Formal Total Synthesis of (–)-5,6-Dihydrocineromycine B

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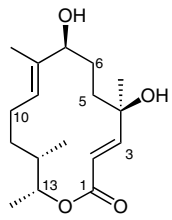
Received: 13.07.2012; Accepted after revision: 11.09.2012

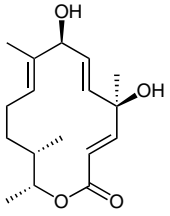
Abstract: An efficient and highly convergent formal total synthesis of the 14-membered macrolide (–)-5,6-dihydrocineromycine B is achieved. Key reaction sequences include a Sharpless asymmetric epoxidation followed by esterification for the formation of a fully functionalized acyclic precursor, Corey–Bakshi–Shibata reduction, and ring-closing metathesis, respectively.

Key words: antibiotic macrolide, (–)-5,6-dihydrocineromycine B, Sharpless asymmetric epoxidation, CBS reduction, ring-closing metathesis

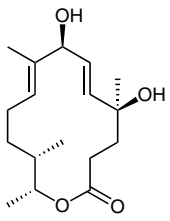
Macrolide antibiotics belong to a class of polyketide natural products that exhibit a wide range of biological activities.[1] These antibiotics are usually produced by certain species of *Streptomyces* and possess a macrolactone ring and double bonds. The cineromycins and 5,6-dihydrocineromycine B are perhaps the best examples of these interesting macrolides that have been isolated from *Streptomyces* sp. (strain Gö 40/10).[2] The cineromycins and albocyclins-18 are structurally related antibiotic natural products which display potent antibiotic activity against *Staphylococci*. As shown in Figure 1, structural features of (–)-5,6-dihydrocineromycine B (**1**) encompasses four stereogenic centers, two hydroxyls and two carbon–carbon double bonds which are embedded in a 14-membered lactone ring.



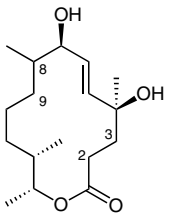
1: (–)-5,6-dihydrocineromycin B



2: cineromycin B



3: 2,3-dihydrocineromycin B



4: 2,3,8,9-tetrahydrocineromycin B

Figure 1 Structures of cineromycin B and its derivatives

SYNLETT 2012, 23, 2677–2681
Advanced online publication: 18.10.2012
DOI: 10.1055/s-0032-1317346; Art ID: ST-2012-D0589-L

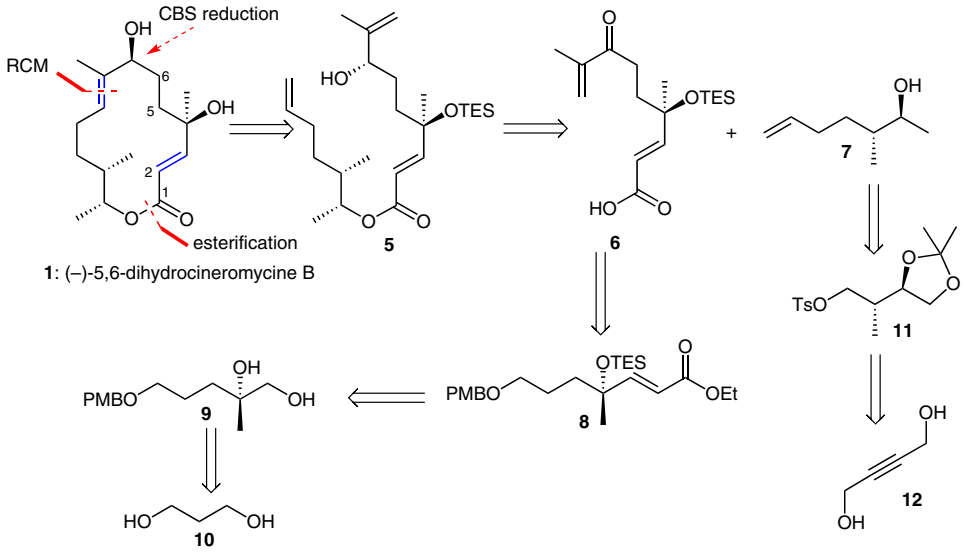
The unique structures of these macrolides, in conjunction with their potent biological activities, have made them attractive synthetic targets.[3] To date two total syntheses[4] of 5,6-dihydrocineromycine B (**1**) have appeared in the literature.

As part of our continuous endeavors in the synthesis of bioactive macrolides,[5] we were attracted to the structural features and antibiotic activity of (–)-5,6-dihydrocineromycine B (**1**). Herein, we report the formal total synthesis of **1**, utilizing Sharpless asymmetric epoxidation, Yamaguchi esterification, Corey–Bakshi–Shibata (CBS) reduction, and ring-closing metathesis (RCM) as key steps.

Our retrosynthetic analysis of **1** is shown in Scheme 1. As indicated, the cyclic framework could be constructed by RCM of **5**, which in turn could be obtained by the Yamaguchi esterification of the building blocks – alkenes **6** and **7**. Fragment **6** could be derived from ester **18** via oxidation followed by Grignard reaction, which is conceived to be obtained through a four-step sequence starting from the inexpensive propane-1,3-diol (**10**). Similarly, we envisioned that fragment **7** can be obtained from but-2-yne-1,4-diol (**12**) through Sharpless asymmetric epoxidation and other functional-group transformations.

As outlined retrosynthetically in Scheme 1, the synthesis of fragment **6** commenced from commercially available propane-1,3-diol (**10**) which was converted into the α,β-unsaturated ester **13** by following a known procedure (Scheme 2).[6] Treatment of α,β-unsaturated ester **13** with DIBAL-H at 0 °C yielded allyl alcohol **14** in 95% yield. Sharpless asymmetric epoxidation[7] of **14** using (+)-diisopropyl L-tartrate, titanium isopropoxide, and TBHP at –20 °C furnished **15** in 95% yield with an excellent enantioselectivity of 98% ee. Regioselective opening of epoxide **15** using LAH provided the corresponding[8] 1,2-diol **9** in 92% yield. The primary hydroxyl group in **9** was oxidized using 2-iodoxybenzoic acid (IBX)[9] to afford an aldehyde, which was immediately subjected to Horner–Wadsworth–Emmons olefination[10] to give **16** exclusively as the *E*-isomer (J = 15.6 Hz) in 90% yield.

The tertiary hydroxyl group in **16** was protected as a TES ether by using TESCl and triethylamine in dichloromethane to give compound **8** in 94% yield and subsequent oxidative removal[11] of the PMB group by using DDQ in dichloromethane, pH buffer (9:1 ratio) afforded **17** in 90% yield. Oxidation of primary alcohol **17** by Dess–Martin periodinane[12] in dichloromethane gave an aldehyde in quantitative yield which was treated with isopropenylmagnesium bromide in THF to afford the secondary alcohol in a 1:1 diastereomeric mixture and further Dess–

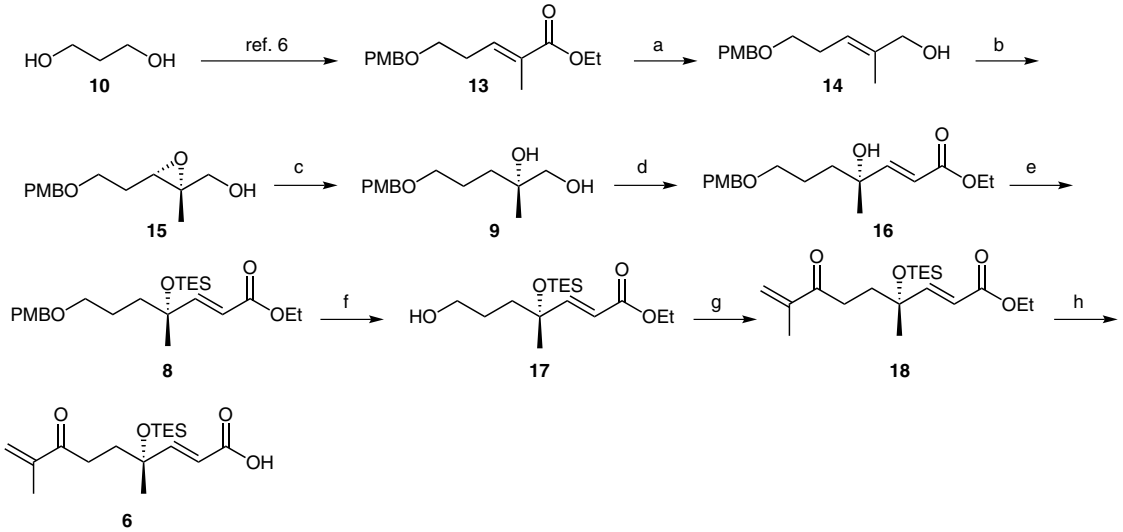


Scheme 1 Retrosynthetic analysis of (–)-5,6-dihydrocineromycine B (**1**) leading to the key building blocks **5**–**7**

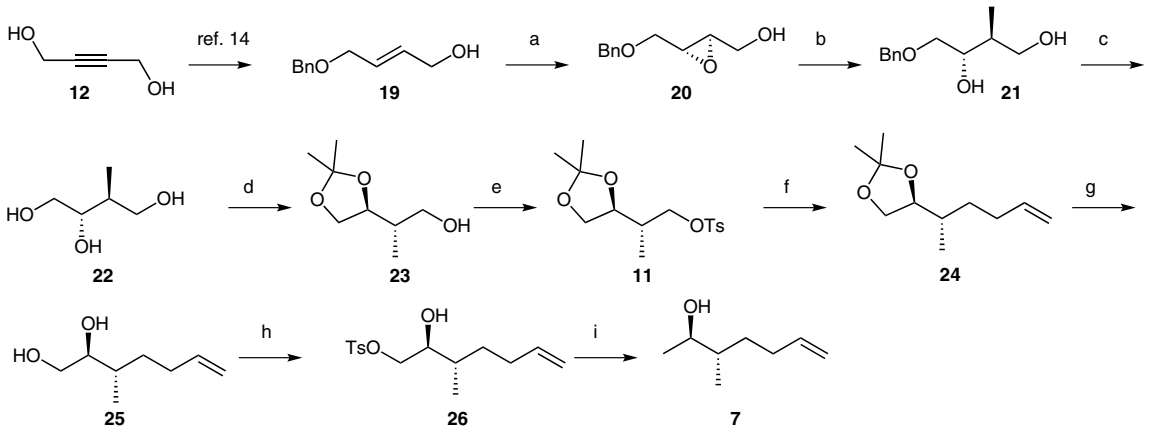
Martin oxidation of the secondary alcohol yielded ketone **18** in 97% yield.

Finally, compound **18** was subjected to ester hydrolysis using LiOH in THF–MeOH–H_2O (4:4:2) and THF–H_2O (1:1) at 0 °C to room temperature to give the corresponding acid **6** with low yields. The reaction was sluggish and resulted in multiple spots by TLC. At this stage, we opted for the Me_3SnOH-mediated nonacidolytic and nonnucleophilic hydrolysis[13] conditions in dichloroethane at 80 °C. As anticipated, the hydrolysis proceeded smoothly to afford the expected acid **3** in 98% yield. We believe this could be a general mild method for the benign cleavage of esters within labile substrates.

The synthesis of building block **7** started from but-2-yne-1,4-diol (**12**) which was converted to allylic alcohol **19** by a known procedure.[14] Sharpless asymmetric epoxidation[7] of allylic alcohol **19** using (–)-DIPT resulted in pure epoxide **20** in 95% yield with 98% ee. Ring opening of the epoxide was carried out by following Tius[15] protocol using MeLi and CuI in Et_2O, which yielded the mixture of 1,3-diol and undesired 1,2-diol (6:1). Subsequently, the minor isomer was readily removed by treating the mixture with sodium periodate to yield 1,3-diol **21** in 71% yield. After debenzylation of **21** by H_2, 10% Pd/C and MeOH at 25 °C for twelve hours afforded triol **22**[16] in 95% yield, the 1,2-hydroxyl groups were protected using 2,2-dimethoxypropane[17] and PTSA in CH_2Cl_2 at 25 °C to give **23** in 90% yield. Tosylation of the primary alcohol in **23** followed by the Grignard reaction with allylmagnesium bromide in the presence of stoichiometric[18] CuI led to the formation of allylated product **24** in 84% yield. Acid hy-



Scheme 2 *Reagents and conditions*: (a) DIBAL-H, CH_2Cl_2, 0 °C, 30 min, 95%; (b) (+)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, –20 °C, 95%; (c) LAH, THF, 0 °C, 30 min, 92%; (d) (i) IBX, DMSO, THF, r.t., 1 h; (ii) $(EtO)_2POCH_2CO_2Et$, *n*-BuLi, THF, 0 °C, 30 min, 90%; (e) TESCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 6 h, 94%; (f) DDQ, CH_2Cl_2–H_2O (9:1), 30 min, 90%; (g) (i) DMP, CH_2Cl_2, 0 °C to r.t., 1 h; (ii) C_3H_5MgBr, THF, –40 °C, 30 min, 70%; (iii) DMP, CH_2Cl_2, 0 °C to r.t., 1 h, 97%; (h) Me_3SnOH, DCE, 80 °C, 10 h, 98%.



Scheme 3 *Reagents and conditions*: (a) (–)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, –20 °C, 95%; (b) Me_2CuLi, Et_2O, –50 °C to 25 °C, 1,3-diol–1,2-diol (6:1); $NaIO_4$, H_2O, 71%; (c) H_2, Pd/C, MeOH, 12 h, 95%; (d) 2,2-dimethoxypropane, PTSA, CH_2Cl_2, 6 h, 90%; (e) TsCl, pyridine, CH_2Cl_2, 12 h, 93%; (f) AllylMgBr, CuI, Et_2O, 0 °C to r.t., 12 h, 82%; (g) AcOH–THF–H_2O (1:1:1), 8 h, 60 °C, 92%; (h) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 10 h, 90%; (i) LAH, THF, 0 °C, 2 h, 85%.

drolysis followed by the tosylation of the primary hydroxyl group in **25** was accomplished **26** in 90% using the Martinelli[19] procedure (Bu_2SnO, TsCl). Finally, reductive cleavage of sulfonate **26** by LAH in THF afforded key fragment **7** in 85% yield.

The key fragment **7** can also be synthesized from 4-penten-1-ol (**27**) shown in Scheme 4. Swern oxidation and subsequent Wittig homologation of **27** yielded α,β-unsaturated ester **28** in 90% yield exclusively as the *E*-isomer (J = 15.6 Hz). The ester was then subjected to reduction by DIBAL-H and afforded allylic alcohol **29**, which was further subjected to Sharpless epoxidation using (–)-DIPT and resulted in pure epoxide **30** in 75% yield with 95% ee. Regioselective ring opening of epoxide **30** with trimethylaluminium[20] in dichloromethane gave 1,2-diol **25**, which was converted into key fragment **7** as shown in Scheme 3.

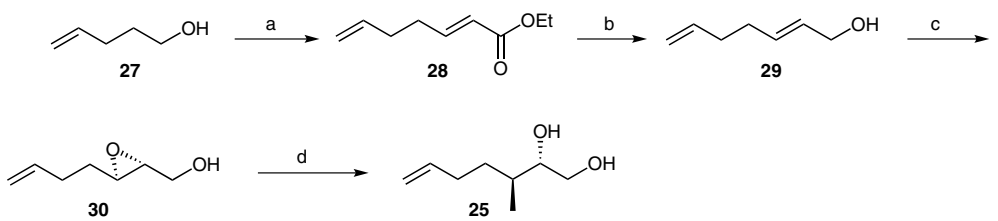
With the two key fragments **6** and **7** in hand, the stage was now set for their assembly and elaboration into (–)-5,6-dihydrocineromycine B (**1**) as shown in Scheme 5. Our fragment assembly began with coupling of fragments **6** and **7**. Esterification of **6** and **7** under Yamaguchi conditions[21] yielded **31** in 97% yield.

The α,β-unsaturated ketone **31** was then treated with (*R*)-(+)-2-methyl-CBS oxazaborolidine[22] and BH_3·DMS at –40 °C to furnish allyl alcohol **5** with an *S*-configuration in 90% yield with 98% de.[23] With a wealth of literature[24] available for sterically crowded or functionalized dienes to undergo RCM,[24] we next submitted the diene **5** to 25 mol% of Grubbs' second-generation catalyst in refluxing dichloromethane. As expected, the RCM proceeded smoothly to afford compound **32** in 40% yield. This late-stage intermediate has been already converted into the target compound in one step.[4b] All the intermediate compounds including macrolide **32** were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data.[25]

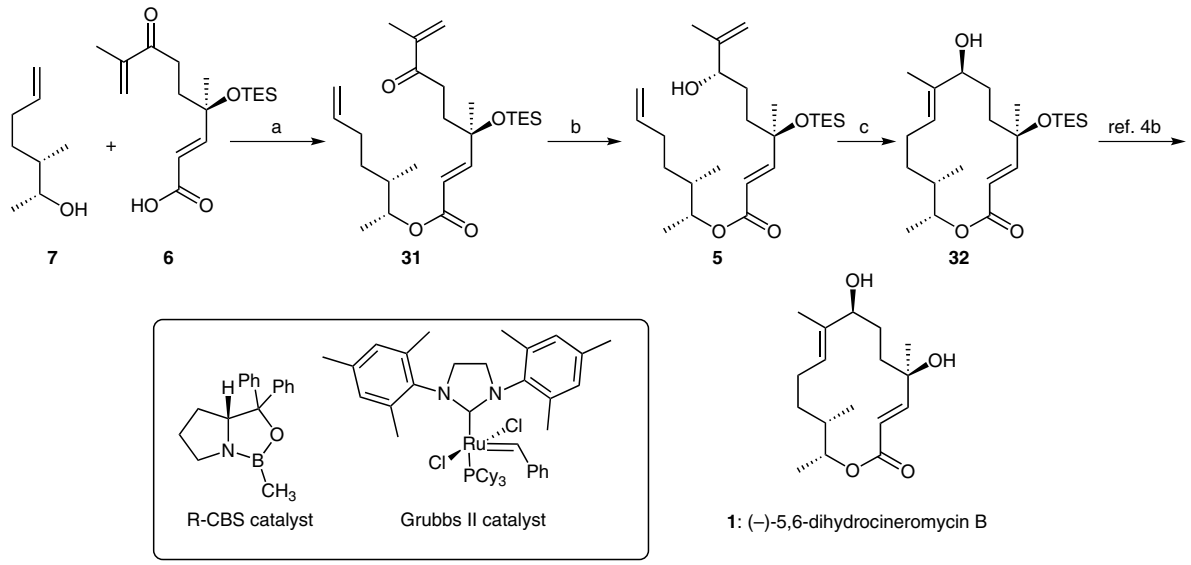
In summary, we have achieved an efficient and elegant formal synthesis of (–)-5,6-dihydrocineromycine B. The synthesis features key fragments which were constructed employing Sharpless asymmetric epoxidation and CBS reduction followed by ring-closing metathesis. A Yamaguchi esterification protocol was utilized to construct the backbone of the natural product, in which the 14-membered lactone moiety was constructed by the ring-closing metathesis. We believe that the presented synthetic method could be of value in the development of novel 14-membered lactone ring analogues for 5,6-dihydrocineromycine B research.

Acknowledgment

The authors gratefully acknowledge keen interest shown by Dr. J. S. Yadav, Director, IICT, Hyderabad. G.V.R thanks UGC, New Delhi for financial support.



Scheme 4 *Reagents and conditions*: (a) (i) Swern oxidation; (ii) $Ph_3PCHCOOEt$, CH_2Cl_2, r.t., 6 h, 90% (2 steps); (b) DIBAL-H, CH_2Cl_2, –78 °C; (c) (–)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, –20 °C, 95%; (d) Me_3Al, toluene, 0 °C to r.t., 6 h, 86%.



Scheme 5 *Reagents and conditions*: (a) benzene, 2,4,6-trichlorobenzoyl chloride, Et_3N then **7**, DMAP, 30 min, 97%; (b) (*R*)-2-methyl-CBS oxazaborolidine, THF, 0 °C, BH_3·DMS, 3 h, 90%, 98% de; (c) Grubbs II (25 mol%), CH_2Cl_2, reflux, 48 h, 40%.

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(25) **Spectral Data for Representative New Compounds**
Compound 9: colorless oil; $[\alpha]_D^{25}$ –5.5 (*c* 1, $CHCl_3$). IR (KBr): 3399, 2933, 1612, 1513, 1248, 1035, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, 2 H, *J* = 8.30 Hz), 6.80 (d, 2 H, *J* = 9.00 Hz), 4.38 (s, 2 H), 3.74 (s, 3 H), 3.40 (t, 2 H, *J* = 5.20 Hz), 3.35–3.21 (m, 2 H), 1.70–1.39 (m, 4 H), 1.06 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 129.2, 113.6, 72.5, 72.4, 70.4, 69.5, 54.8, 35.2, 24.0, 23.1. ESI-MS: *m/z* = 277 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{14}H_{22}NaO_4$: 277.1416; found: 277.1410.
Compound 16: colorless oil; $[\alpha]_D^{25}$ +13.7 (*c* 1, $CHCl_3$). IR (KBr): 3446, 2926, 1722, 1655, 1513, 1219, 1035, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, 2 H, *J* = 8.49 Hz), 6.92–6.77 (m, 3 H), 5.97 (d, 1 H, *J* = 15.67 Hz), 4.40 (s, 2 H), 4.16 (q, 2 H, *J* = 7.17, 14.16 Hz), 3.77 (s, 3 H), 3.47–3.32 (m, 3 H), 1.75–1.56 (m, 4 H), 1.33–1.22 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 159.1, 154.4, 129.7, 129.1, 118.9, 113.6, 72.6, 72.1, 70.0, 59.9, 54.8, 39.5, 28.1, 24.3, 14.3. ESI-MS: *m/z* = 345 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{18}H_{26}NaO_5$: 345.1678; found: 345.1667.
Compound 17: colorless oil; $[\alpha]_D^{25}$ +10.6 (*c* 1, $CHCl_3$). IR (KBr): 3424, 2955, 1720, 1656, 1459, 1299, 1061, 772 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.83 (d, 1 H, *J* = 15.1 Hz), 5.88 (d, 1 H, *J* = 15.1 Hz), 4.18 (q, 2 H, *J* = 6.79, 14.35 Hz), 3.59 (t, 2 H, *J* = 6.04 Hz), 1.67–1.52 (m, 4 H), 1.39 (s, 3 H), 1.31 (t, 3 H, *J* = 6.79 Hz) 0.97 (t, 9 H, *J* = 8.30, 15.86 Hz), 0.61 (q, 6 H, *J* = 7.55, 15.86 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 154.4, 119.0, 75.1, 62.9, 60.2, 39.8, 27.9, 27.4, 14.4, 7.2, 6.8. ESI-MS: *m/z* = 339 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{16}H_{32}NaO_4Si$: 339.1968; found: 339.1961.

Compound 6: colorless oil; $[\alpha]_D^{25}$ –13.5 (*c* 1, $CHCl_3$). IR (KBr): 3414, 2924, 1706, 1454, 1219, 1018, 770 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (d, 1 H, *J* = 15.86 Hz), 5.95 (d, 1 H, *J* = 15.10 Hz), 5.91 (s, 1 H), 5.73 (s, 1 H), 2.83–2.69 (m, 1 H), 2.66–2.52 (m, 1 H), 1.95–1.81 (m, 5 H), 1.43 (s, 3 H), 0.97 (t, 9 H, *J* = 8.30 Hz), 0.61 (q, 6 H, *J* = 7.55, 15.86 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.6, 172.0, 156.7, 144.6, 124.1, 118.8, 74.8, 37.0, 31.9, 28.2, 17.8, 7.2, 6.7. ESI-MS: *m/z* = 349 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{30}NaO_4Si$: 349.1811; found: 349.1820.

Compound 11: colorless oil, $[\alpha]_D^{25}$ –2.5 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, 2 H, *J* = 7.90 Hz), 7.34 (d, *J* = 7.90 Hz), 4.19–4.13 (m, 1 H), 4.03–3.96 (m, 2 H), 3.84 (q, 1 H, *J* = 6.30, 14.30 Hz), 3.58 (t, 1 H, *J* = 7.10 Hz), 2.45 (s, 3 H), 1.96–1.87 (m, 1 H), 1.31 (s, 3 H), 1.27 (s, 3 H), 0.90 (d, 3 H, *J* = 7.10 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 132.9, 129.7, 127.8, 109.0, 76.3, 72.2, 67.6, 37.0, 26.5, 25.3, 21.5, 12.8. ESI-MS: *m/z* = 337 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{15}H_{22}NaO_5S$: 337.1086; found: 337.1091.

Compound 7: colorless oil; $[\alpha]_D^{25}$ –12.8 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.65 (m, 1 H), 5.05–4.85 (m, 2 H), 3.62 (pent, 1 H, *J* = 6.04, 12.08, 18.12 Hz), 2.27–2.06 (m, 1 H), 2.05–1.86 (m, 2 H), 1.66–1.42 (m, 1 H), 1.23–1.13 (m, 1 H), 1.10 (d, 3 H, *J* = 6.04 Hz), 0.87 (d, 3 H, *J* = 6.79 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.73, 114.53, 71.26, 39.41, 31.73, 31.50, 19.39, 14.50.

Compound 31: colorless oil; $[\alpha]_D^{25}$ –17.2 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78 (d, 1 H, *J* = 15.70 Hz), 5.93–5.84 (m, 2 H), 5.77–5.69 (m, 2 H), 5.02–4.38 (m, 3 H), 2.80–2.69 (m, 1 H), 2.67–2.58 (m, 1 H), 2.21–2.09 (m, 1 H), 2.06–1.97 (m, 1 H), 1.91–1.83 (m, 5 H), 1.79–1.69 (m, 1 H), 1.56–1.45 (m, 1 H), 1.41 (s, 3 H), 1.27–1.23 (m, 1 H), 1.20 (d, 3 H, *J* = 6.87 Hz), 0.96 (t, 9 H, *J* = 7.85 Hz), 0.92 (d, 3 H, *J* = 6.87 Hz), 0.61 (q, 6 H, *J* = 7.85, 15.70 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.47, 166.14, 153.78, 144.47, 138.58, 124.34, 119.72, 114.63, 74.67, 74.17, 37.26, 36.80, 32.09, 31.78, 31.29, 28.09, 17.73, 16.07, 14.60, 7.12, 6.71. ESI-MS: *m/z* = 459 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{25}H_{44}NaO_4Si$: 459.2907; found: 459.2910.

Compound 5: colorless oil; $[\alpha]_D^{25}$ –21.7 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (d, 1 H, *J* = 15.48 Hz), 5.93–5.84 (m, 2 H), 5.91 (d, 1 H, *J* = 15.48 Hz), 5.87–5.69 (m, 1 H), 5.07–4.81 (m, 5 H), 4.02 (t, 1 H, *J* = 5.28 Hz), 2.30–2.30 (m, 1 H), 2.23–1.93(m, 2 H), 1.69 (s, 3 H), 1.64–1.44 (m, 4 H), 1.38 (s, 3 H), 1.30–1.23 (m, 2 H), 1.19 (d, 3 H, *J* = 6.7 Hz), 0.96 (t, 9 H, *J* = 7.55 Hz), 0.92 (d, 3 H, *J* = 6.79 Hz), 0.61 (q, 6 H, *J* = 7.55, 15.86 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.17, 154.27, 147.27, 128.58, 127.58, 126.56, 114.75, 111.27, 75.81, 74.96, 74.10, 39.02 36.83, 31.81, 31.34, 29.79, 29.11, 27.71, 17.64, 16.12, 14.68, 7.16, 6.79. ESI-MS: *m/z* 461 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{25}H_{46}NaO_4Si$: 461.3063; found: 461.3044.