 11.3 Hz, 1 H), 3.36 (t, *J* = 10.5 Hz, 1 H), 3.44 (t, *J* = 21.9 Hz, 1 H), 3.53 (dd, *J* = 4.5, 10.5 Hz, 1 H), 3.63 (dd, *J* = 5.2, 11.3 Hz, 1 H), 3.84 (d, *J* = 11.3 Hz, 1 H), 4.60 (q, *J* = 12.0 Hz, 2 H), 7.27–7.33 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.6, 12.5, 18.5, 18.6, 19.5, 29.7, 29.9, 30.3, 32.8, 33.0, 33.3, 36.6, 66.2, 67.2, 73.5, 74.8, 84.4, 98.0, 126.9, 127.2, 128.2, 139.4.

MS (ESI): *m*/*z* = 401 [M + Na]$^+$.

HRMS (ESI-MS): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{38}O_4Na$: 401.2667; found: 401.2675.

(4*S*,5*S*)-4-[(2*S*,3*S*,4*S*,6*S*)-3-(Benzyloxy)-4,6,8-trimethylnonan-2-yl]-2,2,5-trimethyl-1,3-dioxane (9a)

Intermediate iodide: To a stirred soln of alcohol 8a (2.4 g, 6.35 mmol) in anhyd toluene (20 mL) was added Ph_3P (2.16 g, 8.25 mmol) followed by I_2 (3.22 g, 12.69 mmol) and imidazole (0.87 g, 12.69 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t., stirred for 3 h, then quenched with sat. aq $Na_2S_2O_3$ soln and diluted with EtOAc (20 mL). The aq layer was extracted with EtOAc (2 × 30 mL) and the combined organic layer washed with brine (30 mL), dried over anhyd Na_2SO_4 and filtered. Evaporation of the solvent under vacuum gave a crude residue which was purified by silica gel column chromatography (6% EtOAc–hexane) to afford the corresponding iodide (2.92 g, 94%) as a light yellow liquid.

Iodide **a**: $[\alpha]_D^{25}$ +15.0 (*c* 0.7, $CHCl_3$); iodide **b**: $[\alpha]_D^{25}$ –20.5 (*c* 1, $CHCl_3$).

IR (KBr): 2960, 2858, 1457, 1376, 1193, 1064, 734, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.73 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 5.8 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 1.32 (d, *J* = 9.0 Hz, 6 H), 1.23–1.39 (m, 3 H), 1.71–1.95 (m, 3 H), 3.15 (dd, *J* = 4.7, 9.4 Hz, 1 H), 3.23–3.32 (m, 2 H), 3.44 (t, *J* = 11.1 Hz, 1 H), 3.63 (dd, *J* = 6.2, 11.3 Hz, 1 H), 3.86 (d, *J* = 10.5 Hz, 1 H), 4.60 (s, 2 H), 7.19–7.34 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.6, 12.5, 18.5, 18.6, 19.5, 29.7, 29.9, 30.3, 32.8, 33.0, 33.3, 36.6, 66.2, 73.5, 74.8, 84.4, 98.0, 126.9, 127.2, 128.2, 139.4.

MS (ESI): *m*/*z* = 511 [M + Na]$^+$.

HRMS (ESI-MS): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{38}O_3I$: 489.1865; found: 489.1858.

9a: To a round-bottomed flask containing activated Mg turnings (1.79 g, 74.93 mmol) was added 2-chloropropane (5.5 mL, 59.94 mmol) in THF (14.5 mL). The mixture was heated to reflux for ca. 30 min until the conversion into isopropylmagnesium chloride was complete. The freshly prepared isopropylmagnesium chloride (19 mL, 74.9 mmol) was added dropwise to a stirred soln of the iodide **a** (1.9 g, 3.89 mmol) and CuCN (0.348 g, 3.89 mmol) in THF (20 mL). The mixture was stirred for 1 h at r.t. and then quenched with sat. aq NH_4Cl soln. The organic layer was separated and the aq layer extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with brine (30 mL), dried over anhyd Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (4% EtOAc–hexane) to afford **9a** (1.39 g, 88%) as a colorless liquid.

9a: $[\alpha]_D^{25}$ +17.6 (*c* 0.65, $CHCl_3$); **9b**: $[\alpha]_D^{25}$ –20.0 (*c* 1, $CHCl_3$).

IR (KBr): 2957, 2873, 1459, 1378, 1197, 1065, 733, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 (d, *J* = 6.7 Hz, 3 H), 0.83 (t, *J* = 12.8 Hz, 7 H), 0.86–0.91 (m, 6 H), 1.03 (d, *J* = 6.7 Hz, 3 H), 1.15–1.27 (m, 3 H), 1.33 (d, *J* = 6.0 Hz, 6 H), 1.47–1.58 (m, 1 H), 1.60–1.72 (m, 1 H), 1.76–1.91 (m, 3 H), 3.30 (d, *J* = 9.6 Hz, 1 H), 3.44 (t, *J* = 11.3 Hz, 1 H), 3.63 (dd, *J* = 6.2, 11.3 Hz, 1 H), 3.84 (d, *J* = 10.3 Hz, 1 H), 4.59 (q, *J* = 15.4 Hz, 2 H), 7.25–7.32 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.5, 12.4, 18.2, 19.4, 21.1, 21.5, 25.1, 27.6, 29.8, 30.2, 32.3, 36.4, 37.7, 45.2, 66.2, 73.5, 74.6, 74.7, 84.4, 97.9, 126.8, 127.0, 128.1, 139.5.

MS (ESI): *m*/*z* = 427 [M + Na]$^+$.

HRMS (ESI-MS): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{44}O_3Na$: 427.3188; found: 427.3176.

(2*S*,3*S*,4*S*,6*S*)-4,6,8-Trimethyl-2-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]nonan-3-ol (10a)

To a soln of **9a** (1.4 g, 3.46 mmol) in EtOAc (14 mL) under an Ar atm was added $Pd(OH)_2$ (486 mg, 20 wt% on C). The mixture was stirred under an H_2 atm at 50 psi for 8 h at 23 °C. The catalyst was removed by elution with EtOAc through a short pad of Celite. The eluent was concentrated under vacuum and the residue purified by silica gel column chromatography (5% EtOAc–hexane) to afford alcohol **10a** (1.0 g, 92%) as a colorless liquid.

10a: $[\alpha]_D^{25}$ –33.6 (*c* 0.55, $CHCl_3$); **10b**: $[\alpha]_D^{25}$ +33.0 (*c* 0.5, $CHCl_3$).

IR (KBr): 3520, 2953, 1460, 1379, 1159, 1060, 864, 520 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.4 Hz, 7 H), 0.89 (d, *J* = 6.4 Hz, 7 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 1.07–1.18 (m, 1 H), 1.36 (s, 3 H), 1.46 (s, 3 H), 1.54–1.71 (m, 4 H), 1.84–1.97 (m, 2 H), 2.60 (d, *J* = 7.9 Hz, 1 H), 3.10 (q, *J* = 4.9 Hz, 1 H), 3.49 (t, *J* = 22.4 Hz, 1 H), 3.67 (dd, *J* = 6.4, 11.3 Hz, 1 H), 3.88 (d, *J* = 12.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 11.9, 16.7, 19.0, 21.2, 21.6, 24.0, 25.2, 28.0, 29.7, 30.3, 33.4, 33.9, 40.8, 41.3, 45.6, 66.3, 75.3, 80.4.

MS (ESI): *m*/*z* = 337 [M + Na]$^+$.

HRMS (ESI-MS): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{38}O_3Na$: 337.2718; found: 337.2716.

***S*-Methyl *O*-{(2*R*,3*S*,4*S*,6*S*)-4,6,8-trimethyl-2-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]nonan-3-yl} carbonodithioate (11a)**

LiHMDS (3.75 mL, 3.98 mmol, 1.06 M in THF) was added dropwise to a stirred soln of alcohol **10a** (250 mg, 0.79 mmol) in THF (4 mL) at –78 °C under an Ar atm and the resulting mixture stirred for 30 min. CS_2 (0.48 mL, 7.96 mmol) was added at –78 °C after which the mixture was allowed to warm to 0 °C and stirred for 1 h before being cooled to –78 °C. MeI (0.24 mL, 3.98 mmol) was added at –78 °C and the mixture was allowed to warm to r.t. and stirred for 3 h. Sat. aq NH_4Cl soln was added to quench the reaction and the aq layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhyd Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (3% EtOAc–hexane) to afford xanthate **11a** (278 mg, 86%) as a yellow liquid.

11a: $[\alpha]_D^{25}$ –15.2 (*c* 0.75, $CHCl_3$); **11b**: $[\alpha]_D^{25}$ +18.2 (*c* 0.35, $CHCl_3$).

IR (KBr): 2857, 1633, 1460, 1226, 1049, 867, 763 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.71 (d, *J* = 5.9 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.87–0.92 (m, 9 H), 0.96 (d, *J* = 6.9 Hz, 4 H), 1.05–1.15 (m, 2 H), 1.27 (d, *J* = 4.9 Hz, 6 H), 1.30–1.37 (m, 1 H), 1.51–1.58 (m, 1 H), 1.60–1.70 (m, 1 H), 1.74–1.84 (m, 1 H), 1.95–2.04 (m, 1 H), 2.09 (m, 1 H), 2.54 (s, 3 H), 3.39 (d, *J* = 9.8 Hz, 1 H), 3.43 (t, *J* = 10.8 Hz, 1 H), 3.62 (dd, *J* = 4.9, 5.9 Hz, 1 H), 5.83 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.2, 12.3, 17.4, 18.6, 18.8, 21.1, 21.5, 24.1, 25.2, 27.6, 29.5, 30.0, 32.8, 35.4, 38.4, 45.2, 66.0, 72.9, 88.2, 98.2.

MS (ESI): *m*/*z* = 427 [M + Na]$^+$.

HRMS (ESI-MS): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{40}O_3S_2Na$: 427.2316; found: 427.2308.

(4*R*,5*S*)-2,2,5-Trimethyl-4-[(2*S*,4*S*,6*S*)-4,6,8-trimethylnonan-2-yl]-1,3-dioxane (12a)

To a stirred soln of xanthate **11a** (300 mg, 0.74 mmol) in anhyd benzene (10 mL) at 80 °C were added Bu_3SnH (0.4 mL, 1.49 mmol) fol-

lowed by a catalytic amount of AIBN (7.0 mg, 0.037 mmol) and the mixture heated at reflux temperature for 4 h. The solvent was removed under vacuum, the residue treated with aq KF soln (2 × 10 mL) (200 mg KF dissolved in 10 mL H_2O) and extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over anhyd Na_2SO_4, filtered and concentrated under vacuum. The residue was then purified by silica gel column chromatography (3% EtOAc–hexane) to afford **12a** (198 mg, 89%) as a colorless liquid.

12a: $[\alpha]_D^{25}$ +19.5 (*c* 0.75, $CHCl_3$); **12b**: $[\alpha]_D^{25}$ –21.3 (*c* 0.2, $CHCl_3$).

IR (KBr): 2957, 2857, 1461, 1377, 1262, 1104, 1062, 805, 519 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.64 (d, *J* = 6.7 Hz, 3 H), 0.73–0.83 (m, 17 H), 0.84–0.93 (m, 1 H), 0.95–1.11 (m, 2 H), 1.25 (s, 3 H), 1.31 (s, 3 H), 1.37–1.61 (m, 4 H), 1.65–1.82 (m, 2 H), 3.29–3.42 (m, 2 H), 3.58 (dd, *J* = 4.5, 11.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 18.9, 20.1, 20.5, 22.2, 23.5, 25.1, 26.7, 27.4, 29.7, 29.9, 30.7, 40.1, 46.2, 47.0, 66.4, 75.0, 97.9.

(2*S*,3*R*,4*S*,6*S*,8*S*)-2,4,6,8,10-Pentamethylundecane-1,3-diol (13a)

To a stirred soln of **12a** (112 mg, 0.375 mmol) in THF (1.5 mL) was added aq 2 M HCl (0.2 mL) and the resulting mixture stirred for 4 h at r.t. The mixture was diluted with EtOAc (5 mL) and the aq layer extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhyd Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (20% EtOAc–hexane) to afford **13a** (83 mg, 86%) as a colorless liquid.

13a: $[\alpha]_D^{25}$ –18.6 (*c* 1, $CHCl_3$); **13b**: $[\alpha]_D^{25}$ +21.6 (*c* 0.6, $CHCl_3$).

IR (KBr): 3373, 2957, 1461, 1377, 1026, 977 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.9 Hz, 3 H), 0.83–0.86 (m, 12 H), 0.88 (d, *J* = 5.9 Hz, 3 H), 0.90–0.98 (m, 2 H), 1.10 (m, 1 H), 1.14–1.21 (m, 1 H), 1.25 (s, 1 H), 1.35–1.42 (m, 1 H), 1.53–1.69 (m, 3 H), 1.70–1.77 (m, 1 H), 1.78–1.86 (m, 1 H), 2.43 (s, 2 H), 3.42 (dd, *J* = 8.9, 11.8 Hz, 1 H), 3.61 (dd, *J* = 7.9, 10.8 Hz, 1 H), 3.70 (dd, *J* = 7.9, 10.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8, 13.4, 20.4, 20.5, 21.9, 23.7, 25.1, 26.9, 27.4, 31.8, 37.3, 41.3, 45.7, 46.3, 68.7, 79.3.

MS (ESI): *m*/*z* = 281 $[M + Na]^+$.

HRMS (ESI-MS): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{34}O_2Na$: 281.2456; found: 281.2453.

(+)-Vittatalactone (1a)

To a stirred soln of 1,3-diol **13a** (80 mg, 0.310 mmol) in MeCN–H_2O (4:1) at 0 °C were added TEMPO (19 mg, 0.124 mmol) followed by $PhI(OAc)_2$ (399 mg, 1.24 mmol) and the resulting mixture stirred for 3 h. The mixture was quenched with sat. aq $Na_2S_2O_3$ soln and then diluted with EtOAc (5 mL). The organic layer was separated and the aq layer extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhyd Na_2SO_4, filtered and concentrated under vacuum. The crude β-hydroxy acid obtained was used in the next step without any further purification.

To a soln of the crude β-hydroxy acid (80 mg, 0.294 mmol) in anhyd py (1 mL) at 0 °C was added *p*-TsCl (112 mg, 0.588 mmol) and the soln was allowed to warm to r.t. and stirred overnight. After complete consumption of the starting material (as monitored by TLC), the mixture was diluted with Et_2O (5 mL) and H_2O (3 mL). The organic layer was separated and the aq layer extracted with Et_2O (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhyd Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (pentane–Et_2O, 9:1) to afford (+)-**1a** (48 mg, 61%) as a colorless liquid.

1a: $[\alpha]_D^{25}$ +3.0 (*c* 1.5, $CHCl_3$); **1b**: $[\alpha]_D^{25}$ –2.5 (*c* 1.5, $CHCl_3$).

IR (KBr): 2957, 2922, 1827, 1460, 1124, 867 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 6 H), 0.87–0.92 (m, 2 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 0.99–1.05 (m, 1 H), 1.06–1.11 (m, 1 H), 1.13–1.28 (m, 2 H), 1.39 (d, *J* = 7.5 Hz, 3 H), 1.49–1.71 (m, 3 H), 1.78–1.93 (m, 1 H), 3.20 (qd, *J* = 7.5, 4.1 Hz, 1 H), 3.80 (dd, *J* = 8.1, 4.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8, 15.7, 20.7, 20.9, 21.7, 23.8, 25.1, 27.2, 27.5, 34.7, 39.7, 45.0, 45.9, 48.8, 83.6, 172.0.

MS (ESI): *m*/*z* = 277 $[M + Na]^+$.

HRMS (ESI-MS): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{30}O_2Na$: 277.2143; found: 277.2138.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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