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Enantioselective total syntheses of (−)-clavaminol A and deacetyl (+)-clavaminol H

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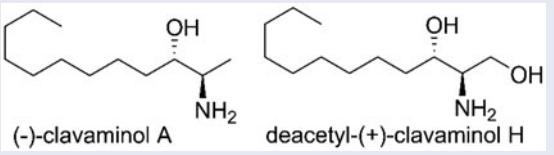
ABSTRACT

An efficient enantioselective approach to the syntheses of (−)-clavaminol A and deacetyl (+)-clavaminol H is presented, starting from *n*-decanol. The synthesis features Sharpless asymmetric dihydroxylation (AD), regioselective epoxide formation/opening and α-tosylation as key steps.

GRAPHICAL ABSTRACT



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2-amino-3-alkanols; clavaminols; cytotoxic; Sharpless AD; regioselective

Introduction

Long chain *anti*-2-amino-3-alkanols sphingoid bases **1**–**7** are important functional motifs possess intriguing biological activities and are important building blocks to synthesize a variety of biologically active natural products and medicinal compounds.[1] Architecturally, these molecules are correlated to the sphingosine derivatives, well known as central core unit of sphingolipids, which are important components of the cell membranes lipid portion in living organisms. Among these sphingoids, clavaminols A–N were isolated from marine Mediterranean ascidian *Clavelina phlegraea*[2] and display cytotoxic activities against various cancer cell lines, namely AGS (gastric carcinoma), A549 (lung carcinoma) and T47D (breast carcinoma), by activation of apoptosis. Among clavaminols A–N, (−)-clavaminol A **1** was found to be the most active member.[3] Deacetyl (+)-clavaminol H **3** was found to be active against AGS-gastric carcinoma, although (+)-clavaminol H **4** showed no substantial activity (Figure 1).

Fascinated by the biological activities and unique structural features of *anti*-2-amino-3-alkanols, hitherto, various asymmetric syntheses for clavaminols have been reported.[4]

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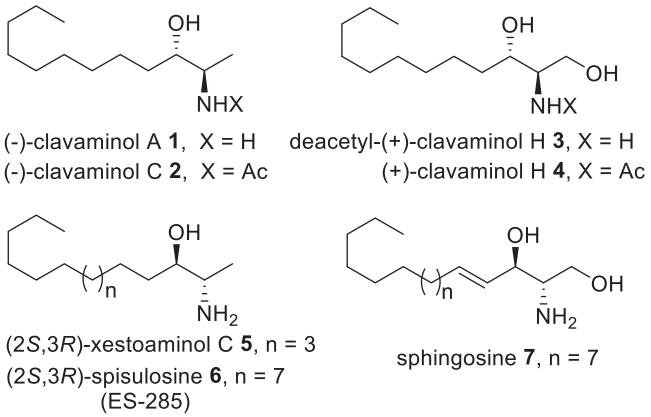


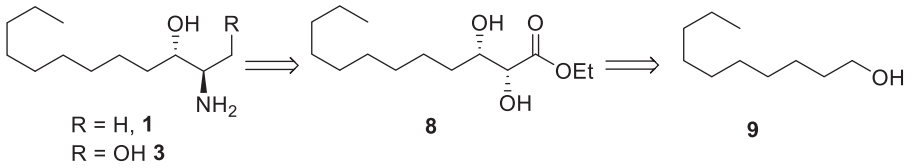
Figure 1. Structures of some representative long-chain *anti*-2-amino-3-alkanols.

Majority of the syntheses for clavaminols employed several steps and used chiral pool such as amino acids as starting material. More recently, Jin and coworker disclosed the stereoselective syntheses of (−)-clavaminol A **1** and deacetyl (+)-clavaminol H **3** from D-serine derived Weinreb amide chiral pool building block[4a] In continuation of our ongoing research program directed towards the asymmetric syntheses of bioactive natural products,[5] we became attentive in developing a flexible and simple approach to clavaminols. Herein, we wish to report an efficient synthesis of (−)-clavaminol A **1** and protecting group free synthesis of deacetyl (+)-clavaminol H **3** employing Sharpless AD as the source of chirality.

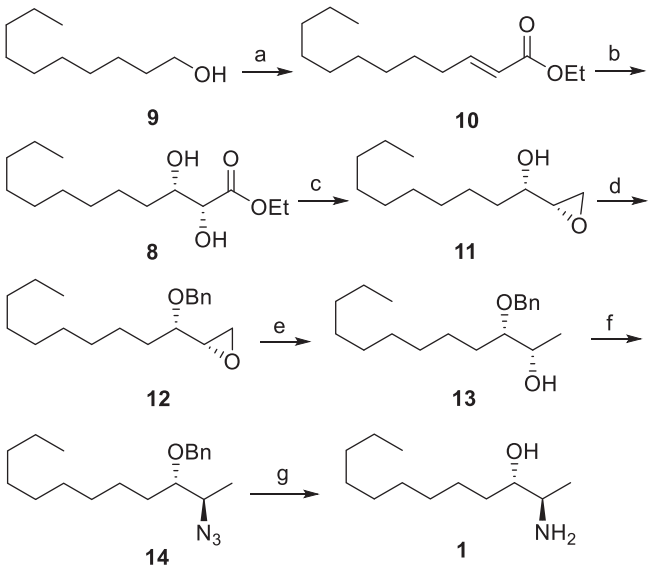
Results and discussion

Our retrosynthetic approach to (−)-clavaminol A **1** and deacetyl (+)-clavaminol H **3** is depicted in Scheme 1. The diol intermediate **8** was imagined as a key intermediate from which (−)-clavaminol A **1** and deacetyl (+)-clavaminol H **3** could be produced. (−)-Clavaminol A **1** could be synthesized from diol **8** via reduction of ester, regioselective terminal epoxide formation and hydride opening, and conversion of α-hydroxyl to amine employing standard organic transformations. Protecting group free synthesis of deacetyl (+)-clavaminol H **3** envisaged from diol **8** via regioselective α-tosylation, azide formation and reduction following standard organic transformation. The diol derivative **8** in turn could be obtained from a commercially available *n*-decanol **9** in simple steps engaging a Swern oxidation, Wittig olefination and Sharpless AD.

Synthesis of (−)-clavaminol A **1** as displayed in Scheme 2, began with achiral *n*-decanol **9** which was oxidized under a Swern oxidation,[6] and subsequent treatment of the intermediate aldehyde with the stabilized Wittig reagent (ethoxycarbonylmethylene)triphenylphosphorane in dry THF furnished the Wittig product **10** in 91% yield.[7] The Sharpless AD[8] of α,β-unsaturated ester derivative **10** with OsO_4 and $K_3[Fe(CN)_6]$ in the presence of catalytic amount of $(DHQ)_2PHAL$ delivered vicinal diol **8** in 92% yield following a literature procedure;[9] $[\alpha]_D^{25}$ −10.55 (*c* 1.0, $CHCl_3$); {lit.[9] $[\alpha]_D^{20}$ −10.54 (*c* 1.0, $CHCl_3$)}. Furthermore, reduction of diol ester **8** with $LiAlH_4$ in dry THF furnished the triol intermediate in essentially quantitative yield. Regioselective primary alcohol



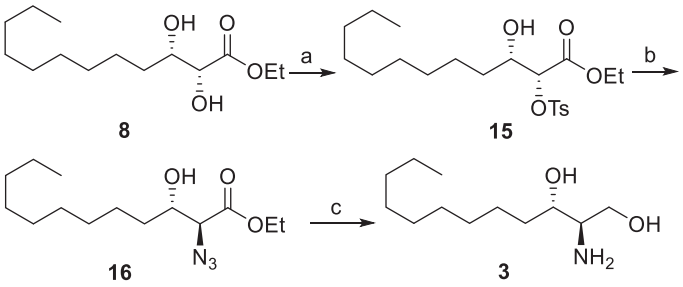
Scheme 1. Retrosynthetic analysis for (−)-clavaminol A **1** and deacetyl (+)-clavaminol H **3**.



Scheme 2. *Reagents and conditions*: (a) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, −78 °C to −60 °C, 2 h; (ii) $Ph_3P=CHCOOEt$, THF, rt, 12 h, 91% (over two steps); (b) 0.5 mol % OsO_4, 1 mol % $(DHQ)_2PHAL$, $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0 °C, 5 h, 92%; (c) (i) $LiAlH_4$, THF, 0 °C to rt, 2 h; (ii) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (iii) K_2CO_3, MeOH, rt, 30 min, 75% (over three steps); (d) NaH, BnBr, DMF, 0 °C, 2 h, 93%; (e) $LiAlH_4$, THF, 0 °C to rt, 3 h, 85%; (f) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min; (ii) NaN_3, DMF, 70 °C, 12 h, 89% (over two steps); (g) H_2, Pd/C (10%), MeOH, rt, 12 h, 91%.

mono-tosylation of triol intermediate with Et_3N and TsCl in the presence of catalytic amount of Bu_2SnO proceeded smoothly and subsequent treatment with K_2CO_3 in MeOH furnished the epoxy alcohol derivative **11**[10] in 75% yield. The remaining hydroxyl group of **11** on treatment with benzyl bromide and NaH in dry DMF afforded the corresponding benzyl ether **12** in excellent yield. Our next aim was to carry out the C-1 regioselective opening of the epoxide **12** by lithium aluminum hydride. Towards this end, the terminal epoxide **12** on treatment with $LiAlH_4$ furnished alcohol **13** in excellent yield.

At this step our initial attempt for conversion of hydroxyl group of compound **13** to azide derivative **14** employing Mitsunobu conditions[11] was very low yielding. Therefore, the free hydroxy group of **13** was subjected to *O*-mesylation with mesyl chloride (MsCl) and Et_3N to furnish the *O*-mesyl intermediate which on S_N2 reaction with NaN_3 in dry DMF at 70 °C for 12 h afforded azide derivative **14** with the desired stereochemistry in 89% yield. Finally, compound **14** on concomitant deprotection of benzyl ether and azide reduction to amine by hydrogenation at one atmospheric



Scheme 3: *Reagents and conditions*: (a) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 78%; (b) NaN_3, DMF, 70 °C, 12 h, 91%; (c) $LiAlH_4$, THF, 0 °C to rt, 3 h, 85%.

pressure in the presence of 10% Pd/C furnished the natural compound (−)-clavaminol A **1** in 91% yield. The spectroscopic and physical data of (−)-clavaminol A **1** $[\alpha]_D^{25}$ −4.56 (*c* 1.0, MeOH), {lit[4b] $[\alpha]_D^{25}$ −4.60 (*c* 1.0, MeOH)} were in consistent with literature data.

As illustrated in Scheme 3, the protecting group free synthesis of deacetyl (+)-clavaminol H **3** began with diol ester derivative **8**. Regioselective monotosylation[12] of diol ester derivative **8** with TsCl (tosyl chloride) resulted in the tosylate derivative **15** in 78% yield. Furthermore, treatment of compound **15** with NaN_3 in dry DMF at 70 °C afforded azide derivative **16** in 91% yield. Finally, concomitant reduction of azide and ester group with $LiAlH_4$ furnished the target compound deacetyl (+)-clavaminol H **3** in 85% yield. The spectroscopic and physical data of deacetyl (+)-clavaminol H **3** $[\alpha]_D^{25}$ +6.44 (*c* 1.00, MeOH), {lit[4b] $[\alpha]_D^{28}$ +6.5 (*c* 1.00, MeOH)} were in consistent with literature data.

Conclusion

In summary, we have developed a simple, flexible and efficient strategy to the synthesis of (−)-clavaminol A **1** in 40% overall yield and protecting group free synthesis of deacetyl (+)-clavaminol H **3** with 50% overall yield from commercially available *n*-decanol **9.** The synthetic steps demonstrate the usefulness of Sharpless AD, regioselective epoxide formation/opening and α-tosylation as the key steps. The synthetic route described has significant potential for further extension and stereochemical variations of clavaminols and their analogs.

Experimental

(S)-2-((S)-1-(benzyloxy)decyl)oxirane, 12

NaH (17 mg, 0.82 mmol) was added to an ice cooled solution of compound **11** (150 mg, 0.75 mmol) in dry DMF (3 mL) under nitrogen atmosphere and stirred for 5 min. Benzyl bromide (0.10 mL, 0.61 mmol) was then added and stirred the mixture for an additional 2 h at room temperature. After completion of the reaction as monitored by TLC, ice cooled water followed by EtOAc were added. The organic layer was separated and the aq. layer was extracted with EtOAc (3 × 15 mL). The combined organic layers was dried over Na_2SO_4, concentrated *in vacuo* and purified using silica gel column

chromatography (ethyl acetate/hexane 1:9) to furnish product **12** (203 mg, 0.70 mmol, 93%) as a colorless liquid; $[\alpha]_D^{25}$ −13.44 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 2921, 2850, 1605, 1465, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.28 (m, 5H), 4.84 (d, $J = 11.88$ Hz, 1H), 4.58 (d, $J = 11.88$ Hz, 1H), 3.03–3.02 (m, 2H), 2.79 (t, $J = 4.12$ Hz, 1H), 2.49 (dd, $J = 5.04$, 2.28 Hz, 1H), 1.71–1.62 (m, 1H), 1.57–1.42 (m, 1H), 1.25 (br s, 14H), 0.88 (t, $J = 6.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.6, 128.3, 127.8, 127.5, 80.5, 71.7, 55.1, 43.2, 32.3, 31.9, 29.6, 29.5, 29.4, 29.3, 25.5, 22.7, 14.1; HRMS (ESI), calcd for $C_{19}H_{30}O_2Na$ $[M + Na]^+$ 313.2143; found 313.2140.

(2S,3S)-3-(benzyloxy)dodecan-2-ol, 13

To a solution of epoxide **12** (150 mg, 0.52 mmol) in dry THF (5 mL) under nitrogen atmosphere at 0 °C was added $LiAlH_4$ (59 mg, 1.55 mmol) portion wise. The resulting suspension was continued to stir at room temperature for 3 h. Then reaction mixture was quenched with 10% aqueous NaOH and diluted with EtOAc. The organic layer was separated and aq. layer was extracted with EtOAc (3 × 15 mL). The collective organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford crude compound. The crude compound was purified using silica gel chromatography ($R_f = 0.4$, EtOAc/hexane 1:9 v/v) to afford alcohol **13** (128 mg, 0.44 mmol, 85%) as a colorless liquid; $[\alpha]_D^{25}$ −8.33 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 3465, 2931, 2859, 1609, 1095, 1045, 975, 914, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.28 (m, 5H), 4.67 (d, $J = 11.4$ Hz, 1H), 4.59 (d, $J = 11.4$ Hz, 1H), 3.78–3.70 (m, 1H), 3.22 (q, $J = 11.44$, 5.48 Hz, 1H), 2.47 (d, $J = 4.12$ Hz, 1H), 1.64–1.46 (m, 2H), 1.28 (br s 13 H), 1.18 (d, $J = 6.4$ Hz, 3H), 0.88 (t, $J = 6.88$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 128.5, 127.8, 127.6, 84.1, 72.4, 68.9, 31.9, 30.1, 29.9, 29.5, 29.3, 24.8, 22.7, 18.9, 14.1; HRMS (ESI), calcd for $C_{19}H_{32}O_2Na$ $[M + Na]^+$ 315.2300; found 315.2294.

((((2R,3S)-2-azidododecan-3-yl)oxy)methyl)benzene, 14

To a stirred solution of alcohol **13** (80 mg, 0.27 mmol) in dry DCM (5 mL) was added Et_3N (49 µL, 0.35 mmol) at 0 °C under N_2 atmosphere. After the mixture was stirred for 5 min, MsCl (25 µL, 0.32 mmol) was added and stirring was continued for 30 min at room temperature. After completion of the reaction, reaction was diluted with H_2O and the aq. layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was used as such for the next step without further purification.

NaN_3 (53 mg, 0.82 mmol) was added to a solution of above crude in dry DMF (5 mL) under nitrogen atmosphere and stirred reaction mixture for 12 h at 70 °C. The reaction mixture was being cooled to room temperature, diluted with water and extracted with Et_2O (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification using silica gel chromatography (EtOAc/hexane 1:49) afforded azide **14** (77 mg, 0.24 mmol, 89%) as a colorless oil; $[\alpha]_D^{25}$ −24.55 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 2935, 2859, 2109, 1659, 975, 914, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 5H), 4.65 (d,

$J = 11.4$ Hz, 1H), 4.55 (d, $J = 11.4$ Hz, 1H), 3.61–3.54 (m, 1H), 3.42–3.36 (m, 1H), 1.63–1.41 (m, 2H), 1.35-1.20 (m, 17H), 0.88 (t, $J = 6.88$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 128.4, 127.9, 127.7, 81.8, 72.5, 59.3, 31.9, 30.7, 29.7, 29.5, 29.3, 25.6, 22.7, 14.3, 14.4, 14.1; HRMS (ESI), calcd for $C_{19}H_{31}N_3ONa$ $[M + Na]^+$ 340.2359; found 340.2363.

(−)-clavaminol a, 1

To a suspension of **14** (50 mg, 0.16 mmol) in methanol was added palladium on activated carbon (10%/Pd/C) and the resulting solution was stirred under an atmosphere of hydrogen for 12 h at room temperature. The Pd catalyst was filtered off through a pad of Celite and the filtrate was concentrated *in vacuo* to provide crude which was purified using silica gel chromatography (MeOH/DCM 1:9 to give target compound **1** (28 mg, 0.14 mmol, 91%) as white solid; m.p. 107–108 °C; $[\alpha]_D^{25}$ −4.56 (*c* 1.0, MeOH), {lit.[4b] $[\alpha]_D^{25}$ −4.60 (*c* 1.0, MeOH)}; IR (MeOH) ν: 3405, 2928, 1023, 725 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ: 3.61 (br m, 1H), 3.18 (d, $J = 4.56$ Hz, 1H), 1.51–1.17 (m, 16H), 1.12 (d, $J = 6.40$ Hz, 3H), 0.80 (t, $J = 6.44$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 71.6, 52.6, 34.0, 33.0, 30.7, 30.6, 30.4, 26.9, 23.7, 14.4, 12.0; HRMS (ESI), calcd for $C_{12}H_{27}NONa$ $[M + H]^+$ 202.2165; found 202.2162.

Ethyl (2R,3S)-3-hydroxy-2-(tosyloxy)dodecanoate, 15

To a solution of diol **8** (100 mg, 0.38 mmol) in DCM (10 mL) was added Et_3N (0.1 mL, 0.42 mmol) at 0 °C under N_2 atmosphere. After the solution was stirred for 5 min, TsCl (80 mg, 0.42 mmol) and catalytic amount of DMAP were added at the same temperature. After an additional stirring for 6 h at room temperature, saturated aqueous solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel column chromatography. (EtOAc/hexane 1:4) to afford tosyl derivative **15** (124 mg, 0.30 mmol, 78%) as a clear liquid; $[\alpha]_D^{25}$ −9.2 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 3410, 2967, 2921, 2896, 2854, 1735, 1596, 1371 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 8.42$ Hz, 2H), 4.81 (d, $J = 3.24$ Hz, 1H), 4.16–4.11 (m, 2H), 3.99–3.94 (m, 1H), 2.45 (S, 3H), 1.93 (d, $J = 8.72$ Hz, 1H), 1.55–1.22 (m, 16H), 1.21 (t, $J = 6.88$ Hz, 3H), 0.88 (t, $J = 6.44$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 145.3, 132.9, 129.8, 128.1, 79.8, 71.8, 62.0, 32.9, 31.8, 29.5, 29.4, 29.3, 25.3, 22.6, 21.7, 14.1, 13.9; HRMS (ESI), calcd for $C_{21}H_{34}O_6SNa$ $[M + Na]^+$ 437.1968; found 437.1972.

Ethyl (2S,3S)-2-azido-3-hydroxydodecanoate, 16

To a stirred solution of tosyl alcohol compound **15** (80 mg, 0.19 mmol) in dry DMF (4 mL) was added NaN_3 (27 mg, 0.42 mmol) at room temperature under N_2 atmosphere. After being stirred for 12 h at 70 °C, the reaction mixture was allowed to cool at the room temperature. Water (5 mL) was added to the reaction mixture and then the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was dried

over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified using silica gel column chromatography (EtOAc/hexane 1:9) to afford azide **16** (50 mg, 0.18 mmol, 91%) as a clear liquid; $[\alpha]_D^{25}$ +17.36 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 3406, 2957, 2931, 2896, 2858, 2106, 1735, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.32–4.27 (m, 2H), 3.96–3.94 (m, 2H), 3.49 (d, $J = 6.88$ Hz, 1H), 2.46–2.42 (m, 1H), 1.54–1.41 (m, 2H), 1.34 (t, $J = 6.88$ Hz, 3H), 1.26 (br s, 13H), 0.88 (t, $J = 6.88$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 71.9, 66.2, 62.1, 62.0, 50.8, 32.9, 31.8, 29.5, 29.4, 29.3, 29.2, 25.3, 22.6, 14.1, 14.0; HRMS (ESI), calcd for $C_{14}H_{27}N_3O_3Na$ $[M + Na]^+$ 308.1945; found 308.1947.

Deacetyl (+)-clavaminol H, 3

To a cold suspension of azide **16** (40 mg, 0.14 mmol) in THF (5 mL) was added lithium aluminum hydride (21 mg, 0.56 mmol) under N_2 atmosphere at 0 °C and stirred for 3 h at room temperature. Water and 10% NaOH (10 mL) was added dropwise until the solid turned gray. After filtration, the solid was washed with EtOAc (2 × 10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel column chromatography (MeOH/DCM 1:9) to afford the final compound **3** (26 mg, 0.12 mmol, 85%) as a colorless oil; [$R_f = 0.35$, MeOH/DCM 1:5 v/v]; $[\alpha]_D^{25}$ +6.44 (*c* 1.00, MeOH), {lit.[4b] $[\alpha]_D^{28}$ +6.5 (*c* 1.00, MeOH)}; ^1H NMR (400 MHz, CD_3OD) δ: 3.72–4.27 (td, $J = 6.44$, 4.12 Hz, 1H), 3.59 (dd, $J = 6.44$, 4.12 Hz, 1H), 3.56-3.43 (m, 1H), 3.22–3.20 (br m, 1H), 1.52–1.16 (m, 16H), 0.80 (t, $J = 6.40$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ:72.3, 62.1, 57.0, 34.8, 33.1, 30.8, 30.7, 30.5, 30.1, 26.9, 23.8, 14.5; HRMS (ESI), calcd for $C_{12}H_{27}NO_2Na$ $[M + Na]^+$ 240.1934; found 240.1935.

Supporting information

Supplemental data (copies of ^1H and ^{13}C NMR spectra of compounds **1, 3, 5,** and **7–13**) for this article can be accessed on the publisher's website.

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