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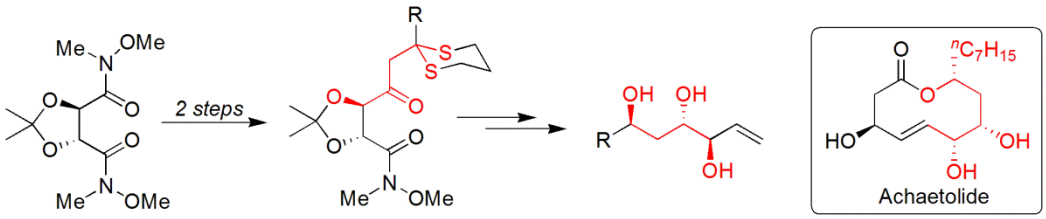

Enantiospecific Synthesis of Functionalized polyols from Tartaric Acid Using Ley's Dithiaketalization: Application to the Total Synthesis of Achaetolide

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Abstract: Synthesis of chiral tetrols and 1,2,4-triols with varied substitutions was accomplished from tartaric acid. Pivotal reaction in the synthesis was the use of Ley's dithianylation of an alkynyl ketone derived from tartaric acid. Application of the strategy was demonstrated in the total synthesis of decanolactone achaetolide.

Keywords: polyols, total synthesis, macrolactones, natural products, polyketides

Introduction

Polyols with varied substitutions are ubiquitous structural units present in a number of polyketide natural products.[1] Amongst the polyol containing compounds, the 1,2,4-triol unit **1** is a core/latent structural unit frequently encountered in a number of macrolactone natural products. Some of the examples include macrolactone natural products such as achaetolide **2**, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone **3**, seimatopolide A **4**, Sch725674 **5,** and the linear polyol containing natural product fostriecin **6** (Fig. 1).

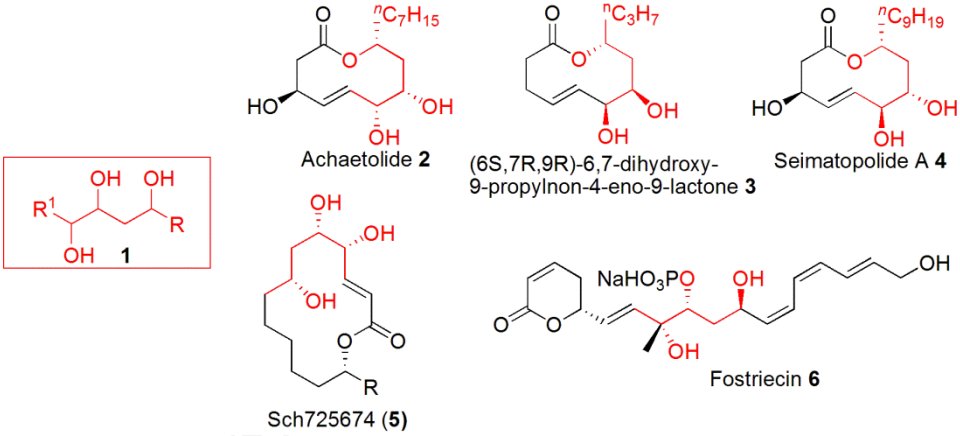


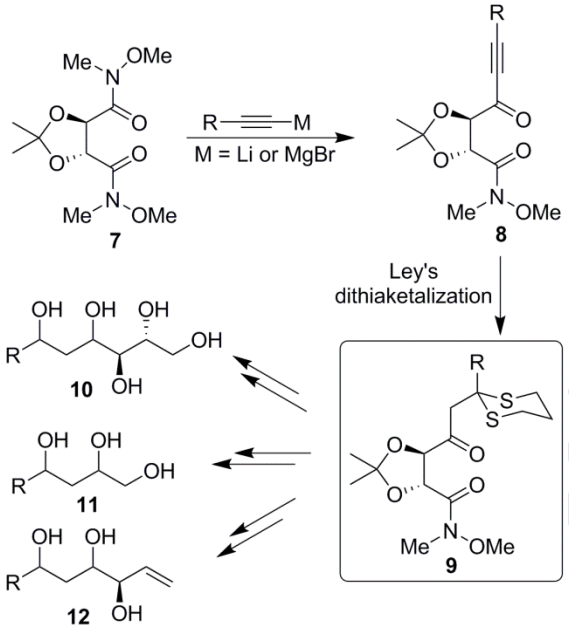
Fig 1. Natural products possessing the 1,2,4-triol unit

One of the best ways to synthesize the 1,3-diol present in a triol system is the reduction of the corresponding β-hydroxy ketone, which in turn can be accessed by the well-established asymmetric aldol reaction.[2] While the aldol reaction strategy renders the products with high degree of selectivity, development of non-aldol reaction for aldol products is of significant importance in organic synthesis. In this context, pioneering work by Smith's group established the use of 1,3-dithiane linchpins as excellent acyl anion equivalents and has exemplified their use in the synthesis of structurally complex natural products.[3] An attractive strategy for the synthesis of β-ketodithianes, a virtual surrogate of 1,3-diols is the procedure reported by Ley's group utilized the addition of 1,3-propanedithiol to alkynyl ketones.[4] Generality of this reaction is showcased by Ley's group by the synthesis of an impressive array of compounds. Herein, we report a facile approach for polyol synthesis, particularly to the synthesis of 1,2,4-triols utilizing a combination of chiral pool tartaric acid and Ley's dithiaketalization reaction and application of the strategy to the total synthesis of decanolactone natural product achaetolide.

Results and Discussion

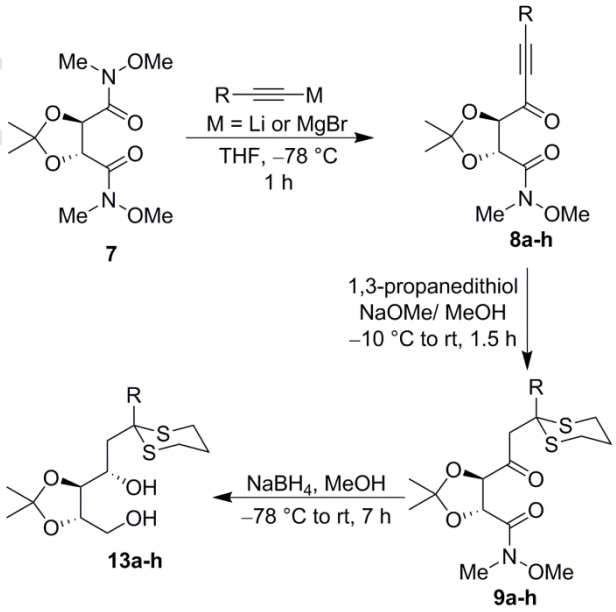
For a decade, our efforts in the use of chiral pool tartaric acid in natural product synthesis culminated in establishing the γ-hydroxy amides derived from tartaric acid as excellent building blocks.[5] Key

reaction in our methodology is the desymmetrization of tartaric acid amide **7** with various alkyl/aryl and alkenyl Grignard reagents followed by stereoselective reduction of the resultant ketones. We reasoned that the addition of alkynyl Grignard reagents would lead to the mono keto amide **8**, which on Ley's dithiaketalization should provide the β-1,3-dithianyl ketone **9**. Elaboration of **9** will lead to the polyol systems **10, 11** or **12** present in a number of natural products (Scheme-1).[6]



Scheme 1: Proposed synthesis of polyols from the bis-Weinreb amide of tartaric acid

Accordingly, the synthetic sequence commenced with the addition of R-C≡C-Li/MgBr to the *bis*-Weinreb amide **7**[7] derived from tartaric acid to afford the mono-keto amides **8a-h** in 48-89% yield. Addition of 1,3-propanedithiol to the alkynyl ketones **8a-h** under Ley's conditions (NaOMe/MeOH) was facile and the corresponding β-dithianyl ketones **9a-h** were obtained in excellent yields (see table-1). Stereoselective reduction of **9a-h** with excess $NaBH_4$ afforded the corresponding 1,4-diol **13a-h** in good yields as a single diastereomer (*erythro* isomer) (Scheme-2).[8] It is worth noting that the reduction of structurally similar γ-oxoamides devoid of the dithiane moiety with K-Selectride furnished the corresponding *threo* isomer.[6a, 8b] This observation has been used for the assignment of stereochemistry at the newly formed center in **13a-h**.



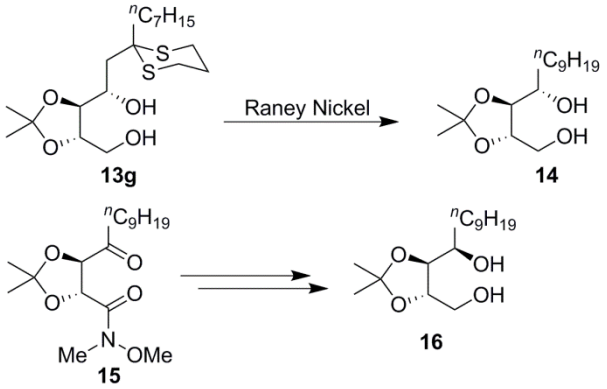
Scheme 2: Synthesis of polyhydroxy 1,3-dithiane from tartaric acid amide

Table 1: Synthesis of alkynyl ketones **8a-h** from the *bis*-Weinreb amide **7** and their elaboration to polyhydroxy 1,3-dithiane **13a-h**

S. No.	R-C≡C-M	Yield % [a]		
		8	**9**	**13**
1	H-C≡C-MgBr	**8a** (48)[b]	**9a** (84)	**13a** (75)
2	H_3C-C≡C-MgBr	**8b** (65)	**9b** (88)	**13b** (81)
3	CH_2=CH-$(CH_2)_2$-C≡C-MgCl	**8i** (63)	**9i** (97)	**13i** (95)
4	Me_3Si-C≡C-Li	**8c**-[c]	**9c** (64)[d,e]	**13a** (75)[f]
5	Ph-C≡C-Li	**8d** (60)	**9d** (90)	**13d** (71)
6	H_7C_3-C≡C-Li	**8e** (88)	**9e** (98)	**13e** (82)
7	$H_{13}C_6$-C≡C-Li	**8f** (63)	**9f** (95)	**13f** (85)
8	$H_{15}C_7$-C≡C-Li	**8g** (89)	**9g** (96)	**13g** (82)
9	TBSO-$(CH_2)_3$-C≡C-Li	**8h** (76)	**9h** (95)	**13h** (87)

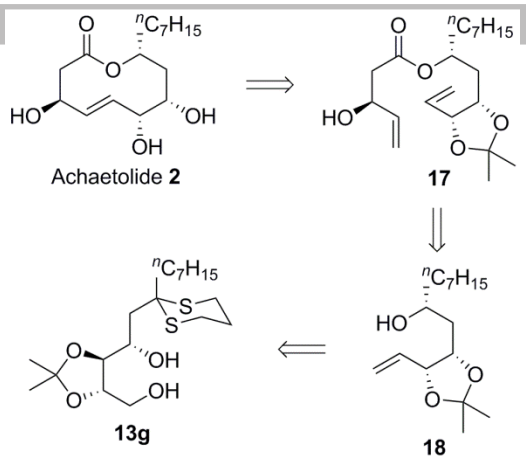
[a]All yields refer to yields after chromatography. [b]Formation of the enamine **8aa** (29% yield) resulting from the addition of *N,O*-dimethoxy hydroxylamine (Weinreb amine) to the alkynone **8a** is observed. See ref. 9 and supporting information. [c]Monoalkyl ketone **8c** is not isolated and is proceeded to the next step without purification. [d]Yield obtained after two steps. [e]24% of the desilyalted product **9a** was also obtained. [f]Reduction always led to the formation of desilylated product **13a**.

Thus, desulfurization of the 1,3-dithiane moiety in **13g** furnished the 1,4-diol **14** possessing the *erythro* stereochemistry was compared with the corresponding known *threo* isomer **16** obtained by from the γ-oxo-amide **15** (see Supporting Information for the synthesis of **16)** (Scheme-3).



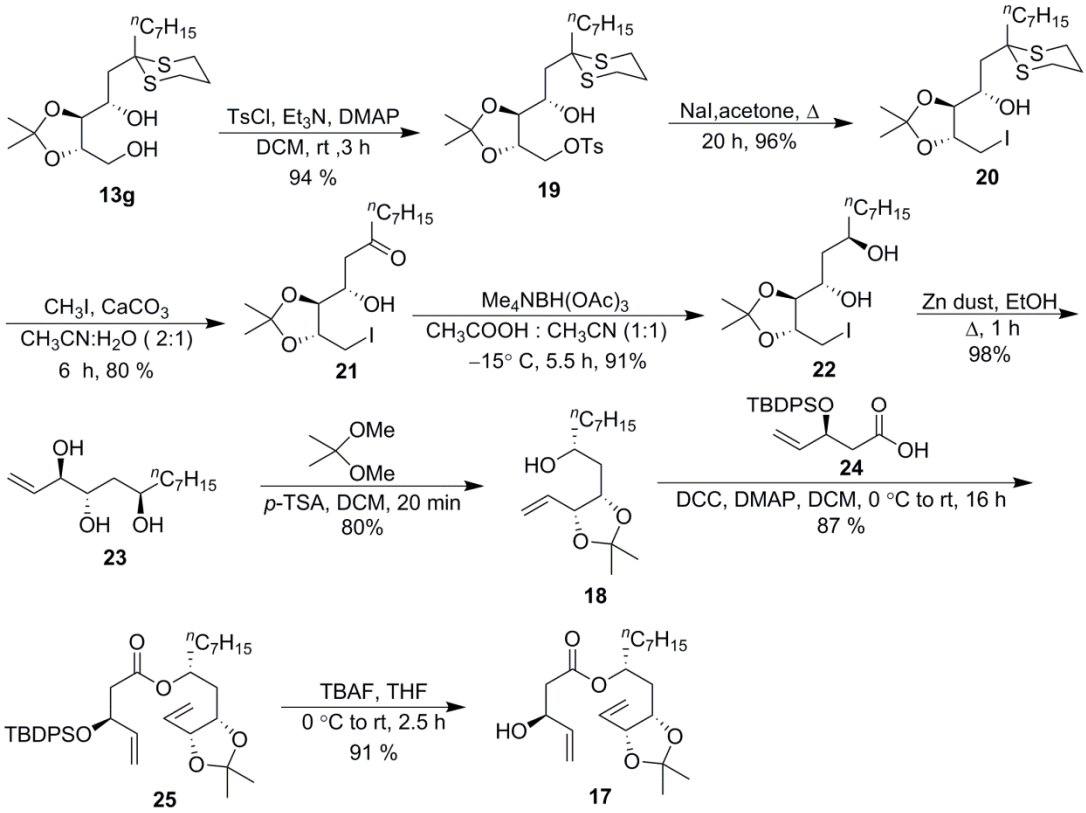
Scheme 3: The assignment of stereochemistry at the newly formed stereogenic center in **13a-h**

After successfully establishing the route for synthesis of the masked polyol unit from tartaric acid, application of the strategy in the total synthesis of achaetolide **2**, a decanolactone natural product was undertaken. Achaetolide (**2**) is a 10-membered lactone isolated in 1983 from the culture broth of *Achaetonium cristalliferum* and the structure was established in 2009 by Takada's group by extensive NMR studies.[10] It was envisaged that formation of the lactone can be accomplished by ring closing metathesis of the diene ester **17**. The alcohol fragment **18** of the ester can be synthesized by elaboration of the triol unit **13g** obtained from tartaric acid (Scheme-4).



Scheme 4: Retrosynthesis for achaetolide

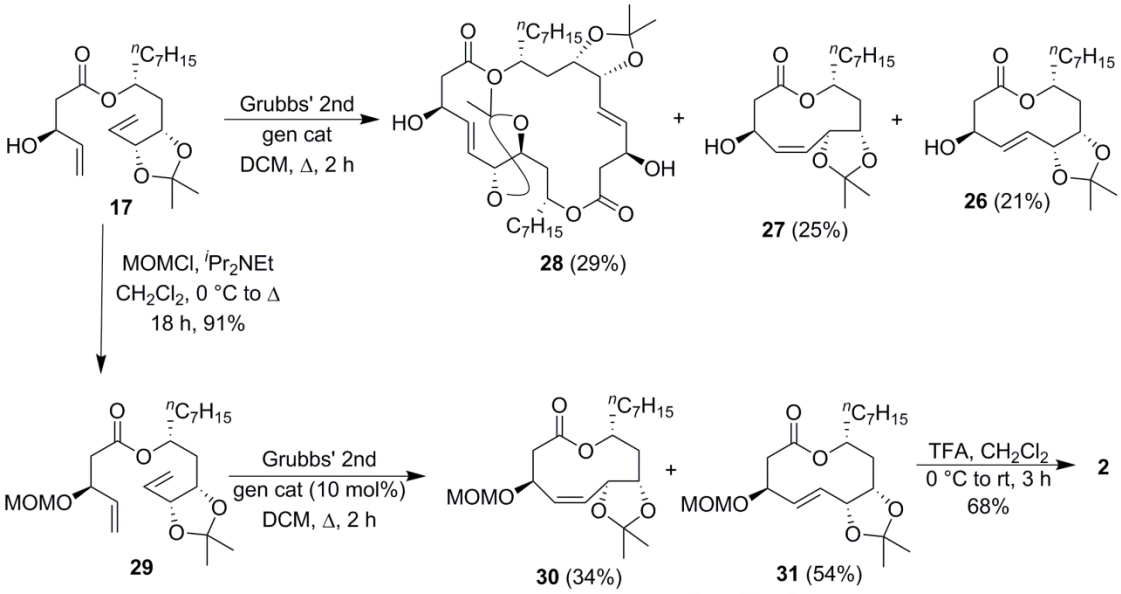
Thus, primary alcohol in **13g** was transformed to the iodide **20**, via the tosylate **19**, which on reaction with MeI and $CaCO_3$ unmasked the dithiane to yield the β-hydroxy ketone **21** in 80% yield. Stereoselective directed reduction of the keto group in **21** with $Me_4NBH(OAc)_3$[11] furnished the 1,3-*anti*-diol **22** in 91% yield. Treatment of **22** with zinc dust in refluxing ethanol produced the 1,2,4-triol **23** in excellent yield. Reaction of the triol **23** with 2,2-dimethoxy propane in DCM afforded the acetonide **18** in 80% yield. Coupling of **18** with the known acid **24**[12] furnished the ester **25** in 87% yield. Deprotection of the TBDPS group in **25** with TBAF gave the diene ester **17** in 91% yield (Scheme-5).



Scheme 5: Synthesis of the diene ester **17**

We then examined the ring closing metathesis (RCM) reaction of the ester **17** with Grubbs' 2nd generation catalyst. In the reported RCM reaction of the ester with Grubbs' catalyst by different groups, an element of discrepancy is observed. Different groups[10c,f,g] reported varied yields of the required lactone **26** along with formation of other products in the RCM reaction of the ester **17**.[13] We investigated this reaction and consistently found that the reaction of the ester **17** with catalytic amount of Grubbs' catalyst furnished the required *E*-lactone **26** in 24% yield, the *Z*-isomer **27** in 25% yield, along with the dimer **28**[14] in 29% yield. Performing the reaction at higher dilutions could not mitigate

the formation of the dimer. Interestingly, protection of the free hydroxy group in **17** as the MOM ether **29** and performing the RCM reaction mitigated the formation of the dimer completely and the *E* and *Z* lactones **31** and **30** respectively were formed in 54% and 34% yields respectively. Deprotection of the acetonide as well as the MOM group in **31** afforded the natural product achaetolide **2** in 68% yield. The spectral data of **2** is in agreement with that reported in the literature (Scheme-6).

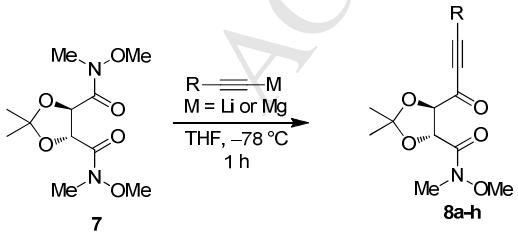


Scheme 6: Total synthesis of achaetolide **2**

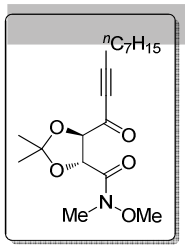
In conclusion, a general procedure for the synthesis of 1,2,4-triol unit frequently encountered in natural products was accomplished from chiral pool tartaric acid using Ley's dithiaketalization strategy. Application of the methodology is exemplified in the total synthesis of decanolactone natural product achaetolide in 14 steps from the *bis*-Weinreb amide of tartaric acid in 9.5% overall yield.

Experimental:

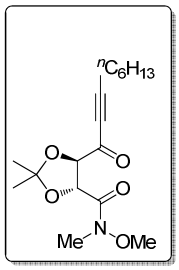
General Procedures: Column chromatography was performed on silica gel, Acme grade 100-200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. All reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a 400 or on a 300 mHz machine in $CDCl_3$ as solvent with TMS as reference unless otherwise indicated. Unless stated otherwise, all the reactions were performed under inert atmosphere. All the specific rotations were determined at 24 °C. HRMS was obtained using a micromass-QTOF spectrometer using electrospray ionization (ESI).



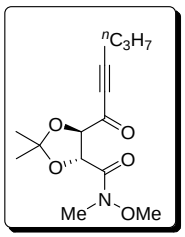
General procedure for the addition of alkynes to the bis-Weinreb amide: The following preparation of 8g is representative:



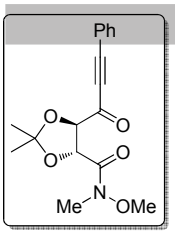
To a stirred solution of 1-nonyne (2.5 mL, 15.1 mmol) in dry THF (15 mL) at −78 °C was added *n*-BuLi (8.8 mL of 1.6 M solution in hexanes, 14 mmol) and the resulting reaction mixture was stirred at the same temperature for 1h. A solution of the *bis*-Weinreb amide **7** (3.0 g, 10.8 mmol) in THF (10 mL) was added dropwise to the pre-formed alkynyllithium at −78 °C. The reaction mixture was stirred at −78 °C for another 40 min. After completion of the reaction (TLC), it was quenched with sat. NH_4Cl solution (20 mL) and was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the resultant residue with petroleum ether: EtOAc (9:1) as eluent afforded the keto-amide **8g** as yellow oil in 89% (3.4 g) yield. $[\alpha]_D^{24}$ −16.7 (*c* 1.0, $CHCl_3$).; IR (neat) 2932, 1684, 1458, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (bd, *J* = 4.0 Hz, 1H), 4.87 (bd, *J* = 4.0 Hz, 1H), 3.71 (s, 3H), 3.23 (s, 3H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.58 (pent., *J* = 7.2 Hz, 2H), 1.50 (s, 3H), 1.48 (s, 3H), 1.45-1.31 (m, 2H), 1.30-1.15 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 169.5, 113.6, 99.8, 83.1, 78.9, 74.9, 61.6, 32.5, 31.6, 28.7, 28.6, 27.5, 26.8, 26.5, 22.5, 19.2, 14.0; HRMS for $C_{18}H_{29}O_5N$+Na calcd 362.1943; found 362.1942.



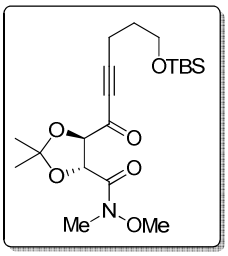
Preparation of 8f: Following the general procedure, reaction of 1-octyne (0.37 mL, 2.53 mmol) with the *bis*-Weinreb amide **7** (0.5 g, 1.81 mmol) afforded the product **8f** in 63% (0.37 g) yield. $[\alpha]_D^{24}$ −17.0 (*c* 1.3, $CHCl_3$); IR (neat) 2927, 2210, 1677, 1428 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (d, *J* = 4.8 Hz, 1H), 4.85 (d, *J* = 4.8 Hz, 1H), 3.69 (s, 3H), 3.21 (s, 3H), 2.39 (t, *J* = 7.2 Hz, 2H), 1.56 (pent., *J* = 7.2 Hz, 2H), 1.48 (s, 3H), 1.46 (s, 3H), 1.41-1.32 (m, 2H), 1.31-1.18 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 169.4, 113.5, 99.7, 83.0, 78.8, 74.9, 61.6, 32.4, 31.1, 28.4, 27.4, 26.7, 26.4, 22.4, 19.1, 13.9; HRMS for $C_{17}H_{27}O_5N$+Na calcd 348.1787; found 348.1786.



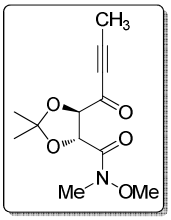
Preparation of 8e: Following the general procedure, reaction of 1-pentyne (0.5 mL, 5.07 mmol) with the *bis*-Weinreb amide **7** (1.0 g, 3.62 mmol) afforded the product **8e** in 88% (0.9 g mg) yield. $[\alpha]_D^{24}$ −20.9 (*c* 1.2, $CHCl_3$).; IR (neat) 2212, 1677, 1383, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.1 (d, *J* = 4.4 Hz, 1H), 4.84 (d, *J* = 4.8 Hz, 1H), 3.68 (s, 3H), 3.19 (s, 3H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.58 (hex, *J* = 7.2 Hz, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 169.3, 113.5, 99.4, 83.0, 78.9, 74.8, 61.5, 32.4, 26.7, 26.4, 20.99, 20.96, 13.3; HRMS for $C_{14}H_{21}O_5N$+Na calcd 306.1317; found 306.1315.



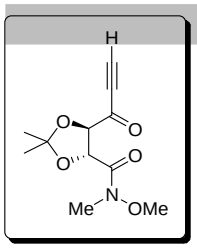
Preparation of 8d: Following the general procedure, reaction of phenyl acetylene (0.3 mL, 2.7 mmol) with the *bis*-Weinreb amide **7** (0.5 g, 1.81 mmol) afforded the product in 60% (0.34 g) yield (73% based on recovery of starting material). $[\alpha]_D^{24}$ –22.1 (*c* 0.9, $CHCl_3$); IR (neat) 2939, 2205, 1668, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 5.21 (d, *J* = 4.8 Hz, 1H), 5.0 (d, *J* = 4.8 Hz, 1H), 3.71 (s, 3H), 3.24 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 169.3, 133.3 (2C), 131.2, 128.7 (2C), 119.4, 113.8, 95.7, 86.0, 83.1, 75.1, 61.6, 32.5, 26.8, 26.5; HRMS for $C_{17}H_{19}O_5N$+Na calcd 340.1161; found 340.1161.



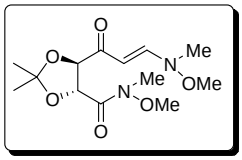
Preparation of 8h: Following the general procedure, reaction of 1-silyloxy-4-pentyne (6.32 g, 31.9 mmol) with the *bis*-Weinreb amide **7** (8.0 g, 28.95 mmol) afforded the product **8h** in 76% (9.1 g) yield. $[\alpha]_D^{25}$ –12.7 (*c* 2.0, $CHCl_3$); IR (Neat): ν_{max} 2953, 1681, 1468, 1257, 1102, 958, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ5.14 (d, *J* = 4.8 Hz, 1H), 4.87 (d, *J* = 4.8 Hz, 1H), 3.71 (s, 3H), 3.68 (t, *J* = 5.6 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.78 (quint, *J* = 6.4 Hz, 2H), 1.51 (s, 3H), 1.48 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.7, 169.6, 113.5, 99.3, 83.0, 78.9, 74.8, 61.5, 61.0, 32.4, 30.6, 26.7, 26.4, 25.8 (3 × C), 18.2, 15.7, –5.4 (2 × C). HRMS: m/z calcd for $C_{20}H_{35}NO_6Si$+Na 436.2131; found: 436.2138.



Preparation of 8b: To a stirred solution of the *bis*-Weinreb amide **7** in (0.5 g, 1.81 mmol) in THF (9 mL) was added propynylmagnesium bromide (5.4 mL of 0.5 M solution in THF, 2.7 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred at the same temperature for 1h. After completion of the reaction (TLC), it was quenched by addition of sat. NH_4Cl (5 mL) solution, poured into water (10 mL) and was extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the resultant residue with petroleum ether:EtOAc (5:5) as eluent afforded **8b** as a colourless oil in 65% (0.3 g) yield. $[\alpha]_D^{24}$ –22.7 (*c* 1.35, $CHCl_3$); IR (neat) 2921, 2214, 1676, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, *J* = 4.8 Hz, 1H), 4.87 (d, *J* = 4.8 Hz, 1H), 3.70 (s, 3H), 3.23 (s, 3H), 2.07 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 169.3, 113.5, 95.3, 82.9, 78.1, 74.7, 61.5, 32.4, 26.6, 26.4, 4.3; HRMS for $C_{12}H_{17}O_5N$+Na calcd 278.1004; found 278.1009.

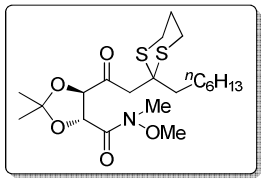


Preparation of 8a: The reaction was performed similar to the procedure described above, except quenching the reaction with ice-cold 1N HCl (2 mL), instead of saturated NH_4Cl. Accordingly, reaction of ethynylmagnesium bromide (0.8 mL of 0.5M solution in THF, 0.4 mmol) with the *bis*-Weinreb amide **7** (0.1 g, 0.37 mmol) afforded the product **8a** in 48% (42 mg) yield (68% based on recovery of starting material) and **8aa** resulting from the Michael addition of *N*,*O*-dimethoxyhydroxylamine to **8a** (0.03 g) in 29% yield. Data for **8a**. $[\alpha]_D^{24}$ −15.0 (*c* 1.0, $CHCl_3$); IR (neat) 3246, 2095, 1685, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (d, *J* = 4.8 Hz, 1H), 4.89 (d, *J* = 4.8 Hz, 1H), 3.71 (s, 3H), 3.48 (s, 1H), 3.22 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 169.1, 113.9, 83.1, 82.8, 79.3, 74.9, 61.6, 32.5, 26.7, 26.4. HRMS for $C_{11}H_{15}O_5N$+Na calcd 264.0848; found 264.0842.

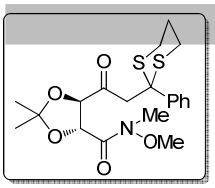


Data for 8aa: $[\alpha]_D^{24}$ −42.1 (*c* 1, $CHCl_3$); IR (neat) 1662, 1575, 1423, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 12.8 Hz, 1H), 5.71 (d, *J* = 12.8 Hz, 1H), 5.12 (d, *J* = 4.8 Hz, 1H), 4.87 (d, *J* = 5.2 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.22 (s, 3H), 3.19 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 170.3, 148.5, 112.5, 92.5, 81.9, 74.6, 61.7, 59.8, 39.5, 32.4, 26.8, 26.5; HRMS for $C_{13}H_{22}O_6N_2$+Na calcd 325.1376; found 325.1373.

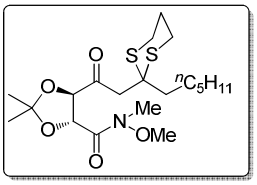
General procedure for the addition of propane 1,3-dithiol to the alkynyl ketone 8a-h: The following preparation for 9g is representative:



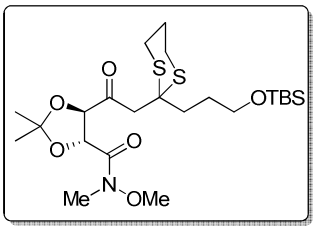
To a stirred solution of the alkynylketone **8g** (0.67 g, 2.0 mmol) in MeOH:CH_2Cl_2 (4:1, 12.0 mL) was added propane-1,3-dithiol (0.21 mL, 2.2 mmol) at room temperature. The reaction mixture was cooled to −10 °C and solid NaOMe (0.14 g, 2.54 mmol) was added in one portion at −10 °C. The reaction mixture was allowed to warm up to room temperature and was stirred at room temperature for 1.5 h. After completion of the reaction (TLC), it was quenched by addition of saturated solution of NH_4Cl (5 mL). The reaction mixture was poured into water (10 mL) and was extracted with diethyl ether (2×10 mL). The combined ethereal extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the resultant residue with petroleum ether: EtOAc (7:3) as eluent afforded the dithioketo-amide **9g** as a viscous pale yellow oil in 98% (0.85 g) yield. $[\alpha]_D^{24}$ +21.9 (*c* 1.2, $CHCl_3$); IR (neat) 2930, 1684, 1438, 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (d, *J* = 3.2 Hz, 1H), 4.85 (d, *J* = 3.6 Hz, 1H), 3.65 (s, 3H), 3.53 (d, *J* = 15.6 Hz, 1H), 3.16 (s, 3H), 3.12 (d, *J* = 16 Hz, 1H), 3.05-2.87 (m, 2H), 2.76-2.63 (m, 2H), 2.09-1.96 (m, 3H), 1.93-1.73 (m, 1H), 1.44 (s, 3H), 1.49-1.39 (m, 2H), 1.37 (s, 3H), 1.28-1.15 (m, 8H), 0.80 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 169.6, 112.5, 83.1, 73.4, 61.5, 49.9, 44.5, 38.8, 32.3, 31.6, 29.4, 28.9, 26.5, 26.2 (2C), 26.1, 24.9, 23.6, 22.4, 13.9; HRMS for $C_{21}H_{37}O_5N$+Na calcd 470.2011; found 470.2010.



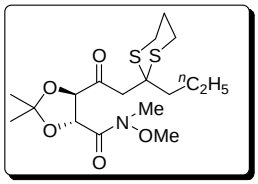
Preparation of 9d: Following the general procedure, reaction of propane 1,3-dithiol with compound **8d** (0.158 g, 0.5 mmol) afforded the product **9d** in 90% (0.19 g) yield. $[\alpha]_D^{24}$ +12.2 (*c* 1.45, $CHCl_3$); IR (neat) 2937, 1728, 1668, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 6.8 Hz, 1H), 4.93 (d, *J* = 4.4 Hz, 1H), 4.48 (d, *J* = 4.4 Hz, 1H), 3.61 (d, *J* = 16.4 Hz, 1H), 3.57 (s, 3H), 3.40 (d, *J* = 16.0 Hz, 1H), 3.16 (s, 3H), 2.83-2.69 (m, 4H), 2.07-1.88 (m, 2H), 1.42 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 169.7, 140.4, 128.6 (2C), 128.4 (2C), 127.4, 112.7, 82.8, 73.4, 61.5, 54.7, 51.5, 32.4, 27.6 (2C), 26.5, 26.2, 24.6; HRMS for $C_{20}H_{27}O_5S_2N$+Na calcd 448.1228; found 448.1228.



Preparation of 9f: Following the general procedure, reaction of propane 1,3-dithiol with compound **8f** (0.044 g, 0.14 mmol) afforded the product **9f** in 95% (0.055 g) yield. $[\alpha]_D^{24}$ +25.3 (*c* 1.15, $CHCl_3$); IR (neat) 2931, 1669, 1374, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (d, *J* = 5.2 Hz, 1H), 4.90 (d, *J* = 5.2 Hz, 1H), 3.71 (s, 3H), 3.59 (d, *J* = 15.6 Hz, 1H), 3.22 (s, 3H), 3.17 (d, *J* = 15.6 Hz, 1H), 3.10-2.91 (m, 2H), 2.83-2.67 (m, 2H), 2.11-2.02 (m, 3H), 1.92-1.85 (m, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.55-1.37 (m, 2H), 1.36-1.18 (m, 6H), 0.86 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 169.8, 112.7, 83.2, 73.6, 61.7, 50.1, 44.7, 39.0, 32.4, 31.5, 29.3, 26.7, 26.4 (2C), 26.3, 25.1, 23.8, 22.5, 14.0; HRMS for $C_{20}H_{35}O_5S_2N$+Na calcd 456.1854; found 456.1853.

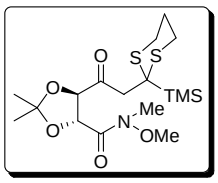


Preparation of 9h: Following the general procedure, reaction of propane 1,3-dithiol with compound **8h** (8.0 g, 19.3 mmol) afforded the product **9h** in 95% (9.58 g) yield. $[\alpha]_D^{25}$ +15.9 (*c* 2.0, $CHCl_3$); IR (Neat): ν_{max} 2934, 1667, 1463, 1383, 1257, 1091, 991, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (d, *J* = 4.8 Hz, 1H), 4.87 (d, *J* = 4.8 Hz, 1H), 3.70 (s, 3H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.55 (d, *J* = 15.6 Hz, 1H), 3.21 (s, 3H), 3.14 (d, *J* = 15.6 Hz, 1H), 2.96 – 3.01 (m, 2H), 2.74–2.80 (m, 2H), 2.08–2.14 (m, 2H), 2.01–2.06 (m, 1H), 1.84–1.93 (m, 1H), 1.65–1.75 (m, 2H), 1.50 (s, 3H), 1.41 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 169.8, 112.7, 83.3, 73.5, 62.8, 61.7, 49.9, 44.9, 35.1, 32.4, 27.4, 26.7, 26.3 (2 × C), 26.2, 25.9 (3 × C), 24.9, 18.2, -5.3 (2 × C). HRMS: m/z calcd for $C_{23}H_{43}NO_6S_2Si$ +Na 544.2199; found: 544.2197.

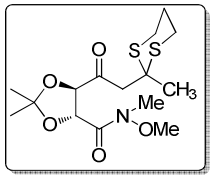


Preparation of 9e: Following the general procedure, reaction of propane 1,3-dithiol with compound **8e** (1.8 g, 6.36 mmol) afforded the product **9e** in 99% (2.47 g) yield. $[\alpha]_D^{24}$ +25.9 (*c* 1.45, $CHCl_3$); IR (neat) 1670, 1382, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (d, *J* = 4.8 Hz, 1H), 4.90 (d, *J* = 5.2 Hz, 1H), 3.71 (s, 3H), 3.59 (d, *J* = 16.0 Hz, 1H), 3.21 (s, 3H), 3.17 (d, *J* = 15.6 Hz, 1H), 3.08-2.94 (m,

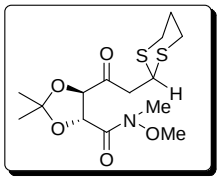
2H), 2.83-2.67 (m, 2H), 2.10-1.99 (m, 3H), 1.92-1.86 (m, 1H), 1.60-1.42 (m, 5H), 1.42 (s, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 169.7, 112.7, 83.2, 73.5, 61.7, 50.0, 44.6, 41.1, 32.4, 26.7, 26.4 (2C), 26.2, 25.1, 17.2, 14.1; HRMS for $C_{17}H_{29}O_5NS_2$+Na calcd 414.1385; found 414.1382.



Preparation of 9c: Following the general procedure, reaction of TMS-acetylene (0.08 mL, 0.5 mmol) with the *bis*-Weinreb amide **7** (0.1 g, 0.36 mmol) afforded the crude keto amide which on treatment with propane 1,3-dithiol gave the product **9c** in 64% (for 2 steps) (0.092 g) yield along with the desilylated product **9a** in 24% (0.029 g) yield. Data for **9c**: $[\alpha]_D^{24}$ +27.7 (*c* 1.0, $CHCl_3$); IR (neat) 1673, 1248, 1085, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, J = 5.2 Hz, 1H), 4.97 (d, J = 4.8 Hz, 1H), 3.89 (d, J = 15.6 Hz, 1H), 3.71 (s, 3H), 3.37 (d, J = 15.6 Hz, 1H), 3.22 (s, 3H), 3.24-3.20 (m, 1H), 3.18-3.14 (m, 1 H), 2.52-2.45 (m, 2H), 2.19-2.05 (m, 1H), 1.89 (qt, J = 12.8, 3.2 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 170.0, 112.7, 83.4, 73.6, 61.7, 45.4, 34.8, 32.5, 26.8, 26.4, 24.8, 23.9, 23.8, –2.6 (3C); HRMS for $C_{17}H_{31}O_5NSiS_2$+Na calcd 444.1311; found 444.1312.

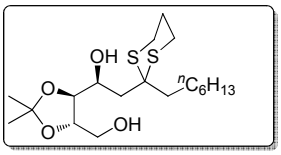


Preparation of 9b: Following the general procedure, reaction of propane 1,3-dithiol with compound **8b** (0.054 g, 0.2 mmol) afforded the product **9b** in 88% (0.071 g) yield. $[\alpha]_D^{24}$ +29.5 (*c* 1.1, $CHCl_3$); IR (neat) 2922, 1668, 1374, 1081 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (d, J = 5.2 Hz, 1H), 4.89 (d, J = 5.2 Hz, 1H), 3.70 (s, 3H), 3.61 (d, J = 15.2 Hz, 1H), 3.20 (s, 3H), 3.16-2.95 (m, 3H), 2.83-2.68 (m, 2H), 2.15-2.00 (m, 1H), 1.91-1.76 (m, 1H), 1.73 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 169.7, 112.7, 83.2, 73.5, 61.7, 47.8, 45.6, 32.4, 27.9, 26.9, 26.8, 26.6, 26.2, 24.6; HRMS for $C_{15}H_{25}O_5S_2N$+Na calcd 386.1072; found 386.1078.

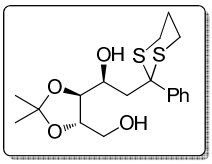


Preparation of 9a: Following the general procedure, reaction of propane 1,3-dithiol with compound **8a** (0.037 g, 0.15 mmol) afforded the product **9a** in 84% (0.042 g) yield. $[\alpha]_D^{24}$ +1.6 (*c* 1.65, $CHCl_3$); IR (neat) 1672, 1382, 1213, 854 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (d, J = 5.2 Hz, 1H), 4.83 (d, J = 5.2 Hz, 1H), 4.51 (t, J = 6.8 Hz, 1H), 3.70 (s, 3H), 3.21 (s, 3H), 3.18 (dd, J = 18.0, 6.4 Hz, 1H), 3.03 (dd, J = 18.0, 6.4 Hz, 1H), 2.95-2.77 (m, 4H), 2.17-2.01 (m, 1H), 1.97-1.78 (m, 1H), 1.48 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 169.4, 113.1, 82.3, 73.8, 61.7, 44.5, 40.0, 32.4, 29.8, 29.7, 26.7, 26.2, 25.1; HRMS for $C_{14}H_{23}O_5NS_2$+Na calcd 372.0915; found 372.0933.

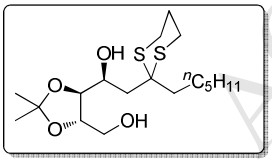
General procedure for the reduction of dithio keto-amide 9a-h to 1,4-diol3a-h : The following preparation of 13g is representative:



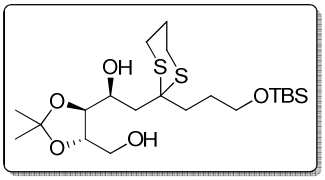
To a stirred solution of dithioketo-amide **9g** (4.2 g, 9.45 mmol) in methanol (50 mL) was added $NaBH_4$ (0.720 g, 19 mmol) at −78 °C and the resulting reaction mixture was stirred at the same temperature for 40 minutes. The progress of the reaction was monitored through TLC. Once the keto reduction is over, the temperature of the reaction was allowed to come to room temperature and additional $NaBH_4$ (3.59 g, 94.5 mmol) was added. The reaction mixture was stirred at room temperature for 7 h. After the completion of the reaction (TLC), it was quenched with water (5 mL), excess MeOH was evaporated, diluted with water (20 mL), extracted with EtOAc (3 × 15 mL), washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue with petroleum ether: EtOAc (7:3) as eluent afforded the diol **13g** as colourless oil in 81% (3 g) yield. $[\alpha]_D^{24}$ –27.1 (*c* 0.8, $CHCl_3$); IR (neat) 3424, 2930, 2857, 1432 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (s,1H), 4.02 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.86 (t, *J* = 8.4 Hz, 1H), 3.77-3.63 (m, 2H), 3.58 (t, *J* = 8.0 Hz, 1H), 3.12 (brs, 1H), 3.01 (t, *J* = 12.0 Hz, 1H), 2.92 (t, *J* = 12.0 Hz, 1H), 2.78-2.65 (m, 2H), 2.41-2.20 (m, 2H), 2.10-1.99 (m, 1H), 1.98-1.77 (m,3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.30-1.19 (m, 10H), 0.84 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.9, 81, 80.7, 70.7, 63.2, 51.7, 40.7, 39.7, 31.6, 29.6, 29.0, 26.9, 26.7, 26.4, 25.8, 24.8, 23.3, 22.5, 14.0; HRMS for $C_{19}H_{36}O_4S_2$+Na calcd 415.1953; found 415.1953.



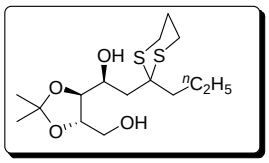
Preparation of 13d: Following the general procedure, reduction of compound **9d** (0.1 g, 0.24 mmol) with $NaBH_4$ afforded the product **13d** in 71% (0.062 g) yield. $[\alpha]_D^{24}$ +13.5 (*c* 1, $CHCl_3$); IR (neat) 3437, 1052, 854, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 3.96 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.84 (t, *J* = 8.8 Hz, 1H), 3.70 (d, *J* = 4.8 Hz, 2H), 3.58 (t, *J* = 7.6 Hz, 1H), 3.03 (brs, 1H), 2.89-2.76 (m, 3H), 2.74-2.71 (m, 2H), 2.64 (d, *J* = 14.8 Hz, 1H), 2.34 (dd, *J* = 14.8, 9.2 Hz, 1H), 2.09-1.89 (m, 2H), 1.37 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 128.8 (2C), 128.2 (2C), 127.6, 109.0, 80.5, 80.4, 70.6, 63.3, 56.7, 27.9 (2C), 27.4, 27.0, 26.6, 24.5; HRMS for $C_{18}H_{26}O_4S_2$+Na calcd 393.1170; found 393.1176.



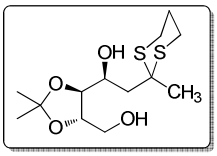
Preparation of 13f: Following the general procedure, reduction of compound **9f** (0.030 g, 0.07 mmol) with $NaBH_4$ afforded the product **13f** in 85% (0.022 g) yield. $[\alpha]_D^{24}$ –29.9 (*c* 1.1, $CHCl_3$); IR (neat) 3422, 1243, 1053, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (brs, 1H), 4.06-4.03 (m, 1H), 3.89 (td, *J* = 8.0, 2.8 Hz, 1H), 3.79 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.73 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.61 (t, *J* = 8.0 Hz, 1H), 3.05 (ddd, *J* = 14.4, 11.2, 2.8 Hz, 1H), 2.96 (ddd, *J* = 14.4, 10.8, 2.8 Hz, 1H), 2.78 (dd, *J* = 5.6, 3.2 Hz, 1H), 2.74 (dd, *J* = 5.6, 3.2 Hz, 1H), 2.44-2.25 (m, 2H), 2.15-1.99 (m, 1H), 2.01-1.82 (m, 3H), 1.68 (brs, 1H), 1.56-1.43 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H), 1.34- 1.20 (m, 6H), 0.88 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0, 81.1, 80.7, 70.8, 63.3, 51.7, 40.7, 39.8, 31.6, 29.4, 27.0, 26.7, 26.5, 25.9, 24.9, 23.3, 22.5, 14.0; HRMS for $C_{18}H_{34}O_4S_2$+Na calcd 401.1796; found 401.1799.



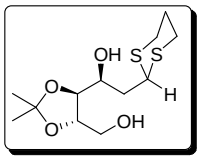
Preparation of 13h: Following the general procedure, reduction of compound **9h** (9.4 g, 18.0 mmol) with $NaBH_4$ afforded the product **13h** in 87% (7.3 g) yield. $[\alpha]_D^{25}$ –21.6 (*c* 0.8, $CHCl_3$); IR (Neat): ν_{max} 3417, 2952, 2930, 1650, 1469, 1371, 1255, 1099, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.16 (bs, 1H), 4.04 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.93 (t, *J* = 8.8 Hz, 1H), 3.70–3.79 (m, 2H), 3.59–3.65 (m, 3H), 2.91–3.04 (m, 3H), 2.74–2.80 (m, 2H), 2.42 (d, *J* = 15.2 Hz, 1H), 2.28 (dd, *J* = 15.2, 9.6 Hz, 1H), 1.99–2.07 (m, 3H), 1.86–1.94 (m, 1H), 1.65–1.81 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 108.9, 81.1, 80.8, 70.7, 63.4, 62.7, 51.5, 41.2, 35.9, 26.9 (2 × C), 26.7 (2 × C), 25.9 (3 × C), 25.8, 24.8, 18.3, -5.4 (2 × C); HRMS: m/z calcd for $C_{21}H_{42}O_5S_2Si$ +Na 489.2141; found: 489.2141.



Preparation of 13e: Following the general procedure, reduction of compound **9e** (0.9 g, 2.94 mmol) with $NaBH_4$ afforded the product **13e** in 82% (0.63 g) yield. $[\alpha]_D^{24}$ –40.8 (*c* 1.05, $CHCl_3$); IR (neat) 3418, 1381, 1051, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (brs, 1H), 4.11-3.96 (m, 1H), 3.88 (t, *J* = 8.4 Hz, 1H), 3.81-3.64 (m, 2H), 3.59 (t, *J* = 7.6 Hz, 1H), 3.13-3.03 (m, 1H), 3.03-2.90 (m, 2H), 2.81-2.66 (m, 2H), 2.36 (dd, *J* = 15.6, 2.0 Hz,1H), 2.29 (dd, *J* = 15.6, 9.2 Hz,1H), 2.12-1.96 (m, 1H), 1.96-1.82 (m, 3H), 1.60-1.42 (m, 2H), 1.38 (s, 3H), 1.35 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.9, 81.0, 80.6, 70.7, 63.2, 51.7, 42.0, 40.8, 26.9, 26.7, 26.4, 25.8, 24.8, 16.8, 14.1; HRMS for $C_{15}H_{28}O_4S_2$+Na calcd 359.1327; found 359.1325.

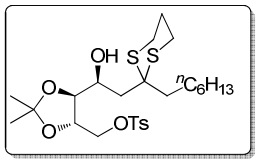


Preparation of 13b: Following the general procedure, reduction of compound **9b** (0.055 g, 0.14 mmol) with $NaBH_4$ afforded the product **13b** in 81% (0.035 g) yield. $[\alpha]_D^{24}$ –45.9 (*c* 1.6, $CHCl_3$); IR (neat) 3422, 1215, 1077, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (m, 1H), 3.94 (t, *J* = 8.0 Hz, 1H), 3.79 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.74 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.63 (t, *J* = 7.6 Hz, 1H), 3.11-2.92 (m, 2H), 2.86-2.69 (m, 2H), 2.36 (dd, *J* = 14.8, 9.2 Hz, 1H), 2.28 (dd, *J* = 15.2, 1.6 Hz, 1H), 2.13-1.99 (m, 1H), 1.97-1.78 (m, 1H), 1.66 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0, 81.0, 80.5, 70.9, 63.3, 47.4, 44.0, 28.4, 27.0, 26.82, 26.76, 26.5, 24.4; HRMS for $C_{13}H_{24}O_4S_2$+Na calcd 331.1014; found 317.1017.

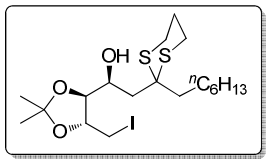


Preparation of 13a: Following the general procedure, reduction of compound **9a** (0.033 g, 0.1 mmol) with $NaBH_4$ afforded the product **13a** in 75% (0.020 g) yield. $[\alpha]_D^{24}$ –22.4 (*c* 0.45, $CHCl_3$); IR (neat) 3413, 1250, 1067, 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 8.8, 5.6 Hz, 1H), 4.12-3.93 (m, 2H), 3.77 (d, *J* = 4.8 Hz, 2H), 3.70 (t, *J* = 7.2 Hz, 1H), 2.96-2.81 (m, 4H), 2.19 (ddd, *J* = 14.4, 8.8, 2.4 Hz,1H), 2.16-2.11 (m, 1H), 2.00-1.85 (m, 2H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.2,

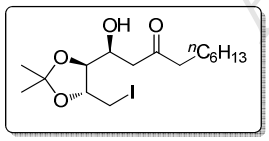
80.6, 79.5, 70.1, 63.1, 43.8, 39.1, 29.9, 29.7, 27.0, 26.9, 25.7. HRMS for $C_{12}H_{22}O_4S_2$+Na calcd 317.0857; found 317.0854.



Preparation of 19: To a solution of diol (2.7 g, 6.88 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added Et_3N (1.06 mL, 7.56 mmol), TsCl (1.4 g, 7.56 mmol) followed by DMAP (0.17 g, 1.37 mmol). The reaction mixture was stirred at room temperature for 3.5 h. After completion of the reaction (TLC), it was quenched with ice-cold water (10 mL), extracted with diethyl ether (3 × 15 mL), washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue with petroleum ether:EtOAc (9:1) as eluent afforded the monotosylate **19** as colourless viscous liquid in 92% (3.4 g) yield. $[\alpha]_D^{24}$ –39.3 (*c* 1.9, $CHCl_3$); IR (neat) 3445, 2923, 1600, 1372 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.36 (d, *J* = 10.4 Hz, 1H), 4.22-4.14 (m, 1H), 4.13-4.09 (m, 1H), 3.87 (t, *J* = 8.0 Hz, 1H), 3.67-3.55 (m, 2H), 3.10-2.85 (m, 2H), 2.83-2.68 (m, 2H), 2.44 (s, 3H), 2.36-2.13 (m, 2H), 2.08-1.98 (m, 1H), 1.98-1.84 (m, 3H),1.57-1.38 (m, 2H), 1.33 (s, 6H), 1.32-1.22 (m, 8H), 0.87 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 132.7, 129.6 (2C), 127.8 (2C), 109.8, 78.4, 77.7, 70.6, 70.1, 51.5, 40.8, 39.6, 31.5, 29.5, 28.9, 26.7, 26.6, 26.2, 25.6, 24.7, 23.2, 22.4, 21.4, 13.9; HRMS for $C_{26}H_{42}O_6S_3$+Na calcd 569.2041; found 569.2041.

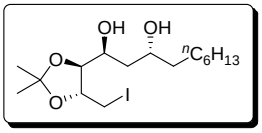


Preparation of 20: To a solution of **19** (3.3 g, 6.04 mmol) in acetone (25 mL) was added NaI (14.5 g, 96.6 mmol) and the resulting reaction mixture was refluxed for 20 h. After the completion of the reaction, it was diluted with water (10 mL) and extracted with diethyl ether (3 × 10 mL), washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue with petroleum ether: EtOAc (9:1) as eluent afforded the iodide **20** as colourless viscous liquid in 96% (3.0 g) yield. $[\alpha]_D^{24}$ –46.6 (*c* 1.8, $CHCl_3$); IR (neat) 3441, 2930, 1635, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93-3.81 (m, 2H), 3.67 (s,1H), 3.58-3.45 (m,2H), 3.32 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.03-2.97 (m, 1H), 2.94-2.89 (m, 1H), 2.79-2.62 (m, 2H), 2.32-2.21 (m, 2H), 2.08-1.94 (m, 1H), 1.96-1.76 (m, 3H), 1.54-1.34 (m, 2H), 1.42 (s, 3H), 1.33 (s, 3H), 1.29-1.14 (m, 8H), 0.83 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 82.6, 78.9, 70.7, 51.6, 40.7, 39.7, 31.6, 29.6, 28.9, 27.3, 27.1, 26.4, 25.7, 24.8, 23.3, 22.4, 13.9, 8.7; HRMS for $C_{19}H_{35}O_3S_2I$+Na calcd 525.0970; found 525.0968.

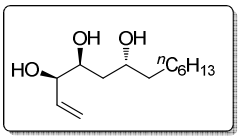


Preparation of 21: To a solution of iodide **20** (0.52 g, 1.04 mmol) in 2:1 CH_3CN: water mixture (9 mL) was added MeI (0.64 mL, 10.38 mmol) followed by $CaCO_3$ (0.42 g, 4.2 mmol) at room temperature. The reaction mixture was then heated to 45 °C and stirred for 6 h. After completion of the reaction (TLC), it was cool down to room temperature and excess CH_3CN was removed under reduced pressure, the crude reaction mixture was poured into water (5mL), extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue with

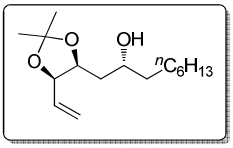
petroleum ether: EtOAc (8:2) as eluent afforded the beta hydroxy ketone **21** as colourless oil in 81% (0.35 g) yield. $[\alpha]_D^{24}$ –42.8 (*c* 1.6, $CHCl_3$); IR (neat) 3487, 2928, 1713, 1372 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09-3.94 (m, 1H), 3.93-3.79 (m, 1H), 3.56 (t, *J* = 7.6 Hz,1H), 3.51 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.48 (d, *J* = 3.6 Hz, 1H). 3.33 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.84 (dd, *J* = 18.0, 2.0 Hz, 1H), 2.58 (dd, *J* = 18.0, 9.2 Hz, 1H), 2.42 (t, *J* = 7.6 Hz, 2H), 1.61-1.48 (m, 2H), 1.43 (s, 3H), 1.34 (s, 3H), 1.24 (brs, 8H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 109.6, 82.0, 79.2, 69.5, 45.7, 43.6, 31.5, 29.0, 28.9, 27.3, 27.2, 23.5, 22.5, 14.0, 8.2; HRMS for $C_{16}H_{29}O_4I$+Na calcd 435.1008; found 435.1005.



Preparation of 22: Tetramethylammoniumtriacetoxy borohydride (2.2 g, 8.48 mmol) was added to a solution of anhydrous 1:1 mixture of CH_3CN: AcOH (10 mL) at room temperature and stirred for 30 min. The reaction mixture was then cooled to –20 °C and a solution of beta–hydroxy ketone **21** (1.6 g, 4.24 mmol) in CH_3CN: AcOH (1:1, 10 mL) was added dropwise and stirred at the same temperature for additional 5 h. After completion of the reaction (TLC), it was carefully quenched by the addition of sat. solution of sodium–potassium tartrate (10 mL). The reaction mixture was diluted with EtOAc (20 mL) and was washed with sat. solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue with petroleum ether: EtOAc (7:3) as eluent afforded the 1,3 anti-diol **22** as colourless oil in 93% (1.5 g) yield. $[\alpha]_D^{24}$ –24.9 (*c* 1.8, $CHCl_3$); IR (neat) 3424, 2929, 1638, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99-3.81 (m, 3H), 3.67 (t, *J* = 6.8 Hz, 2H), 3.50 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.33 (dd, *J* = 10.8, 5.6 Hz, 1H), 1.68 (t, *J* = 5.6 Hz, 2H), 1.40 (s, 3H), 1.54-1.35 (m, 2H), 1.36 (s, 3H), 1.26 (brs, 10H), 0.85 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 82.8, 78.2, 70.0, 69.3, 38.9, 37.5, 31.7, 29.4, 29.1, 27.4, 27.3, 25.6, 22.5, 14.0, 8.6; HRMS for $C_{16}H_{31}O_4I$+Na calcd 437.1165; found 437.1164.

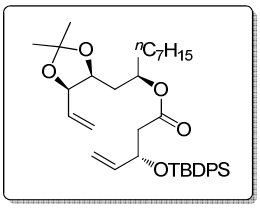


Preparation of 23: To a solution of the iodide **22** (0.21 g, 0.48 mmol) in ethanol (5 mL) was added freshly activated Zn dust (0.25 g, 3.84 mmol) and the resulting reaction mixture was stirred under refluxing conditions for 2 h. After completion of the reaction (TLC), the reaction mixture was filtered through a short pad of celite with EtOAc (10 mL). Evaporation of the solvent followed by silica gel column chromatography of the residue with petroleum ether: EtOAc (1:1) as eluent afforded the triol **23** as amorphous solid in 98% (0.115 g) yield. mp: 79-80 °C; $[\alpha]_D^{24}$ –3.2 (*c* 0.75, $CHCl_3$); IR (neat) 3403, 2922, 1942, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.33 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.20-4.09 (m, 1H), 4.01 (d, *J* = 10.0 Hz, 1H), 3.91 (brs, 2H), 3.75 (brs, 1H), 3.45 (brs, 1H), 1.66-1.61 (m, 1H), 1.55-1.36 (m, 4H), 1.26 (brs, 9H), 0.87 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 117.7, 76.1, 71.0, 69.2, 37.7, 37.4, 31.8, 29.6, 29.3, 25.8, 22.6, 14.1; HRMS for $C_{13}H_{26}O_3$+Na calcd 253.1780; found 253.1790.

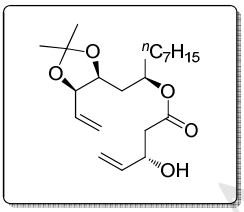


Preparation of 18: To a solution of the triol **23** (0.1 g, 0.478 mmol) in CH_2Cl_2 (4 mL) was added 2,2-dimethoxy propane (0.1 mL, 0.96 mmol) followed by *p*-TSA (0.005 g, 0.02 mmol) and the resulting

reaction mixture was stirred at rt for 20 minutes. After completion of the reaction (TLC), it was quenched with sat. solution of $NaHCO_3$ (5 mL), extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue with petroleum ether: EtOAc (4:1) as eluent afforded **18** as yellow oil in 80% (0.094 g) yield. $[\alpha]_D^{24}$ −19.6 (*c* 0.85, $CHCl_3$). Lit[10c] $[\alpha]_D$ −14.0 (*c* 0.2, $CHCl_3$).; IR (neat) 3431, 2929, 1458, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, *J* = 17.2, 10.4, 7.6 Hz, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.53 (t, *J* = 6.8 Hz, 1H), 4.52-4.37 (m, 1H), 3.85-3.74 (m, 1H), 2.14 (brs, 1H), 1.65-1.58 (m, 1H), 1.47 (s, 3H), 1.52-1.31 (m, 3H), 1.36 (s, 3H), 1.32-1.22 (m, 10H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 118.2, 108.3, 79.6, 74.9, 68.9, 37.8, 37.4, 31.8, 29.5, 29.2, 28.1, 25.7, 25.6, 22.6, 14.0; HRMS for $C_{16}H_{30}O_3$+Na calcd 293.2093; found 293.2099.

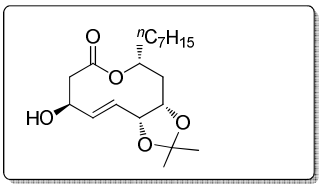


Preparation of 25: To a solution of the alcohol **18** (0.075 g, 0.28 mmol) and acid **24** (0.14 g, 0.39 mmol) in DCM (10 mL) was added DCC (0.086 g, 0.42 mmol) followed by DMAP (0.051 g, 0.42 mmol) at 0 °C and the resulting reaction mixture was stirred at room temperature for 14 h. After completion of the reaction (TLC), excess CH_2Cl_2 was evaporated off and the crude residue was filtered through a short pad of celite and the celite pad was washed with diethyl ether (10 mL). Evaporation of the solvent followed by silica gel column chromatography of the residue with petroleum ether: EtOAc (9:1) as eluent afforded the ester **25** as colourless oil in 92% (0.16 g) yield; $[\alpha]_D^{24}$ −3.4 (*c* 2.1, $CHCl_3$); IR (neat) 2932, 1736, 1370, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.60 (m, 4H), 7.48-7.30 (m, 6H), 5.87 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.76 (ddd, *J* = 17.6, 10.4, 7.6 Hz, 1H), 5.37-5.17 (m, 2H), 5.10-4.91 (m, 3H), 4.58 (q, *J* = 6.4 Hz, 1H), 4.43 (t, *J* = 6.8 Hz, 1H), 4.08 (ddd, *J* = 9.6, 6.4, 3.2 Hz, 1H), 2.55 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.46 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.61-1.55 (m, 1H), 1.53-1.50 (m, 3H), 1.45 (s, 3H), 1.30 (s, 3H), 1.35-1.19 (m, 10H), 1.07 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 139.2, 135.89 (2C), 135.87 (2C), 134.2, 133.8, 133.7, 129.7, 129.6, 127.5 (2C), 127.4 (2C), 118.3, 115.3, 108.3, 79.4, 74.7, 72.1, 71.5, 43.4, 35.1, 34.7, 31.7, 29.4, 29.1, 28.2, 26.9 (3C), 25.6, 25.0, 22.6, 19.2, 14.0; HRMS for $C_{37}H_{54}O_5Si$+Na calcd 629.3638; found 629.3633.

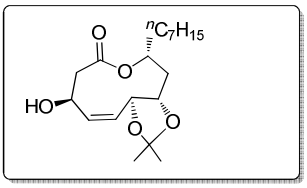


Preparation of 17: To a solution of **25** (0.085 g, 0.14 mmol) in THF (1 mL) was added TBAF (0.17 mL, 0.17 mmol) at 0 °C and the resulting reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (TLC), it was diluted with ice-cold water (2 mL) and extracted with EtOAc (2 × 5 mL), The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue with petroleum ether: EtOAc (4:1) as eluent afforded the ester **17** as colourless oil in 91% (0.047 g) yield. $[\alpha]_D^{24}$ −23.3 (*c* 0.6, $CHCl_3$). Lit[10c] −19.8 (*c* 0.53, $CHCl_3$). ; IR (neat) 3450, 2930, 1720, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.77 (ddd, *J* = 17.2, 10.4, 7.6 Hz, 1H), 5.34-5.24 (m, 3H), 5.22-5.03 (m, 2H), 4.59-4.43 (m, 2H), 4.19 (ddd, *J* = 10.0, 6.4, 2.8 Hz, 1H), 3.12 (s, 1H), 2.58 (dd, *J* = 15.6, 4.0 Hz, 1H), 2.50 (dd, *J* = 15.6, 8.0 Hz, 1H), 1.77-1.50 (m, 5H), 1.47 (s, 3H), 1.34 (s, 3H), 1.39-1.21 (m, 9H), 0.87 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100

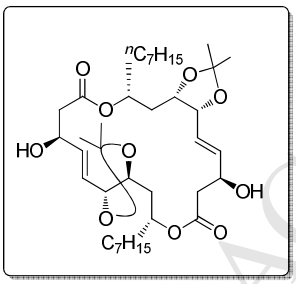
MHz, $CDCl_3$) δ 171.8, 138.8, 134.0, 118.5, 115.3, 108.5, 79.5, 74.4, 72.5, 69.0, 41.5, 35.0, 34.6, 31.7, 29.4, 29.1, 28.2, 25.6, 25.1, 22.6, 14.0; HRMS for $C_{21}H_{36}O_5$+Na calcd 391.2460; found 391.2462.



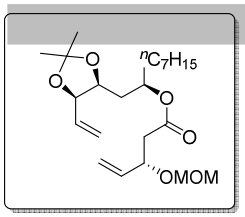
Preparation of 26: To a solution of the diene **17** (0.056 g, 0.15 mmol) in freshly distilled dry CH_2Cl_2 (75 mL) was added Grubbs' 2nd gen catalyst (0.013 g, 0.015 mmol) at room temperature. The reaction mixture was refluxed under argon atmosphere for 2 h. After completion of the reaction (TLC), excess CH_2Cl_2 was evaporated off and the crude reaction mixture was purified by silica gel column chromatography using petroleum ether: EtOAc (3:2) as eluent to afford the *E*-lactone **26** as brown oil in (0.011 g, 21%) yield along with the Z-lactone **27** (0.013g) 25% yield and the dimer **28** (0.015g) in 29% yield. **Data for E-lactone 26**: $[\alpha]_D^{24}$ –26.4 (*c* 0.25, $CHCl_3$) Lit[10f] –30 (*c* 0.4, $CHCl_3$); IR (neat) 3422, 2929, 1640, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+C_6D_6 (1:1)) δ 5.56 (dd, *J* = 16.0, 9.2 Hz, 1H), 5.42 (dd, *J* = 16.0, 8.0 Hz, 1H), 4.72-4.56 (m, 1H), 4.39 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.30-4.18 (m, 1H), 3.92 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.64 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.24-2.01 (m, 2H), 1.55-1.36 (m, 2H), 1.42-1.22 (m, 1H), 1.34 (s, 3H), 1.25-1.09 (m, 14H), 0.81 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+C_6D_6 (1:1)) δ 170.0, 133.5, 129.7, 108.6, 80.8, 77.3, 74.9, 70.0, 43.8, 38.0, 35.7, 31.8, 29.3, 29.2, 28.1, 25.6, 25.3, 22.6, 14.0; HRMS for $C_{19}H_{32}O_5$+Na calcd 363.2147; found 363.2147.



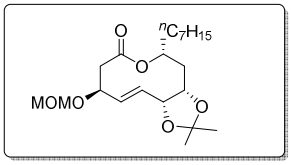
Data for Z-lactone 27: $[\alpha]_D^{24}$ +27.2 (*c* 0.5, $CHCl_3$); IR (neat) 3422, 2929,1637, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72-5.59 (m, 2H), 5.59-5.45 (m, 1H), 5.20-5.04 (m, 1H), 4.82-4.71 (m, 1H), 4.34-4.19 (m,1H), 2.66 (dd, *J* = 12.0, 5.2 Hz, 1H), 2.47 (dd, *J* = 12.0, 2.8 Hz, 2H), 2.03-1.89 (m, 2H), 1.72-1.42 (m, 4H), 1.34 (s, 3H), 1.25 (s, 3H), 1.34-1.25 (m, 8H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 132.1, 130.8, 107.3, 77.8, 74.1, 72.0, 68.4, 41.2, 35.5, 31.7, 30.9, 29.3, 29.1, 28.4, 25.7, 25.2, 22.6, 14.1; HRMS for $C_{19}H_{32}O_5$+Na calcd 363.2147; found 363.2144.



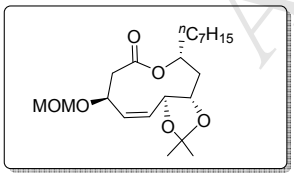
Data for dimer 28: $[\alpha]_D^{24}$ +5.7 (*c* 0.35, $CHCl_3$); IR (neat) 3407, 2920, 1733, 1570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.75 (dd, *J* = 15.6, 7.2 Hz, 1H), 4.96 (t, *J* = 6.0 Hz, 1H), 4.51 (t, *J* = 6.0 Hz, 2H), 4.14 (q, *J* = 6.4 Hz, 1H), 2.86 (brs, 1H), 2.67 (dd, *J* = 15.6, 5.6 Hz, 1H), 2.54 (dd, *J* = 15.6, 5.2 Hz, 1H), 1.81-1.56 (m, 5H), 1.46 (s, 3H), 1.35 (s, 3H), 1.46-1.26 (m, 9H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 135.4, 127.7, 108.3, 78.4, 75.7, 72.9, 68.7, 41.4, 35.1, 34.2, 31.7, 29.3, 29.1, 28.2, 25.6, 25.2, 22.6, 14.1; HRMS for $C_{38}H_{64}O_{10}$+Na calcd 703.4397; found 703.4396.



Preparation of 29: To a solution of **17** (0.100 g, 0.27 mmol) in dry CH_2Cl_2 (2 mL) were added diisopropylethyl amine (0.94 mL, 5.4 mmol), DMAP (14 mg, 0.1 mmol) and MOMCl (0.16 mL, 2.17 mmol) at 0 °C and the resulting reaction mixture was refluxed for 19 h. After completion of the reaction (TLC), it was diluted with water (2 mL) and extracted with diethyl ether (2 × 10 mL). Combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue with petroleum ether: EtOAc (9:1) as eluent afforded **29** as colourless oil in 91% (0.102 g) yield. $[\alpha]_D^{24}$ –47.3 (*c* 1.15, $CHCl_3$); IR (neat) 2928, 1737, 1373, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.69 (m, 2H), 5.34-5.31 (m, 1H), 5.29-5.25 (m, 1H), 5.23-5.20 (m, 2H), 5.10-5.03 (m, 1H), 4.68 (d, *J* = 6.4 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H), 4.50 (d, *J* = 7.2 Hz, 1H), 4.47(d, *J* = 7.2 Hz, 1H), 4.18 (ddd, J = 9.2, 6.4, 4.0 Hz, 1H), 3.35 (s, 3H), 2.62 (dd, J = 15.2, 8.4 Hz, 1H), 2.48 (dd, J = 15.2, 8.4 Hz, 1H), 1.66-1.54 (m, 4H), 1.45 (s, 3H), 1.32 (s, 3H), 1.30-1.22 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 136.8, 134.2, 118.3, 118.1, 108.2, 94.1, 79.5, 74.7, 73.9, 72.3, 55.6, 41.1, 35.2, 34.8, 31.7, 29.4, 29.1, 28.2, 25.6, 25.1, 22.6, 14.0; HRMS for $C_{23}H_{40}O_6$+Na calcd 435.2723; found 435.2726.

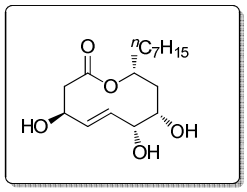


Preparation of 31: To a solution of the diene **29** (0.022 g, 0.053 mmol) in freshly distilled dry CH_2Cl_2 (30 mL, 0.0018 M) was added Grubbs' II catalyst (0.0045 g, 0.005 mmol) at room temperature. The reaction mixture was refluxed under argon atmosphere for 2.5 h. After completion of the reaction (TLC), excess CH_2Cl_2 was evaporated off and the crude reaction mixture was purified by silica gel column chromatography using petroleum ether: EtOAc (85:15) as eluent to afford the *E*-lactone **31** as colourless oil in (0.011 g, 54%) yield and the Z-lactone (0.007g) in 34% yield. **Data for E-lactone 31**: $[\alpha]_D^{24}$ –57.1 (*c* 0.45, $CHCl_3$); IR (neat) 2928, 1730, 1374, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (dd, *J* = 15.6, 9.2 Hz, 1H), 5.62 (dd, *J* = 16.0, 9.2 Hz, 1H), 4.89-4.83 (m, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.64 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.53 (dd, J = 17.2, 9.2 Hz, 1H), 4.14 (dd, J = 10.4, 6.4 Hz, 1H), 3.36 (s, 3H), 3.00 (dd, J = 13.2, 8.0 Hz, 1H), 2.40 (dd, J = 13.6, 9.2 Hz, 1H), 2.28-2.18 (m, 1H), 1.68-1.48 (m, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.31-1.24 (m, 12H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 131.9, 131.3, 108.9, 94.5, 80.8, 77.1, 74.9, 74.1, 55.5, 42.1, 38.0, 35.7, 31.7, 29.2, 29.1, 28.1, 25.6, 25.4, 22.6, 14.0; HRMS for $C_{21}H_{36}O_6$+Na calcd 407.2410; found 407.2409.

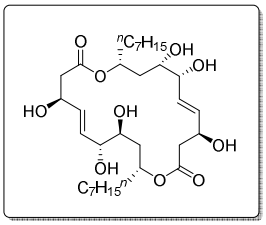


Data for Z-lactone 30: $[\alpha]_D^{24}$ +4.0 (*c* 0.2, $CHCl_3$); IR (neat) 2928,1735, 1373, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71-5.65 (m, 1H), 5.54 (dd, J = 11.6, 5.6 Hz, 1H), 5.30 (dd, J = 10.4, 6.0 Hz, 1H), 5.12-5.06 (m, 1H), 4.79 (d, J = 7.2 Hz, 1H), 4.68 (d, J = 6.8 Hz,1H), 4.60 (td, J = 5.2, 3.2 Hz, 1H), 4.23 (dd, J = 14.0, 6.0 Hz, 1H), 3.41 (s, 3H), 2.70 (dd, *J* = 12.4, 5.2 Hz, 1H), 2.45 (dd, *J* = 12.4, 3.2 Hz, 1H), 1.97-1.93 (m, 2H), 1.62-1.56 (m, 2H), 1.46 (s, 3H), 1.32 (s, 3H), 1.30-1.23 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 132.9, 127.6, 107.2, 94.5, 77.7, 74.2,

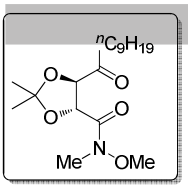
71.8, 71.1, 55.8, 39.7, 35.5, 35.4, 31.7, 29.3, 29.1, 28.5, 25.7, 25.2, 22.6, 14.0; HRMS for $C_{21}H_{36}O_6$+Na calcd 407.2410; found 407.2410.



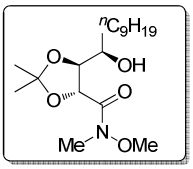
Preparation of 2: To a solution of the lactone **31** (0.011 g, 0.029 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.013 mL, 0.17 mmol) at 0 °C and the resulting reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (TLC), the volatiles were evaporated off and the resulting crude reaction mixture was purified through silica gel column chromatography using petroleum ether: EtOAc (1:9) as eluent to afford achaetolide **2** in 68% (0.006 g) yield. $[\alpha]_D^{24}$ –26.0 (*c* 0.2, MeOH); Lit[10b] $[\alpha]_D^{24}$ –27.0 (*c* 0.52, MeOH); IR (KBr) 3436, 2925, 1703, 1636 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) **(67:33 mixture of major and minor conformers)** δ 5.97 (ddd, *J* = 16.0, 3.2, 2.4 Hz, 1H major), 5.69 (ddd, *J* = 16.0, 2.4, 1.2 Hz, 1H major), 5.58 (dd, J = 16.4, 7.2 Hz, 1H minor), 5.42 (dd, J = 16.4, 8.8 Hz, 1H minor), 4.92 (m, 1H minor), 4.75-4.70 (m, 1H), 4.69-4.64 (m, 1H), 4.44 (m, 1H × b), 4.44 (m, 1H major), 4.28 (dd, J = 7.2, 3.2 Hz, 1H minor), 3.64 (d, J = 10.0 Hz, 1H major), 3.45 (m, 1H minor), 2.93 (dd, *J* = 13.2, 7.6 Hz, 1H minor), 2.53 (dd, J = 12.0, 4.0 Hz, 1H major), 2.49 (dd, *J* = 12.0, 3.6 Hz, 1H major), 2.37 (m, 1H minor), 2.37 (m, 1H major), 2.27 (dd, *J* = 13.6, 8.8 Hz, 1H minor), 1.70 (m, 1H minor), 1.55 (m, 1H minor), 1.52 (m, 2H major), 1.45-1.41 (m, 1H major), 1.40-1.37 (m, 1H minor), 1.28 (m, 10H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.3 (minor), 172.1 (major), 136.6 (minor), 131.6(major), 131.1 (minor), 127.6 (major), 78.3 (minor), 77.6 (minor), 76.7 (major), 74.8 (major), 74.6 (minor), 74.5 (major), 71.6 (minor), 68.0 (major), 44.9 (major), 38.3 (minor), 37.9 (major), 37.6 (major), 36.0 (minor), 32.9 (major), 30.8 (minor), 30.5 (major), 30.3 (major), 26.9 (minor), 26.2 (major), 23.7, 14.4; HRMS for $C_{16}H_{28}O_5$+Na calcd 323.1834; found 323.1834.



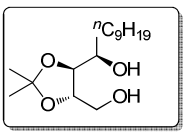
(4*S*,5*E*,7*R*,8*S*,10*R*,14*S*,15*E*,17*R*,18*S*,20*R*)-10,20-diheptyl-4,7,8,14,17,18-hexahydroxy-1,11-dioxacycloicosa-5,15-diene-2,12-dione (32): To a solution of **28** (0.004 g, 0.0058 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.0008 mL, 0.0012 mmol) at 0 °C and the resulting reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (TLC), the volatiles were evaporated off and the resulted crude reaction mixture was purified through silica gel column chromatography using EtOAc as eluent to afford achaetolide dimer **32** as white solid in 86% (0.003 g) yield. mp: 184-186 °C; $[\alpha]_D^{24}$ –5.0 (*c* 0.1, MeOH); IR (KBr) 3433, 1640, 1406, 1018 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) *δ* 5.78-5.56 (m, 2H), 5.20-5.08 (m, 1H), 4.55-4.42 (m, 1H), 3.68 (t, *J* = 8.0 Hz, 1H), 3.32-3.20 (m, 1H), 2.76 (dd, *J* = 12.4, 4.4 Hz, 1H), 2.37 (t, *J* = 11.6 Hz, 1H), 2.13 (t, *J* = 12.8, 1H), 1.61-1.51 (m, 2H), 1.47-1.25 (m, 11H), 0.90 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) *δ* 171.7, 136.0, 135.9, 77.8, 72.5, 70.93, 70.87, 45.4, 39.0, 36.4, 33.1, 30.8, 30.5, 26.4, 23.9, 14.6. HRMS for $C_{32}H_{56}O_{10}$+Na calcd 623.3771; found 623.3776.



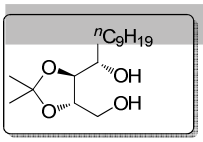
Preparation of 15: To a solution of bis-Weinrebamide **7** (0.1 g, 0.36 mmol) in THF (5 mL) was added nonylmagnesiumbromide (1.5 mL, 0.54 mmol) dropwise at −20 °C. The resulting reaction mixture was stirred for 15 minutes at the same temperature. After completion of the reaction (TLC), it was quenched with saturated solution of NH_4Cl (5 mL), extracted with EtOAc (2 × 5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue with petroleum ether: EtOAc (7:3) as eluent afforded the keto-amide **15** as colourless oil in 81% (0.1 g) yield. $[\alpha]_D^{24}$ +5.0 (*c* 0.8, $CHCl_3$); IR (neat) 2928, 1716, 1674, 1382 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (d, J = 5.2 Hz, 1H), 4.80 (d, J = 4.8 Hz, 1H), 3.69 (s, 3H), 3.21 (s, 3H), 2.76-2.48 (m, 2H), 1.64-1.51 (m, 2H), 1.48 (s, 3H), 1.42 (s, 3H), 1.30-1.19 (m, 12H), 0.85 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 169.8, 112.7, 82.2, 73.9, 61.6, 39.3, 32.4, 31.8, 29.35, 29.31, 29.2, 29.1, 26.6, 26.2, 23.0, 22.6, 14.0; HRMS for $C_{18}H_{33}O_5N$+Na calcd 366.2256; found 366.2258.



(4*R*,5*S*)-5-((*R*)-1-hydroxydecyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (15a): To a stirred solution of keto–amide **15** (0.062 g, 0.18 mmol) in THF (2.0 mL) was added K-selectride (0.36 mL, 0.36 mmol) at −78 °C. The reaction mixture was allowed to stir at the same temperature for 2 h. After completion of the reaction (TLC), it was quenched with brine (5 mL), extracted with EtOAc (2 × 5 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of solvent was subjected to silica gel column chromatography using petroleum ether: EtOAc (3:2) as eluent afforded the compound **15a** as colourless oil in 90% (0.056 g) yield. $[\alpha]_D^{24}$ −8.2 (*c* 0.15, $CHCl_3$); IR (neat) 3448, 2928, 1676, 1376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.35 (s, 1H), 3.73 (s, 3H), 3.64-3.53 (m, 1H), 3.21 (s, 3H), 1.99 (d, J = 8.0 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.55-1.38 (m, 2H), 1.29-1.19 (m, 14H), 0.85 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 111.0, 80.9, 73.8, 70.3, 61.7, 34.6, 32.4, 31.9, 29.5 (3C), 29.3, 27.0, 26.1, 25.8, 22.6, 14.1; HRMS for $C_{18}H_{35}O_5N$+Na calcd 368.2413; found 368.2413.



Preparation of 16: To a solution of the amide **15** (0.048 g, 0.14 mmol) in MeOH (3 mL) was added $NaBH_4$ (0.054 g, 1.4 mmol) at room temperature and the reaction mixture was stirred at the same temperature for 2 h. Progress of the reaction was monitored by TLC. After completion of the reaction (TLC), it was quenched with water (3 mL), extracted with EtOAc (3 × 5 mL), washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue with petroleum ether: EtOAc (3:2) as eluent afforded the diol **16** as colourless oil in 95% (0.038g) yield. $[\alpha]_D^{24}$ −5.7 (*c* 1.4, $CHCl_3$); IR (neat) 3418, 2926, 1380, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (dt, J = 8.0, 3.6 Hz, 1H), 3.88-3.71 (m, 2H), 3.63 (dd, J = 12.0, 4.0 Hz, 1H), 3.58-3.48 (m, 1H), 2.4-2.16 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 1.54-1.40 (m, 2H), 1.30-1.20 (m, 14H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.2, 80.0, 77.7, 70.5, 62.0, 34.3, 31.8, 29.5 (3C), 29.3, 27.2, 27.1, 25.7, 22.6, 14.1; HRMS for $C_{16}H_{32}O_4$+Na calcd 311.2198; found 311.2198.



Preparation of 14: To a solution of the diol **13g** (0.043 g, 0.11 mmol) in EtOH (2 mL) under hydrogen atmosphere was added Raney Nickel (2 mL suspension in ethanol) and was allowed to reflux for 12 h. After completion of the reaction (TLC), it was filtered through a short pad of celite and the celite pad was washed with EtOAc (10 mL), evaporation of the solvent followed by purification of the crude residue with silica gel column chromatography using petroleum ether: EtOAc (3:2) as eluent afforded diol **14** as colourless oil in (0.026 g, 84%) yield. $[\alpha]_D^{24}$ –6.7 (*c* 1.2, $CHCl_3$); IR (neat) 3418, 2926, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12-3.98 (m, 1H), 3.84-3.63 (m, 4H), 2.70 (brs, 2H), 1.92-1.21 (m, 16H), 1.40 (s, 3H), 1.26 (s, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.8, 80.7, 78.7, 71.9, 63.1, 33.5, 31.9, 29.5 (3C), 29.3, 27.0 (2C), 25.4, 22.6, 14.1; HRMS for $C_{16}H_{32}O_4$+Na calcd 311.2198; found 311.2198.

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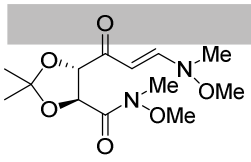
References

1) For a review on polyol natural products see: Rychnovsky, S. D. *Chem. Rev*., **1995**, *95*, 2021.
2) Modern methods in stereoselective aldol reactions, Mahrwald, R (Ed). Wiley-VCH, 2013.
3) Smith, A. B. III, Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.
4) Snedden, H. F.; van den Heuvel, A.; Hirsch, A. K. H.; Booth, R. A.; Shaw, D. M.; Gaunt, M. G.; Ley, S. V. *J. Org. Chem*. **2006**, *71*, 2715.
5) For a general approach to the synthesis of γ-keto amides by addition of alkyl or aryl Grignard reagents to tartaric acid derived amides see: (a) Prasad, K. R.; Chandrakumar, A. *Tetrahedron* **2007**, *63*, 1798. For some applications of γ-keto amides derived from tartaric acid in natural product synthesis from our group see: (b) Prasad, K. R.; Kumar, S. M. *Synthesis* **2013**, 785. (c) Prasad, K. R.; Metri, P. K. Scheiss, R. *Chem. Asian J.* **2013**, *8*, 488. (d) Prasad, K. R.; Pawar, A. B. *Chem. –Eur. J.* **2012**, *18*, 15202 (e) Prasad, K. R.; Kumar, S. M. *Synlett* **2011**, 1602. (f) Prasad, K. R.; Swain, B. *J. Org. Chem.* **2011**, *76*, 2029. (h) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2.
6) Preliminary communication with solitary example of addition of alkynyl Grignard reagent to the *bis*-Weinreb amide **7** and application to the total synthesis of macrolactone natural product Sch725674: Bali, A.; Sunnam, S. K.; Prasad, K. R. *Org. Lett*, **2014**, *16*, 4001.
7) Nugiel, D. A.; Jakobs, K.; Worley, T.; Patel, M.; Kaltenbach III, R. F.,; Meyer, D. T.; Jadhav, P. K.; De Lucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem*. **1996**, *39*, 2156.
8) Controlled exclusive reduction of the keto group in **9a-h** was always accompanied with formation of the 1,4-diol **13** and the purification was very cumbersome. Hence, both the keto and amide groups were reduced to the 1,4-diol **13a-h** with excess $NaBH_4$. Formation of the other diastereomer was not observed within detectable limits in ^1H NMR. b) Investigations concerning the influence of the dithianyl moiety in the exclusive formation of the *erythro* diastereomer in the reduction of the keto group in **9a-h** are currently underway.
9) The following enamine **8aa** is obtained in 29% yield, formed possibly by the addition of Weinreb amine to the unsaturated ketone **8a**. See Supporting Information for the spectral data of **8aa**. Formation of enamino ketones by in the addition of alkynyl Grignard reagents to Weinreb amides is reported in literature. a) Persson, T.; Nielsen, J. *Org. Lett*. **2006**, *8*, 3219. b) Pirc, S.; Bevk, D.; Golobic, A.; Stanovnik, B.; Svete, J. *Helv. Chim. Acta*, **2006**, *89*, 30.



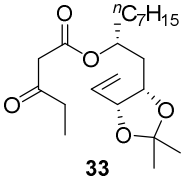
8aa

10) a) Bodo, B.; Molho, L.; Davoust, D.; Molho, D. *Phytochemistry*, **1983**, *22*, 447. b) Tayone, W. C.; Shindo, S.; Murakami, T.; Hashimoto, M.; Tanaka, K.; Takada, N. *Tetrahedron* **2009**, *65*, 7464. For earlier synthesis of achaetolide see: c) Chandrasekhar, S.; Balaji, S. V.; Rajesh, G. *Tetrahedron Lett*, **2010**, *51*, 5164. d) Das, T.; Bhuniya, R.; Nanda, S. *Tetrahedron: Asymmetry*, **2010**, *21*, 2206. e) Rao, K. S.; Chattapadyay, A. K.; Ghosh, S. *Synlett*, **2010**, 3078. f) Srihari, P.; Kumaraswamy, B.; Shankar, P.; Ravishashidhar, V.; Yadav, J. S. *Tetrahedron Lett* **2010**, *51*, 6174. g) Thakur, P.; Kumaraswamy, B.; Reddy, G. R.; Bandichor, R.; Mukkanti, K. *Tetrahedron: Asymmetry*, **2012**, *23*, 547.

11) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

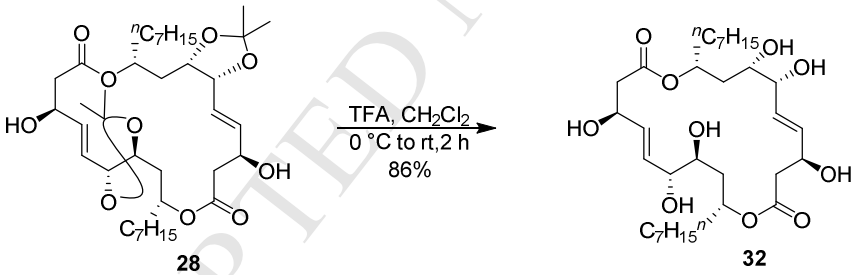
12) The known β-hydroxy acid **24** was prepared by hydrolysis of the corresponding *tert*-butyl ester.

13) Chadrasekhar *et. al*. (ref. 10c) reported the formation of required *E*-lactone **26** in 47% yield along with the *Z*-isomer **27** in 23% yield, while Srihari *et. al*. (ref. 10f) reported the formation of **26** in 40% yield along with the ester **33** in 24% yield in the RCM of reaction of **17** with Grubbs' 2nd generation catalyst. Thakur *et. al*. (ref. 10g) reported the formation of **26** in 61% yield with no other side products.



33

14) Formation of the dimer is further confirmed by deprotection of the acetonide in **28** to yield the known achaetolide dimer **32**. For dimer of achaetolide See Zhang, S. – M.; Lu, X. – W.; Wu, Y. *Asian. J. Org. Chem.* **2012,** *1*, 245.



28 **32**