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A unified strategy for the synthesis of the C1–C14 fragment of marinolic acids, mupirocins, pseudomonic acids and thiomarinols: total synthesis of pseudomonic acid methyl monate C†‡

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A flexible stereoselective approach to the common C1–C14 skeleton present in natural products of the pseudomonic acid family is described. The strategy has been extended and the total synthesis of pseudomonic acid methyl monate C was achieved. The key synthetic reactions utilized include Achmatowicz rearrangement, Johnson–Claisen rearrangement, Julia–Kocienski olefination, and Horner–Wadsworth–Emmons olefination reaction.

Introduction

Pseudomonic acids isolated from the bacterium *Pseudomonas fluorescens* NCIB 10586 species[1] are strong inhibitors of Gram positive bacteria and mycoplasmal pathogens. Mupirocin, a mixture of pseudomonic acids comprised of 90% of pseudomonic acid A along with other pseudomonic acids B–D is used as a clinical agent for bacterial skin infections. Mupirocin W and H belong to another class of antibiotics isolated from *Pseudomonas fluorescens* showing similar bioactivity to pseudomonic acids.[2] A series of natural hybrids of pseudomonic acids namely thiomarinols (TMs) were recently isolated from marine bacterium *Pseudoalteromonas* sp. SANK 733903 and found to display potent activity particularly against *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA) (MIC < 0.01 μg mL^{-1}). Very recently another class of thiomarinols isolated from the same species *Pseudoalteromonas* SANK 73390 namely marinolic acids[3d] were found to be active against *Bacillus subtilis* and MRSA. Structurally, all these molecules bear a similar C1–C14 carbon frame (Fig. 1). The structural architecture of pseudomonic acids along with the impressive biological properties have stimulated many synthetic groups and culminated in the synthesis of individual members of this class.[4] Our interest in the expedient synthesis of 2,6-disubstituted di/tetra-hydropyran containing natural products by elaborating the Achmatowicz rearrangement,[5]

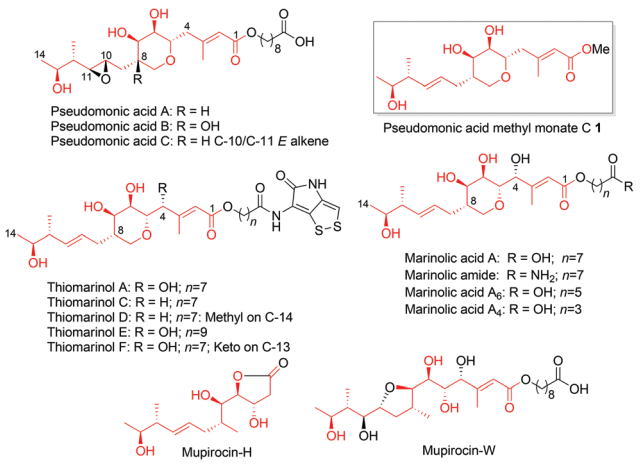

Fig. 1 Structures of pseudomonic acids, thiomarinols, marinolic acids and mupirocins.

prompted us to target pseudomonic acids for total synthesis. Since all the pseudomonic acids have a similar C1–C14 carbon frame (Fig. 1) with/without tetrahydropyran ring, our intention was to construct this frame as the key intermediate involving a common synthetic route which can be further elaborated for the total synthesis of related natural products. Herein, we disclose the stereoselective synthesis of a common and advanced precursor for the pseudomonic acid family of natural products and its utility for the total synthesis of pseudomonic acid methyl monate C **1**.

We designed our strategy based on a diversity oriented approach and anticipated that pseudomonic acids bearing a similar C1–C14 framework (showed in red Fig. 1) can be synthesized from a common intermediate **2** by further chemical manipulations (Scheme 1). Intermediate **2** can be synthesized

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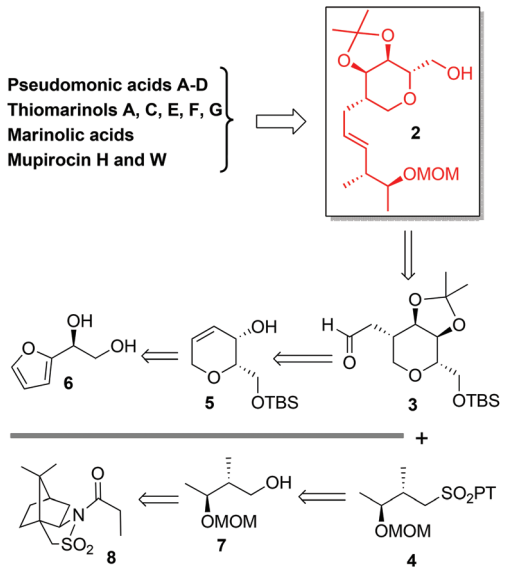


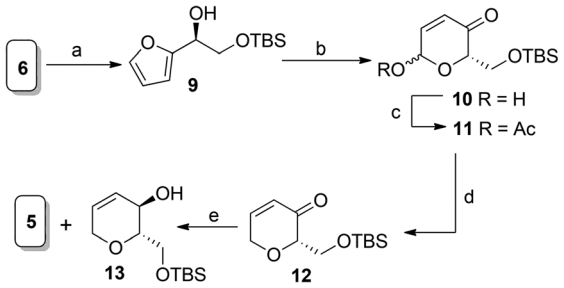
Scheme 1 Retrosynthetic analysis of pseudomonic acids, thiomarinols and mupirocins.

by coupling aldehyde **3** and sulfone **4** by means of an olefination reaction. Aldehyde **3** can be synthesized from allyl alcohol **5** utilizing a Johnson–Claisen rearrangement and *syn* dihydroxylation. Allyl alcohol **5** can be prepared from chiral furyl alcohol **6** by means of an Achmatowicz rearrangement and further functional group modifications of the derived pyranone-acetal. The sulfone side arm **4** can be obtained from alcohol **7** which in turn can be synthesized from propionoyl sultam **8** by an aldol protocol.

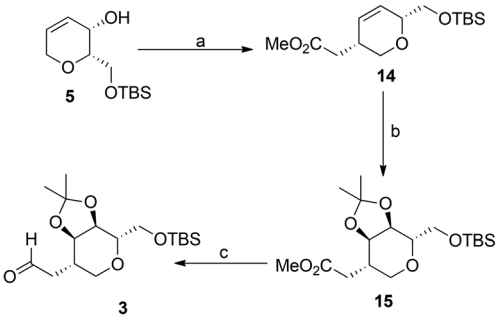
Results and discussion

Our initial focus was towards the construction of the allyl alcohol **5** in sufficient amounts for which we relied on Achmatowicz oxidative rearrangement of furfuryl alcohol **9**. Accordingly, the diol **6** synthesized by following earlier known methods[6] was mono protected as the TBS ether to obtain the secondary furfuryl alcohol **9**. Under standard Achmatowicz conditions,[7] **9** cleanly underwent the rearrangement to reveal the acetal **10**, which was further transformed to the corresponding acetate **11**. Anomeric acetate displacement was achieved by hydride addition to the cyclic oxocarbenium ion by exposure of **11** to $BF_3{\cdot}OEt_2$ in presence of triethylsilane at −78 °C to yield enone **12**. Substrate controlled 1,2-*syn* reduction of enone **12** was achieved with DIBAL-H in 95% yield with 5 : 1 diastereoselectivity providing allyl alcohols **5** and **13** that were easily separable by silica gel column chromatography (Scheme 2).[8]

Allyl alcohol **5** was subjected to Johnson–Claisen rearrangement[9] with trimethyl orthoacetate to afford the ester **14** (Scheme 3). Substrate controlled dihydroxylation[4d] of dihydropyran **14** with OsO_4 afforded β *syn* diol as a single diastereomer which was masked with 2,2-dimethoxy propane in presence of



Scheme 2 Synthesis of **5**. Reagents and conditions: (a) imidazole, TBDMSCl, CH_2Cl_2, rt, 90%; (b) NBS, $NaOAc{\cdot}3H_2O$, $NaHCO_3$, $THF–H_2O$ (4 : 1), 0 °C, 5 min, 95%; (c) pyridine, Ac_2O, CH_2Cl_2, 0 °C, 1 h, 90%; (d) Et_3SiH, $BF_3–OEt_2$, CH_2Cl_2, −78 °C, 1 h, 80%; (e) DIBAL-H, THF, −78 °C, 5 min, 95%, dr for **5** : **13** = 5 : 1.

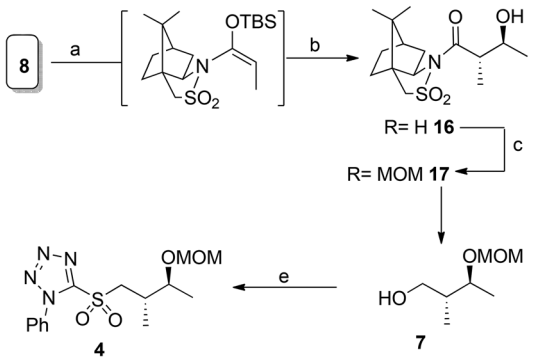


Scheme 3 Reagents and conditions: (a) trimethyl orthoacetate, propionic acid, 140 °C, 16 h, 90%; (b) (i) OsO_4, NMO, acetone–H_2O (1 : 1), rt, 24 h, 85%; (ii) 2,2-dimethoxypropane, *p*TsOH, EtOAc, 0 °C, 30 min, 95%; (c) (i) $LiAlH_4$, THF, 0 °C, 5 min, 96%, (ii) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 95%.

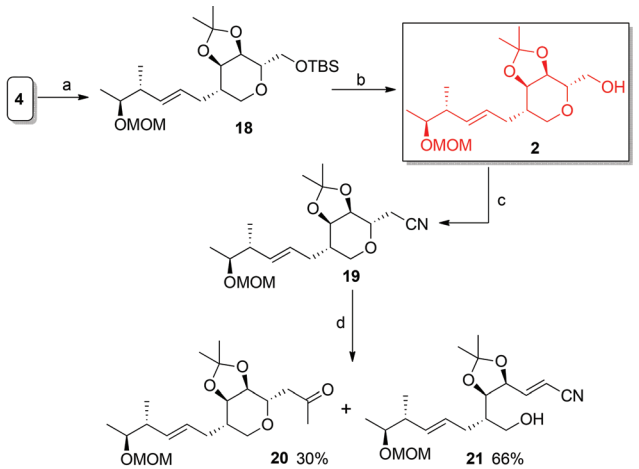
*p*TsOH to yield the corresponding isopropylidene derivative **15**. A two-step process was required to transform ester functionality in **15** to aldehyde **3**, as the controlled reduction with DIBAL-H resulted in a complex mixture. Treatment of ester **15** with $LiAlH_4$ followed by oxidation with Dess–Martin periodinane afforded aldehyde **3** in good yield.

The sulfone fragment **4** was synthesized by adoption of Oppolzer's aldol protocol[10] wherein the propionoyl sultam **8** was converted to TBS enolate and was added to a mixture of acetaldehyde and $TiCl_4$ at −78 °C to afford aldol adduct **16** with 59% yield [98%, based on recovered starting material (brsm)] (Scheme 4). Alcohol **16** was protected as the corresponding MOM ether **17** and the sultam auxiliary was cleaved with $LiAlH_4$ to afford the alcohol **7**. Under Mitsunobu conditions, alcohol **7** was converted to sulfide, which upon oxidation with H_2O_2 in presence of ammonium molybdate afforded the required sulfone fragment **4**.

Julia–Kocienski coupling[11] of the two fragments **3** and **4** was optimized after screening several conditions by varying base, temperature, stoichiometries and additives (solvating agents) (see ESI‡). Finally, sulfone **4** was treated with two equivalents of KHMDS and then with aldehyde **3** at −78 °C to afford the coupled product **18** (Scheme 5) in 72% yield. The geometry of the newly formed olefin was confirmed as the



Scheme 4 Reagents and conditions: (a) Et_3N, TBSOTf, CH_2Cl_2, rt, 24 h; (b) CH_3CHO, $TiCl_4$, CH_2Cl_2, −78 °C, 5 min, 59%, 98% (brsm); (c) MOMCl, DIPEA, DMAP, CH_2Cl_2, 16 h, 96%; (d) $LiAlH_4$, THF, 0 °C, 5 min, 90%; (e) (i) PPh_3, DIAD, 1-phenyl-1*H*-tetrazole-5-thiol, THF, 0 °C, 30 min, 90%; (ii) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, rt, 6 h, 85%.

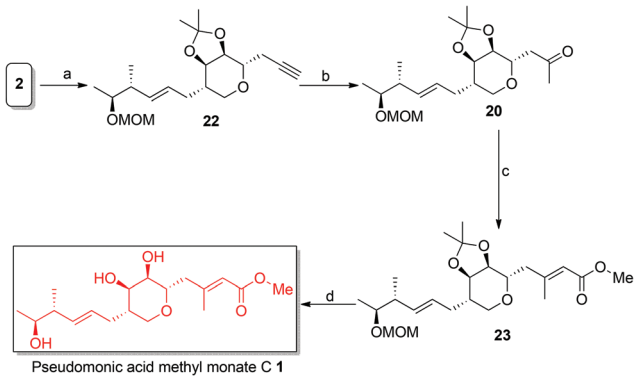


Scheme 5 Reagents and conditions: (a) KHMDS, then **3**, −78 °C, THF, 3 h, 72%; (b) TBAF, THF, rt, 6 h, 90%; (c) (i) Et_3N, MsCl, CH_2Cl_2, 0 °C, 5 min; (ii) NaCN, 18-crown-6, DMSO, 90 °C, 1 h, 86% from **2**; (d) MeLi, Et_2O, 0 °C, 1 h.

E diastereomer (based on coupling constants 15.4 Hz and 15.3 Hz in ^{1}H NMR) after cleavage of the silyl ether.

Having the required central tetrahydropyran nucleus along with the side arm with required stereochemistry, we focussed further on one carbon homologated ketone formation. Towards this, we initially adopted the nitrile path, wherein the alcohol **2** was converted to nitrile **19** in a two step process and was then treated with MeLi to obtain the required ketone **20**. However, coincidentally when the nitrile was treated with MeLi, a retro oxy-Michael product **21** was always formed predominantly along with the desired ketone **20** in minor amounts.

To get better yields of the ketone, we chose an alternate strategy *i.e.*, an alkyne hydration sequence.[12] Accordingly, the alcohol **2** was converted to the corresponding triflate and then coupled with trimethylsilyl acetylene and subjected to desilylation with K_2CO_3 to afford alkyne **22**. Alkyne **22** was subjected to Hg^{2+} catalyzed hydration to afford ketone **20** in 88% yield (Scheme 6). Ketone **20** upon Horner–Wadsworth–Emmons



Scheme 6 Reagents and conditions: (a) (i) 2,6-lutidine, Tf_2O, CH_2Cl_2, −78 °C, 5 min; (ii) LDA, TMS-acetylene, HMPA, THF −78 °C–rt, 2 h; (iii) K_2CO_3, MeOH, rt, 2 h, 76% from **2**; (b) $Hg(OAc)_2$, PPTS, THF, pH = 7 buffer, 50 °C, 30 min, 88%; (c) methyl diethylphosphanoacetate, KHMDS, then ketone **24**, rt, 16 h, 80%; (f) 2 N HCl, THF, rt, 2 h, 90%.

olefination[4b] with methyl diethylphosphanoacetate gave α,β-unsaturated ester **23**, the precursor for methyl monate C. Finally, deprotection of acid sensitive groups (MOM and acetonide) in **23** with aq. HCl afforded pseudomonic acid methyl monate C **1**. The analytical data of this synthetic compound was found to be in good agreement with the data reported earlier.[4e]

Intermediate **23** has a unique C1–C14 pseudomonic acid family carbon skeleton with appropriate chirality and functional groups for further manipulations towards other related natural products: pseudomonic acids, marinolic acids and thiomarinols. In addition, the retro oxy-Michael intermediate **21** forms a promising intermediate for the synthesis of mupirocins.

Conclusion

In conclusion, we have established a stereoselective strategy for the synthesis of the advanced key intermediates **23** and **21** which can be used for the synthesis of thiomarinols and mupirocins. The strategy has been successfully applied to the total synthesis of pseudomonic acid methyl monate C (in 18 longest linear steps with an overall yield of 10.1% from known diol **6**). Functional group manipulations of **2**/**21**/**23** for further elaboration towards the synthesis of thiomarinols and mupirocins are currently being investigated.

Experimental section

General methods

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent on a 300 MHz or 500 MHz spectrometer at ambient temperature. The coupling constant J is given in Hz. The chemical shifts are reported in ppm on a scale downfield from TMS as internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sext =

sextet, m = multiplet, br = broad. FTIR spectra were recorded on KBr pellets and reported in wave number (cm^{-1}). Optical rotations were measured on a digital polarimeter using a 1 mL cell with a 1 dm path length. For low (MS) and high (HRMS) resolution, *m*/*z* ratios are reported as values in atomic mass units. Mass analysis was done in ESI mode. All reagents were reagent grade and used without further purification unless specified otherwise. Solvents for reactions were distilled prior to use: THF, and diethyl ether were distilled from Na and benzophenone ketyl; CH_2Cl_2 from CaH_2. All air- or moisture-sensitive reactions were conducted under a nitrogen or argon atmosphere in flame-dried or oven-dried glassware with magnetic stirring. Column chromatography was carried out using silica gel (100–200 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use.

(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-(furan-2-yl)ethanol (9)

To a magnetically stirred solution of diol **6** (4.00 g, 31.3 mmol) in CH_2Cl_2 (100 mL), imidazole (4.25 g, 62.5 mmol) was added at 0 °C temperature. After 5 min TBDMSCl (4.94 g, 32.8 mmol) was added at the same temperature. Stirring was continued at rt until complete consumption of starting material occurred (monitored by TLC, *ca*. 16 h). The reaction mixture was diluted with water (100 mL), the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product which upon column purification (hexane–EtOAc 9 : 1) gave alcohol **9** (6.80 g, 90%) as a colourless oil. R_f = 0.55 (hexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ = −19.68 (*c* 1.20, $CHCl_3$), Lit[6e] $[\alpha]_D^{22}$ = +20.8 (*c* 0.6, $CHCl_3$) (for opposite enantiomer); IR (KBr): 3422, 2954, 2931, 2858, 1467, 1255, 119, 840, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (dd, *J* = 1.5, 0.6 Hz, 1H), 6.34 (dd, *J* = 3.0, 2.2 Hz, 1H), 6.31 (d, *J* = 3.2, Hz, 1H), 4.77–4.74 (m, 1H), 3.90–3.82 (m, 2H), 2.85 (d, *J* = 4.0 Hz, 1H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.7, 141.9, 110.1, 106.9, 68.3, 65.7, 25.8, 18.2, −5.5 ppm; HRMS (ESI) for $C_{12}H_{22}O_3SiNa$ $[M + Na]^+$ found 265.1229, calcd 265.1230.

(2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-hydroxy-2*H*-pyran-3(6*H*)-one (10)

To a magnetically stirred solution of furfuryl alcohol **9** (3.00 g, 12.4 mmol) in THF–H_2O (4 : 1, 40 mL), solid $NaHCO_3$ (2.08 g, 24.8 mmol), NaOAc·$3H_2O$ (1.85 g, 13.6 mmol) and finally NBS (2.20 g, 12.4 mmol) were added at 0 °C temperature. Within 5 min all the starting material was consumed and the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with sat. aq. $Na_2S_2O_3$ (30 mL) followed by brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue obtained was purified by silica gel column chromatography (hexane–EtOAc 4 : 1) to give **10** (1 : 3 mixture of α, β anomers) as a yellow oil (3.04 g, 95%); R_f = 0.55 (hexane–EtOAc 3 : 2); IR (KBr): 3387, 2931, 2858, 1700, 1466, 1367, 1124, 1030, 835, 779 cm^{-1}; **Major anomer**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.94 (dd, *J* = 10.4, 3.1 Hz, 1H), 6.16 (d, *J* = 10.5 Hz, 1H), 5.49–5.43 (m, 1H), 4.38 (t, *J* = 2.1 Hz, 1H), 4.06 (dd, *J* = 11.1, 2.4 Hz, 1H), 4.04 (d, *J* = 3.7 Hz, 1H), 3.91 (dd, *J* = 11.1, 2.0 Hz, 1H), 0.85 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H) ppm. **Minor anomer** δ 6.92 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.14 (d, *J* = 10.7 Hz, 1H), 4.56 (t, *J* = 3.7 Hz, 1H) ppm; **Major anomer**: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.7, 147.0, 127.2, 86.8, 79.6, 65.4, 25.5, 18.1, −5.9 ppm; **Minor anomer** δ 145.7, 127.8, 87.8, 76.4, 63.2, 25.7, −5.5 ppm; HRMS (ESI) for $C_{12}H_{22}O_4SiNa$ $[M + Na]^+$ found 281.11714, calcd 281.11796.

(6*S*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yl acetate (11)

To a magnetically stirred solution of lactol **10** (3.0 g, 11.6 mmol) in CH_2Cl_2 (30 mL) pyridine (1.87 mL, 23.25 mmol) was added at 0 °C followed by Ac_2O (1.3 mL, 12.8 mmol) at the same temperature. Within 1 h all the lactol was consumed and the reaction was then neutralized with 0.5 N HCl (51 mL) at 0 °C and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water (30 mL) followed by sat. aq. $NaHCO_3$ (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of CH_2Cl_2 *in vacuo* gave the crude product, which in turn was purified by column chromatography (hexane–EtOAc, 9 : 1) to give desired acetate **11** (1 : 2 mixture of α, β anomers) as a yellow viscous oil (3.14 g, 90%); R_f = 0.50 (hexane–EtOAc 7 : 3). IR (KBr): 2930, 2857, 1757, 1701, 1467, 1217, 1133, 934, 836, 778 cm^{-1}; **Major anomer**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.91 (dd, *J* = 10.3, 3.4 Hz, 1H), 6.61 (d, *J* = 3.4 Hz, 1H), 6.24 (d, *J* = 10.3 Hz, 1H), 4.49 (dd, *J* = 4.3, 2.7 Hz, 1H), 4.08 (dd, *J* = 11.4, 4.3 Hz, 1H), 4.02 (dd, *J* = 11.4, 2.3 Hz, 1H), 2.85 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. **Minor anomer**: δ 6.85 (dd, *J* = 10.3, 2.5 Hz, 1H), 6.58 (dd, *J* = 2.5, 1.1 Hz, 1H), 6.24 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.33 (dd, *J* = 6.4, 3.7 Hz, 1H), 3.96 (dd, *J* = 11.2, 3.7 Hz, 1H), 2.14 (s, 3H) ppm; **Major anomer**: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.7, 169.4, 142.1, 129.1, 87.1, 77.9, 62.7, 25.7, 20.9, 18.2, −5.4 ppm; **Minor anomer**: δ 193.5, 143.0, 129.0, 87.1, 80.5, 64.0, 21.0 ppm; HRMS (ESI) for $C_{14}H_{24}O_5SiNa$ $[M + Na]^+$ found 323.1281, calcd 323.1285.

(*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2*H*-pyran-3(6*H*)-one (12)

To a magnetically stirred solution of acetate **11** (1.5 g, 5.00 mmol) and triethylsilane (1.59 mL, 10.0 mmol) in CH_2Cl_2 (20 mL), $BF_3{\cdot}OEt_2$ (0.18 mL, 1.25 mmol) was added at −78 °C, stirring was continued until complete consumption of starting material occurred (*ca*. 1 h). The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) then extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (20 mL), and dried over anhydrous Na_2SO_4. Evaporation of CH_2Cl_2 *in vacuo* gave the crude product, which was subjected to silica gel column chromatography (hexane–EtOAc 19 : 1) to give desired enone **12** as a light yellow oil (0.97 g, 80%). R_f = 0.60 (hexane–EtOAc 4 : 1); $[\alpha]_D^{25}$ = +9.58 (*c* 0.95, $CHCl_3$); IR (KBr): 2930, 2857, 1694, 1466, 1255, 1130, 836, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (ddd, *J* = 18.5, 3.4, 1.8 Hz, 1H), 6.15 (dt, *J* = 10.4, 2.0 Hz, 1H),

4.62 (ddd, J = 18.3, 3.6, 1.8 Hz, 1H), 4.40 (dddd, J = 18.5, 3.7, 2.4, 1.2 Hz, 1H), 4.11 (ddd, J = 5.3, 2.4, 1.4 Hz, 1H), 4.08 (dd, J = 11.3, 2.4 Hz, 1H), 3.99 (dd, J = 11.3, 5.3 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.7, 148.3, 126.9, 81.4, 64.0, 63.5, 25.8, 18.3, −5.5 ppm; HRMS (ESI) for $C_{12}H_{23}O_3Si$ $[M + H]^+$ found 243.14050, calcd 243.14110.

(2*S*,3*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3,6-dihydro-2*H*-pyran-3-ol (5)

To a magnetically stirred solution of enone **12** (2.00 g, 8.20 mmol) in CH_2Cl_2 (20 mL), DIBAL-H (5.1 mL of 25% in toluene, 9.00 mmol) was added at −78 °C temperature. Within 5 min all the enone was consumed (monitored by TLC) and the reaction mixture was quenched with sat. aq. sodium potassium tartrate (20 mL) then diluted with CH_2Cl_2 (20 mL) and stirred at rt for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 9 : 1) afforded *anti* alcohol **13** (319 mg, 15.8%) followed by *syn* alcohol **5** (1.59 g, 79.2%) as a colourless oil. R_f = 0.55 (hexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ = +135.07 (c 1.40, $CHCl_3$) Lit.[8a] $[\alpha]_D^{24}$ = −144.3 (c 2.84, $CHCl_3$) for the opposite enantiomer; IR (KBr): cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.09–6.03 (m, 1H), 5.95 (ddd, J = 10.1, 5.0, 1.6 Hz, 1H), 4.26 (ddd, J = 16.9, 3.4, 1.7 Hz, 1H), 4.15 (ddd, J = 16.9, 4.0, 2.0 Hz, 1H), 3.97 (br s, 1H), 3.87 (dd, J = 10.6, 6.6 Hz, 1H), 3.81 (dd, J = 9.6, 5.1 Hz, 1H), 3.54 (dt, J = 6.3, 2.0 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 130.1, 126.6, 78.2, 66.0, 62.7, 62.4, 25.8, 18.2, −5.4, −5.5 ppm; HRMS (ESI) for $C_{12}H_{25}O_3Si$ $[M + H]^+$ found 245.15611, calcd 245.15675.

Methyl 2-((3*R*,6*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,6-dihydro-2*H*-pyran-3-yl)acetate (14)

To a magnetically stirred solution of alcohol **5** (4.00 g, 16.4 mmol) in trimethyl orthoacetate (10 mL), propionic acid (0.12 mL, 1.64 mmol) was added at rt and the reaction mixture was heated up to 140 °C while continuing the stirring until complete consumption of starting material occurred (*ca*. 6 h). The reaction mixture was quenched by the addition of solid $NaHCO_3$ (100 mg) and filtered. The filtrate was concentrated under reduced pressure to give the crude product which upon flash column purification (hexane–EtOAc 49 : 1) gave ester **14** (4.42 g, 90%) as a colourless oil. R_f = 0.55 (hexane–EtOAc 19 : 1); $[\alpha]_D^{25}$ = +11.67 (c 0.60, $CHCl_3$); IR (KBr): 2927, 2856, 1739, 1253, 1096, 838, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.94–5.86 (m, 1H), 5.76 (d, J = 10.4 Hz, 1H), 4.16–4.08 (m, 1H), 3.78–3.69 (m, 3H), 3.68 (s, 3H), 3.55 (dd, J = 10.2, 5.7 Hz, 1H), 2.57–2.38 (m, 3H), 0.90 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.8, 128.7, 128.3, 75.1, 67.0, 65.7, 51.5, 37.3, 31.4, 25.9, 18.4, −5.4 ppm; HRMS (ESI) for $C_{15}H_{28}O_4SiNa$ $[M + H]^+$ found 323.16384, calcd 323.16491.

Methyl 2-((3a*R*,4*S*,7*S*,7a*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl)acetate (15)

To a magnetically stirred solution of ester **14** (2.5 g, 8.30 mmol) in acetone–H_2O (1 : 1, 50 mL), *N*-methylmorpholine *N*-oxide (1.48 g, 12.5 mmol) followed by OsO_4 (16.7 mL of 0.025 M solution in toluene, 0.416 mmol) were added at 0 °C, stirring was continued at rt for 24 h by which time all the starting material was consumed and the reaction was then quenched with sat. aq. Na_2SO_3 (25 mL), and extracted with EtOAc (4 × 20 mL), washed with brine (20 mL), and dried over anhydrous Na_2SO_4. Evaporation of solvents *in vacuo* gave the crude product, which was subjected to silica gel column chromatography (hexane–EtOAc 3 : 2) to give diol **15a** as a colorless oil (2.37 g, 85%). R_f = 0.50 (hexane–EtOAc 1 : 1); $[\alpha]_D^{25}$ = +32.95 (c 1.2, $CHCl_3$); IR (KBr): 3448, 2930, 2859, 1736, 1465, 1254, 1091, 836, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.97–3.83 (m, 3H), 3.71–3.53 (m, 4H), 3.68 (s, 3H), 2.82 (br s, 1H), 2.58 (dd, J = 17.4, 10.5 Hz, 1H), 2.38 (dd, J = 17.3, 5.7 Hz, 1H), 2.41–2.35 (m, 1H), 1.67 (br s, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.7, 74.0, 69.4, 69.2, 65.7, 64.9, 51.7, 37.2, 33.5, 25.7, 18.1, −5.6, −5.7 ppm; HRMS (ESI) for $C_{15}H_{30}O_6SiNa$ $[M + Na]^+$ found 357.17062, calcd 357.17039.

To a magnetically stirred suspension of diol **15a** (2.00 g, 5.99 mmol) in EtOAc (10 mL), 2,2-dimethoxypropane (2.93 mL, 24.0 mmol), anhydrous Na_2SO_4 (5 g) and *p*-toluenesulfonic acid (0.1 g, 0.6 mmol) were added at 0 °C. Stirring was continued until complete consumption of starting material was observed (*ca*. 1 h) and then the reaction was quenched with solid $NaHCO_3$ (100 mg). The mixture was filtered and the filtrate was concentrated under reduced pressure to give the crude product which upon column purification through a short pad of silica gel (hexane–EtOAc 19 : 1) gave acetonide **15** (2.13 g, 95%) as a colourless oil. R_f = 0.50 (hexane–EtOAc 4 : 1); $[\alpha]_D^{25}$ = −11.70 (c 1.00, $CHCl_3$); IR (KBr): 2931, 2859, 1742, 1375, 1252, 1220, 1061, 837, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.10 (dd, J = 5.0, 1.6 Hz, 1H), 3.92 (dd, J = 8.7, 5.0 Hz, 1H), 3.82 (dd J = 11.5, 2.2 Hz, 1H), 3.80–3.76 (m, 1H), 3.70–3.62 (m, 2H), 3.69 (s, 3H), 3.34 (ddd, J = 8.7, 5.6, 2.2 Hz, 1H), 2.57 (dd, J = 13.4, 7.1 Hz, 1H), 2.53–2.47 (m, 1H), 2.42 (dd, J = 13.3, 4.6 Hz, 1H), 1.50 (s, 3H), 1.36 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 108.9, 79.1, 75.2, 69.7, 65.9, 63.7, 51.7, 34.7, 33.7, 28.2, 26.4, 25.9, 18.4, −5.3 ppm; HRMS (ESI) for $C_{18}H_{34}O_6SiNa$ $[M + Na]^+$ found 397.20175, calcd 397.20169.

2-((3a*R*,4*S*,7*S*,7a*R*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-7-yl)-acetaldehyde (3)

To a magnetically stirred suspension of $LiAlH_4$ (0.41 g, 10.7 mmol) in THF (20 mL) ester **15** (4.00 g, 10.7 mmol) was added at 0 °C. Within 5 min all the starting material was consumed and the reaction mixture was then quenched with sat. aq. Na_2SO_4 (5 mL). Silica gel (5.00 g) was added and the result-

ing white suspension was stirred at rt for 30 min and filtered. The filtrate was concentrated under reduced pressure to give the crude product which upon column purification through a short pad of silica gel (hexane–EtOAc 4 : 1) gave alcohol **3a** (3.55 g, 96%) as a colourless oil. R_f = 0.50 (hexane–EtOAc 3 : 2); $[\alpha]_D^{25}$ = +18.40 (*c* 0.80, $CHCl_3$); IR (KBr): 3447, 2930, 2859, 1382, 1251, 1058, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.14–4.11 (m, 1H), 4.02 (dd, *J* = 8.1, 5.5 Hz, 1H), 3.85 (dd, *J* = 11.3, 2.3 Hz, 1H), 3.78–3.66 (m, 5H), 3.48 (ddd *J* = 7.7, 5.1, 2.3 Hz, 1H), 2.35 (br s, 1H), 2.19–2.11 (m, 1H), 1.82–1.63 (m, 2H), 1.50 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 108.4, 78.3, 76.3, 70.3, 66.1, 63.8, 60.2, 34.4, 33.8, 28.1, 26.2, 25.9, 18.4, −5.4 ppm; HRMS (ESI) for $C_{17}H_{34}O_5SiNa$ $[M + Na]^+$ found 369.20703, calcd 369.20677.

To a magnetically stirred solution of alcohol **3a** (1.00 g, 2.90 mmol) in CH_2Cl_2 (20 mL), Dess–Martin periodinane (1.46 g, 3.48 mmol) was added at 0 °C temperature. Stirring was continued until complete consumption of starting material was observed (*ca.* 2 h). The reaction mixture was filtered through a pad of celite and the filtrate was washed with sat. aq. $NaHCO_3$ (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 9 : 1) gave aldehyde **3** (0.94 g, 95%) as a colourless oil. R_f = 0.55 (hexane–EtOAc 5 : 1); $[\alpha]_D^{25}$ = −24.50 (*c* 0.90, $CHCl_3$); IR (KBr): 2930, 2858, 1727, 1375, 1253, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.81 (t, *J* = 1.3 Hz, 1H), 4.06 (dd, *J* = 5.2, 2.5 Hz, 1H), 3.93 (dd, *J* = 8.7, 5.1 Hz, 1H), 3.81 (td, *J* = 11.4, 2.2 Hz, 2H), 3.66 (dd, *J* = 11.6, 5.3 Hz, 1H), 3.63 (ddd, *J* = 11.9, 2.3, 0.8 Hz, 1H), 3.35 (ddd, *J* = 8.6, 5.3, 2.2 Hz, 1H), 2.75 (ddd, *J* = 16.4, 6.9, 1.0 Hz, 1H), 2.66–2.59 (m, 1H), 2.42 (dd, *J* = 16.5, 5.7 Hz, 1H), 1.50 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.2, 108.9, 79.0, 75.3, 69.7, 65.9, 63.6, 44.5, 31.4, 28.2, 26.3, 25.9, 18.4, −5.3 ppm; HRMS (ESI) for $C_{17}H_{32}O_5SiNa$ $[M + Na]^+$ found 367.19162, calcd 367.19112.

(2*S*,3*S*)-1-((6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[*c*]isothiazol-1-yl)-3-hydroxy-2-methylbutan-1-one (16)

To a magnetically stirred solution of propionate **8** (5.00 g, 18.5 mmol) in CH_2Cl_2 (40 mL), triethylamine (2.82 mL, 20.3 mmol) followed by *tert*-butyldimethylsilyl-*O*-triflate (4.66 mL, 20.3 mL) were added at room temperature. Stirring was continued for 24 h and then the resulting solution was added to a solution of acetaldehyde (1.14 mL, 20.3 mmol) and $TiCl_4$ (2.23 mL, 20.3 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After 5 min the reaction was quenched with sat. aq. NH_4Cl (20 mL), diluted with water (50 mL) and stirred at room temperature for 15 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 5 : 1) gave unreacted propionate **8** (2.00 g) and finally alcohol **16** (3.42 g, 59%, (98% brsm)) as a white solid (mp = 119–120). R_f = 0.45 (hexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ = −46.17 (*c* 1.2, $CHCl_3$); IR (KBr): 3526, 2959, 1698, 1683, 1307, 1216, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.90 (dd, *J* = 7.6, 5.1 Hz, 1H), 3.88–3.79 (m, 1H), 3.54 (d, *J* = 13.9 Hz, 1H), 3.45 (d, *J* = 13.9 Hz, 1H), 3.16–3.07 (m, 1H), 2.40–2.24 (m, 1H), 2.22–2.03 (m, 2H), 1.98–1.81 (m, 2H), 1.47–1.32 (m, 2H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 3H), 0.97 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.1, 71.5, 65.3, 53.1, 48.2, 47.6, 46.9, 44.6, 38.4, 32.8, 26.3, 21.8, 20.7, 19.8, 14.0 ppm; HRMS (ESI) for $C_{15}H_{26}O_4NS$ $[M + H]^+$ found 316.15682, calcd 316.15771.

(2*S*,3*S*)-1-((6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[*c*]isothiazol-1-yl)-3-(methoxymethoxy)-2-methylbutan-1-one (17)

To a stirred solution of alcohol **16** (4.00 g, 12.70 mmol) in CH_2Cl_2 (40 mL), MOMCl (4.06 mL of 50% solution in MeOAc, 25.4 mmol) followed by *N*,*N*-diisopropylethylamine (4.4 mL, 25.4 mmol) were added at 0 °C. Stirring was continued for 16 h by which time all the starting material was consumed. Sat. aq. NH_4Cl (10 mL) was added and the reaction was further diluted with water (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 9 : 1) gave MOM ether **17** (4.38 g, 96%) as a white solid (mp = 110–111). R_f = 0.65 (hexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ = −31.64 (*c* 1.1, $CHCl_3$); IR (KBr): 2989, 2960, 1684, 1460, 1334, 1233, 1133, 1035, 539 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.62 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 3.97–3.87 (m, 2H), 3.51 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 3.33 (s, 3H), 3.27–3.18 (m, 1H), 2.10–1.97 (m, 2H), 1.95–1.80 (m, 3H), 1.44–1.28 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.19 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.18 (s, 3H), 0.97 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.4, 95.2, 75.9, 65.0, 55.5, 53.0, 48.1, 47.6, 46.1, 44.6, 38.4, 32.7, 26.3, 20.6, 19.8, 17.2, 12.8 ppm; HRMS (ESI) for $C_{17}H_{29}O_5NSNa$ $[M + Na]^+$ found 382.16627, calcd 382.16586.

(2*R*,3*S*)-3-(Methoxymethoxy)-2-methylbutan-1-ol (7)

To a magnetically stirred suspension of $LiAlH_4$ (0.42 g, 11.1 mmol) in THF (20 mL) amide **17** (2.00 g, 5.57 mmol) was added at 0 °C. Within 5 min all the starting material was consumed and the reaction was quenched with sat. aq. Na_2SO_4 (5 mL) and then silica gel (5.00 g) was added and the resulting white suspension was further stirred at room temperature for 30 min and filtered. The filtrate was concentrated under reduced pressure to give the crude product which upon column purification through a short pad of silica gel (hexane–EtOAc 9 : 1 to 5 : 1) gave free sultam auxiliary (1.17 g, 98%) and alcohol **7** (0.74 g, 90%) as a colourless oil. Data for **7**: R_f = 0.30 (hexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ = +58.4 (*c* 0.55, $CHCl_3$); IR (KBr): 3446, 2931, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.74 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 3.72 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.69–3.63 (m, 1H), 3.57 (dd, *J* = 11.1, 6.1 Hz, 1H),

3.41 (s, 3H), 1.78–1.70 (m, 1H), 1.21 (d, J = 6.1 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 94.9, 77.0, 65.7, 55.5, 40.9, 17.6, 13.5 ppm; HRMS (ESI) for $C_7H_{16}O_3Na$ $[M + Na]^+$ found 171.0991, calcd 171.0992.

5-(((2*S*,3*S*)-3-(Methoxymethoxy)-2-methylbutyl)sulfonyl)-1-phenyl-1*H*-tetrazole (4)

To a magnetically stirred solution of alcohol **7** (0.50 g, 3.38 mmol) in THF (20 mL), PPh_3 (1.33 g, 5.07 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (0.90 g, 5.07 mmol) and finally diisopropyl azodicarboxylate (1.02 mL, 5.07 mmol) were added at 0 °C. Within 30 min all the starting material was consumed. THF was evaporated under reduced pressure and the crude mass was purified by silica gel column chromatography (hexane–EtOAc 19 : 1) to give the sulfide **4a** (0.94 g, 90%) as a colourless oil. R_f = 0.55 (hexane–EtOAc 5 : 1); $[\alpha]_D^{25}$ = +26.91 (c 0.55, $CHCl_3$); IR (KBr): 2930, 1633, 1597, 1498, 1385, 1097, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60–7.51 (m, 5H), 4.70 (d, J = 6.9 Hz, 1H), 4.60 (d, J = 6.9 Hz, 1H), 3.71–3.63 (m, 2H), 3.37 (s, 3H), 3.31 (dd, J = 12.7, 8.1 Hz, 1H), 2.14–2.03 (m, 1H), 1.21 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, 133.7, 130.0, 129.7, 123.8, 95.2, 75.8, 55.5, 38.6, 36.6, 16.9, 15.2 ppm; HRMS (ESI) for $C_{14}H_{21}O_2N_4S$ $[M + H]^+$ found 309.13715, calcd 309.13797.

To a magnetically stirred solution of sulfide **4a** (0.90 g, 2.92 mmol) in EtOH (10 mL), a precooled solution of ammonium molybdate tetrahydrate (1.08 g, 0.88 mmol) in 30% H_2O_2 (4 mL) was added at 0 °C. Stirring was continued until complete consumption of starting material occurred (*ca.* 12 h). Saturated aq. NaCl (10 mL) was added and the organic layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 9 : 1) gave sulfone **4** (0.84 g, 85%) as a colourless oil. R_f = 0.50 (hexane–EtOAc 5 : 1); $[\alpha]_D^{25}$ = +21.38 (c 0.75, $CHCl_3$); IR (KBr): 2932, 1343, 1153, 1038, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70–7.58 (m, 5H), 4.68 (d, J = 6.9 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.10 (dd, J = 14.6, 2.9 Hz, 1H), 3.68–3.63 (m, 1H), 3.55 (dd, J = 14.7, 9.2 Hz, 1H), 3.38 (s, 3H), 2.44–2.35 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.0, 133.0, 131.4, 129.6, 125.1, 95.1, 75.7, 58.2, 55.7, 33.9, 17.2, 16.6 ppm; HRMS (ESI) for $C_{14}H_{20}O_4N_4NaS$ $[M + Na]^+$ found 363.11041, calcd 363.10975.

tert-Butyl(((3a*R*,4*S*,7*S*,7a*R*)-7-((4*R*,5*S*,*E*)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran-4-yl)methoxy)dimethylsilane (18)

To a magnetically stirred solution of sulfone **4** (1.00 g, 2.94 mmol) in THF (20 mL), KHMDS (11.8 mL of 0.5 M solution in toluene, 5.88 mmol) was added at −78 °C. After stirring for 1 h, aldehyde **3** (1.01 g, 2.94 mmol) was added (5 mL THF) at the same temperature and stirred for 1 h. The mixture was allowed to warm to room temperature over 1 h by which time the reaction mixture turned into white cloudy suspension and the TLC analysis indicated complete consumption of the starting material. Solvents were removed under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 19 : 1) gave alkene **18** (0.97 g, 72%) as a colourless oil. R_f = 0.55 (hexane–EtOAc 9 : 1); $[\alpha]_D^{25}$ = −7.1 (c 1.4, $CHCl_3$); IR (KBr): 2929, 2858, 1459, 1375, 1250, 1041, 836, cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.50–5.37 (m, 2H), 4.67 (d, J = 7.0 Hz, 1H), 4.60 (d, J = 6.8 Hz, 1H), 4.13 (dd, J = 4.7, 2.1 Hz, 1H), 3.90 (dd, J = 8.9, 5.1 Hz, 1H), 3.82 (dd, J = 11.5, 1.9 Hz, 1H), 3.73–3.55 (m, 4H), 3.36 (s, 3H), 3.33–3.28 (m, 1H), 2.35–2.09 (m, 3H), 2.00–1.91 (m, 1H), 1.49 (s, 3H), 1.35 (s, 3H), 1.09 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.0, 127.8, 108.5, 95.1, 79.1, 76.5, 75.4, 69.8, 65.8, 63.8, 55.3, 42.1, 36.8, 33.7, 28.3, 26.3, 25.9, 18.4, 16.9, 15.7, −5.3 ppm; HRMS (ESI) for $C_{24}H_{46}O_6SiNa$ $[M + Na]^+$ found 481.29590, calcd 481.29559.

((3a*R*,4*S*,7*S*,7a*R*)-7-((4*R*,5*S*,*E*)-5-(Methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran-4-yl)methanol (2)

TBAF (2.62 mL of 1 M solution in THF, 2.62 mmol) was added dropwise to a magnetically stirred solution of TBS ether **18** (0.80 g, 1.75 mmol) in THF (10 mL) at 0 °C. Stirring was continued at rt until complete consumption of starting material occurred (*ca.* 2 h). THF was removed *in vacuo* to give the crude product which upon column purification (hexane–EtOAc 4 : 1) gave alcohol **2** (540 mg, 90%) as a colourless oil. R_f = 0.55 (hexane–EtOAc 3 : 2); $[\alpha]_D^{25}$ = −5.18 (c 1.1, $CHCl_3$); IR (KBr): 3454, 2930, 1456, 1244, 1050, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.47 (dd, J = 15.4, 6.6 Hz, 1H), 5.42 (dd, J = 15.3, 6.1 Hz, 1H), 4.67 (d, J = 6.9 Hz, 1H), 4.60 (d, J = 6.9 Hz, 1H), 4.14 (dd, J = 5.2, 2.1 Hz, 1H), 3.87 (dd, J = 9.2, 5.0 Hz, 1H), 3.81 (dd, J = 11.7, 2.9 Hz, 1H), 3.75 (dd, J = 11.4, 2.9 Hz, 1H), 3.68 (d, J = 11.6 Hz, 1H), 3.62–3.55 (m, 2H), 3.36 (s, 3H), 3.37–3.33 (m, 1H), 2.34–2.27 (m, 1H), 2.25–2.14 (m, 2H), 2.06–1.98 (m, 1H), 1.49 (s, 3H), 1.34 (s, 3H), 1.09 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.2, 127.6, 108.8, 95.1, 78.4, 76.5, 75.2, 70.1, 66.0, 63.3, 55.3, 42.2, 36.7, 33.8, 28.2, 26.3, 17.1, 15.8 ppm; HRMS (ESI) for $C_{18}H_{32}O_6Na$ $[M + Na]^+$ found 367.20954, calcd 367.20911.

2-((3a*S*,4*S*,7*S*,7a*R*)-7-((4*R*,5*S*,*E*)-5-(Methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran-4-yl)acetonitrile (19)

To a stirred solution of alcohol **2** (0.35 g, 1.01 mmol) in CH_2Cl_2 (5 mL), Et_3N (0.42 mL, 3.05 mmol) followed by methanesulfonyl chloride (0.12 mL, 1.52 mmol) were added at 0 °C. Within 5 min all the starting material was consumed, the reaction mixture was quenched with sat. aq. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the mesylate which was directly used for the next step. To a stirred solution of mesylate in DMSO (5 mL) were added 18-crown-6 (66 mg, 0.25 mmol) and NaCN (0.25 g, 5.05 mmol) and the mixture was heated up to 90 °C. Within 1 h all the starting material was consumed

and the reaction mixture was then diluted with ice cold water (20 mL), and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure to give crude product, which upon column purification (hexane–EtOAc 9 : 1) gave cyanide **19** (0.31 g, 86%) as a colourless oil. R_f = 0.55 (hexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ = −10.00 (*c* 0.7, $CHCl_3$); IR (KBr): 2974, 2930, 2251, 1456, 1376, 1218, 1040, 977 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.53–5.37 (m, 2H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 4.16 (dd, *J* = 4.9, 1.9 Hz, 1H), 3.79 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.73 (d, *J* = 2.1 Hz, 2H), 3.63–3.55 (m, 1H), 3.47–3.40 (m, 1H), 3.37 (s, 3H), 2.72 (dd, *J* = 16.8, 3.6 Hz, 1H), 2.52 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.36–2.14 (m, 3H), 2.07–1.98 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.6, 127.2, 117.0, 109.2, 95.0, 76.4, 75.3, 74.0, 72.7, 66.5, 55.3, 42.2, 36.3, 33.8, 28.2, 26.9, 21.74, 17.0, 15.8 ppm; HRMS (ESI) for $C_{19}H_{31}O_5NNa$ $[M + Na]^+$ found 376.21008, calcd 376.20944.

(3a*S*,4*S*,7*S*,7a*R*)-7-((4*R*,5*S*,*E*)-5-(Methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyl-4-(prop-2-yn-1-yl)tetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran (22)

To a stirred solution of alcohol **2** (0.50 g, 1.453 mmol) in CH_2Cl_2 (10 mL), 2,6-lutidine (0.34 mL, 2.90 mmol) was added followed by trifluoromethanesulfonic anhydride (0.37 mL, 2.18 mmol) at −78 °C. After 10 min all the starting material was consumed and the reaction was quenched with sat. aq. NH_4Cl (5 mL) while allowing the reaction mixture to attain room temperature. The reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product which upon column purification (hexane–EtOAc 19 : 1) through a short pad of silica gel gave the corresponding triflate (0.68 g, 98%) which was directly utilized for the next step.

HMPA (2.55 mL, 14.5 mmol) was added to the freshly generated lithium diisopropylamide (0.78 g, 7.27 mmol) in THF (20 mL) at −78 °C. After 5 min trimethylsilyl acetylene (1.03 mL, 7.27 mmol) was added at the same temperature, stirred for 30 min and a solution of the above prepared triflate in THF (5 mL) was added slowly. Stirring was continued for 1 h then the reaction mixture was warmed to rt during 1 h whereupon TLC analysis showed clean conversion of triflate to alkyne. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which was dissolved in MeOH (5 mL) and K_2CO_3 (0.30 g, 2.18 mmol) was added at 0 °C and stirring continued until complete consumption of starting material was observed (*ca*. 2 h). Brine (10 mL) was added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 19 : 1) through a short pad of silica gel afforded alkyne **22** (0.39 g, 76%). R_f = 0.50 (hexane–EtOAc 5 : 1); $[\alpha]_D^{25}$ = −8.00 (*c* 0.25, $CHCl_3$); IR (KBr): 2927, 2125, 1459, 1374, 1217, 1105, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.48 (dd, *J* = 15.4, 6.4 Hz, 1H), 5.44 (dd, *J* = 15.3, 5.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.15 (dd, *J* = 4.8, 2.0 Hz, 1H), 3.89 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.76 (dd, *J* = 11.6, 3.0 Hz, 1H), 3.72 (dd, *J* = 11.6, 1.1 Hz, 1H), 3.62–3.53 (m, 1H), 3.40–3.35 (m, 1H), 3.36 (s, 3H), 2.63–2.59 (m, 1H), 2.40 (ddd, *J* = 17.0, 6.7, 2.6 Hz, 1H), 2.34–2.17 (m, 3H), 2.04–1.97 (m, 1H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.49 (s, 3H), 1.35 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.2, 127.7, 108.8, 95.2, 80.6, 76.5, 76.2, 75.4, 72.9, 69.7, 66.6, 55.4, 42.2, 36.7, 33.9, 28.3, 26.3, 22.7, 17.0, 15.8 ppm; HRMS (ESI) for $C_{20}H_{32}O_5Na$ $[M + Na]^+$ found 375.21182, calcd 375.21420.

1-((3a*S*,4*S*,7*S*,7a*R*)-7-((4*R*,5*S*,*E*)-5-(Methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran-4-yl)propan-2-one (20)

From **19**: MeLi (0.27 mL of 1.6 M solution in Et_2O, 0.42 mmol) was added dropwise to a magnetically stirred solution of nitrile **19** (0.10 g, 0.28 mmol) in Et_2O (5 mL) at 0 °C. Stirring was continued at room temperature until complete consumption of starting material occurred (*ca*. 30 min). The reaction mixture was quenched with sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (2 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 9 : 1) gave ketone **20** (30 mg, 30%) as a colourless oil and retro oxy-Michael product **21** (66 mg, 66%) as a colourless oil.

From **22**: To a magnetically stirred solution of alkyne **22** (0.40 g, 1.14 mmol) in THF pH = 7 buffer (9 : 1, 8 mL), TsOH (0.43 g, 1.71 mmol) followed by $Hg(OAc)_2$ (0.11 g, 0.342 mmol) were added at 0 °C and the reaction mixture was stirred at 50 °C until complete consumption of starting material (*ca*. 30 min), the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which upon column purification through a short pad of silica gel (hexane–EtOAc 9 : 1) gave ketone **20** (370 mg, 88%) as a colourless oil. R_f = 0.50 (hexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ = −4.0 (*c* 0.2, $CHCl_3$); IR (KBr): 2926, 2856, 1739, 1456, 1375, 1225, 1044, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.48–5.39 (m, 2H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.13–4.11 (br m, 1H), 3.78–3.68 (m, 3H), 3.63–3.54 (m, 2H), 3.36 (s, 3H), 2.69–2.65 (m, 1H), 2.59–2.53 (m, 1H), 2.33–2.15 (m, 3H), 2.19 (s, 3H), 2.02–1.97 (m, 1H), 1.50 (s, 3H), 1.34 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.8, 135.2, 127.6, 108.8, 95.1, 76.4, 75.3, 74.5, 73.6, 66.5, 55.3, 46.9, 42.2, 36.6, 34.0, 30.8, 28.2, 26.3, 17.0, 15.8 ppm; HRMS (ESI) for $C_{20}H_{34}O_6Na$ $[M + Na]^+$ found 393.22577, calcd 393.22476.

(*E*)-3-((4*S*,5*R*)-5-((2*S*,6*R*,7*S*,*E*)-1-Hydroxy-7-(methoxymethoxy)-6-methyloct-4-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-acrylonitrile (21)

R_f = 0.40 (hexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ = +1.6 (*c* 0.65, $CHCl_3$); IR (KBr): 3468, 2931, 2226, 1634, 1454, 1377, 1217, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.87 (dd, *J* = 16.2, 5.2 Hz, 1H), 5.67 (dd, *J* = 16.3, 1.8 Hz, 1H), 5.49–5.39 (m, 2H), 4.73–4.70 (m, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.22 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.67 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.61–3.48 (m, 2H), 3.37 (s, 3H), 2.36–2.31 (m, 1H), 2.30–2.24 (m, 1H), 2.12–2.04 (m, 1H), 1.83–1.76 (m, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.0, 135.1, 127.2, 117.1, 108.5, 101.4, 95.1, 79.2, 77.2, 76.7, 63.2, 55.4, 42.4, 40.3, 31.8, 27.6, 25.2, 17.3, 16.1 ppm; HRMS (ESI) for $C_{19}H_{31}O_5NNa$ $[M + Na]^+$ found 376.20941, calcd 376.20944.

(*E*)-Methyl 4-((3a*S*,4*S*,7*S*,7a*R*)-7-((4*R*,5*S*,*E*)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran-4-yl)-3-methylbut-2-enoate (23)

To a magnetically stirred solution of methyl diethyl phosphonoacetate (0.28 g, 1.35 mmol) in THF (10 mL), KHMDS (2.70 mL of 0.5 M solution in toluene, 1.35 mmol) was added at rt. After 1 h, ketone **20** (0.10 g, 0.270 mmol) was added (2 mL, THF) at room temperature while stirring was continued until complete consumption of starting material occurred (*ca.* 16 h). Solvents were removed under reduced pressure and the residue was column chromatographed (hexane–EtOAc 19 : 1) through a short pad of silica gel to give ester **23** (92 mg, 80%) as a colourless oil. R_f = 0.65 (hexane–EtOAc 5 : 1); $[\alpha]_D^{25}$ = −12.40 (*c* 0.25, $CHCl_3$); IR (KBr): 2925, 2854, 1718, 1648, 1459, 1376, 1220, 1150, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.75 (br s, 1H), 5.50–5.37 (m, 2H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.12 (dd, *J* = 4.5, 1.7 Hz, 1H), 3.79–3.48 (m, 4H), 3.68 (s, 3H), 3.44–3.34 (m, 1H), 3.36 (s, 3H), 2.49 (br d, *J* = 14.2 Hz, 1H), 2.35–2.10 (m, 3H), 2.20 (s, 3H), 2.08–1.85 (m, 2H), 1.49 (s, 3H), 1.35 (s, 3H), 1.09 (d, *J* = 6.2 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0, 156.8, 135.2, 127.7, 117.1, 108.6, 95.1, 76.5, 76.4, 75.4, 74.1, 66.5, 55.4, 50.8, 44.0, 42.2, 36.7, 34.1, 28.3, 26.3, 19.1, 17.0, 15.8 ppm; HRMS (ESI) for $C_{23}H_{38}O_7Na$ $[M + Na]^+$ found 449.24763, calcd 449.25097.

Pseudomonic acid methyl monate C (1)

To a magnetically stirred solution of ester **23** (20 mg, 47.0 μmol) in THF (2 mL), 2 N HCl (2 mL) was added at 0 °C. Stirring was continued until complete consumption of starting material (*ca.* 4 h) was observed. The reaction mixture was neutralized with solid $NaHCO_3$ and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which upon column purification (hexane–EtOAc 1 : 1) gave pseudomonic acid methyl monate C **1** (14.4 mg, 90%) as a colourless oil. R_f = 0.55 (EtOAc); $[\alpha]_D^{25}$ = +9.60 (*c* 0.2, $CHCl_3$); IR (KBr): 3424, 2924, 2854, 1714, 1645, 1440, 1379, 1229, 1154 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.75 (br s, 1H), 5.47 (dt, *J* = 15.3, 6.7 Hz, 1H), 5.38 (dd, *J* = 15.4, 8.1 Hz, 1H), 3.88 (m, 1H), 3.77 (dd, *J* = 11.7, 2.9 Hz, 1H), 3.70–3.67 (m, 1H), 3.66 (s, 3H), 3.54–3.46 (m, 2H), 3.44–3.39 (m, 1H), 2.60 (br d, *J* = 14.6 Hz, 1H), 2.28–2.22 (m, 2H), 2.19 (s, 3H), 2.16–2.00 (m, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0, 157.2, 134.5, 129.4, 117.1, 74.6, 71.1, 70.4, 68.9, 64.8, 50.8, 44.8, 43.1, 41.9, 32.3, 20.3, 19.1, 16.7 ppm; HRMS (ESI) for $C_{23}H_{38}O_7Na$ $[M + Na]^+$ found 365.19316, calcd 365.19346.

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