Enantioselective Synthesis of the Lyngbouilloside Macrolactone Core

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Abstract: The macrocyclic core of the marine natural product lyngbouilloside has been prepared in a convergent and enantioselective manner.

Key words: lyngbouilloside, lactone, ring-closing metathesis, dithiane

The cyanobacteria have been identified as a prolific source from which to isolate bioactive natural products that often possess unique molecular structures.[1] Following a collection of the 'cobweb-like' cyanobacterial species *Lyngbya bouillonii* from the Northern Coast of Papua New Guinea, the Gerwick group recently reported the isolation and characterization of the novel and cytotoxic natural product lyngbouilloside (**1**, $IC_{50} = 17$ μM against neuroblastoma cells).[2] At the time of isolation, lyngbouilloside was only the second macrolide glycoside to be isolated from a marine cyanobacterium.[3a] However, **1** bears resemblance to a number of other secondary metabolites that have been isolated from various marine sources suggesting a common cyanobacterial origin.[3]

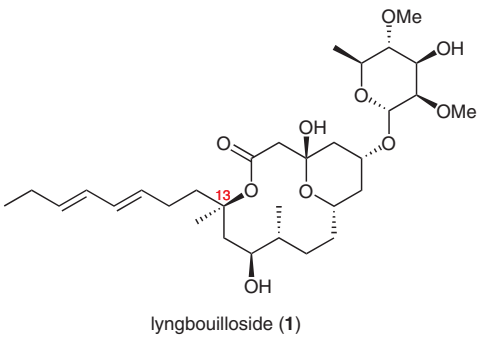
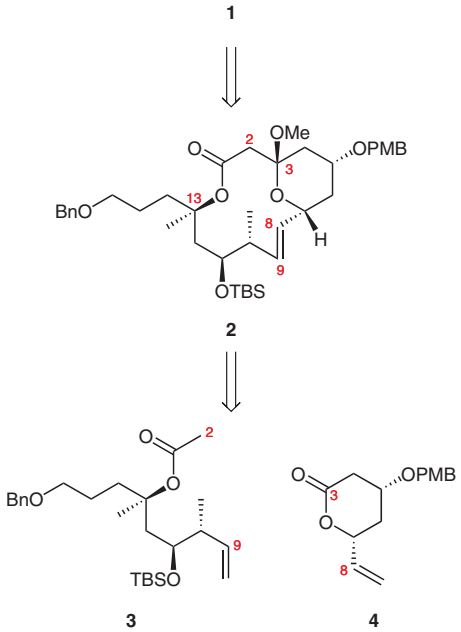


Figure 1 Proposed structure of lyngbouilloside

The molecular structure of **1** was elucidated primarily by NMR spectroscopic techniques and revealed a cyclic trisubstituted six-membered hemiacetal embedded within a 14-membered macrolactone (Figure 1). The macrocyclic ester linkage onto the fully substituted C13 stereocenter is a particularly unusual and challenging motif for synthesis.

To date no total synthesis of lyngbouilloside has been reported. Recently, however, Cossy disclosed the preparation of a linear and uncyclized C1–C13 fragment of lyngbouilloside and this remains the only published venture towards the natural product.[4] In light of this communication we wish to report our initial studies towards lyngbouilloside that have resulted in an effective route to the macrocyclic core of the natural product.

Our strategy to lyngbouilloside involves late-stage *E*,*E*-diene installation and glycosylation[5] of macrocycle **2** (Scheme 1). Preliminary studies indicated that macrolactonization at the sterically encumbered C13 tertiary alcohol would prove highly challenging.[6] To avoid this difficult transformation we elected to disconnect macrocycle **2** at the C2–C3 and C8–C9 bonds. This retrosynthetic simplification revealed fragments **3** and **4**, which are of similar complexity. It was anticipated that the C8–C9 bond would be established through ring-closing metathesis[7] whilst the C3 substituent of the pyran could be installed through the addition of the enolate of ester **3** to lactone fragment **4**.



Scheme 1 Retrosynthetic analysis of **1**

The preparation of lactone **4** commenced from known ynone **5**, itself available in two steps from (*S*)-glycidol (Scheme 2).[8] Double conjugate addition of propane-1,3-

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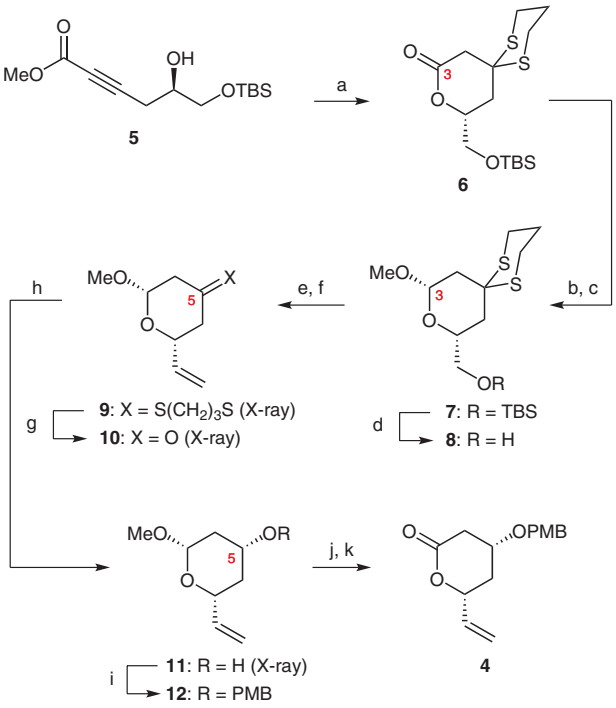
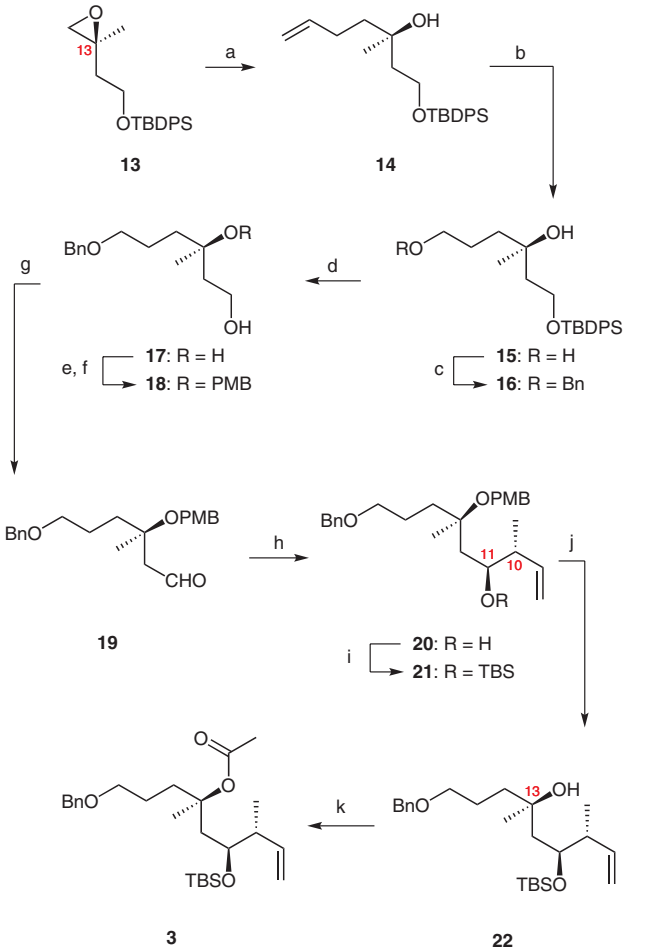
dithiol, with concomitant in situ cyclization, proceeded efficiently to provide lactone **6** in high yield and establish the required latent oxygenation pattern.[9] Reduction (DIBAL-H, CH_2Cl_2, –78 °C) and alkylation of the resulting mixture of lactol diastereomers (ca. 1.5:1 dr) afforded nonfully anomerically stabilized acetal **7** in high yield and as a single C3 diastereomer.[10] Installation of the terminal olefin occurred without incident to afford dithiane **9** that was oxidatively hydrolyzed using bis(trifluoroacetoxy)iodobenzene[11] to yield crystalline ketone **10**. Reduction of **10** with sodium borohydride generated the desired C5 alcohol **11** as a single diastereomer in essentially quantitative yield. X-ray crystallographic and NOE analysis confirmed the relative configuration of **11**.[12] Formation of PMB ether **12** and a hydrolysis–oxidation sequence to reintroduce the lactone motif (PPTS, H_2O–MeOH, reflux, then TPAP–NMO[13]) completed the synthesis of key fragment **4**.[14]



Scheme 2 Synthesis of lactone **4**. *Reagents and conditions*: (a) $HS(CH_2)_3SH$, NaOMe, THF, –78 °C to r.t., 87%; (b) DIBAL-H, CH_2Cl_2, –78 °C, 99%, 1.5:1 dr; (c) KHMDS, 18-crown-6, MeI, THF, –78 °C, 82%; (d) TBAF, THF, r.t., 99%; (e) SO_3·py, *i*-Pr_2NEt, CH_2Cl_2, DMSO, 0 °C; (f) Ph_3PCH_3Br, KO*t*-Bu, THF, 0 °C to r.t., 91% (2 steps); (g) BTI, MeCN–H_2O (7:1), 0 °C to r.t., 95%; (h) $NaBH_4$, MeOH, –78 °C; (i) PMBBr, NaH, DMF, 0 °C, 61% (2 steps); (j) PPTS, MeCN–H_2O (3:1), reflux, ca. 2:1 dr; (k) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C, 75% (2 steps).

Our route to ester **3** began from enantiomerically enriched epoxide **13** which was prepared using Jacobsen's enantioselective ring-opening procedure in multigram quantities with >99:1 er (Scheme 3).[15] Regioselective epoxide opening of **13** with allyl magnesium chloride proceeded cleanly to generate **14** that was ozonolyzed with a reductive workup ($NaBH_4$) to afford primary alcohol **15**. Protecting-group manipulations gave PMB ether **18** which could then be oxidized to aldehyde **19**. Exposure of **19** to Brown's (+)-Ipc-derived crotylborane reagent (formed in situ) provided compound **20** with almost complete stereocontrol (>19:1 dr).[16] The configuration of the C10 and C11 stereocenters was confirmed by Mosher ester[17] and coupling-constant-based analysis[18] of a derivative and is in accord with previously reported additions employing the (+)-Ipc-derived crotylborane reagent. After silylation of crude **20** the now superfluous PMB ether was oxidatively cleaved (1.1 equiv DDQ then scavenging of the generated anisaldehyde with polymer-supported benzylamine) to liberate the C13 tertiary alcohol. Finally, desired ester **3** was obtained in good yield after prolonged exposure of **22** to isopropenyl acetate in the presence of a resin-bound toluenesulfonic acid equivalent.[19]



Scheme 3 Synthesis of ester **3**. *Reagents and conditions*: (a) AllylMgCl, THF, 0 °C to r.t.; (b) O_3, CH_2Cl_2–MeOH (5:1), –78 °C, then $NaBH_4$, –78 °C to r.t.; (c) NaH, BnBr, THF, 0 °C to r.t.; (d) TBAF, THF, r.t., 71% (4 steps); (e) 1-(dimethoxymethyl)-4-methoxybenzene, PPTS, CH_2Cl_2, r.t.; (f) DIBAL, CH_2Cl_2, –78 °C, 93% (2 steps); (g) SO_3·py, *i*-Pr_2NEt, DMSO, CH_2Cl_2, 0 °C, 99%; (h) (*E*)-but-2-ene, KO*t*-Bu, *n*-BuLi, THF–Et_2O, –78 °C to –45 °C, $(+)\text{-(Ipc)}_2BOMe$, BF_3·OEt_2, then aldehyde **19**, –78 °C, >19:1 dr; (i) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 70% (2 steps); (j) DDQ, CH_2Cl_2, buffer pH 7, r.t., then Quadrapure BZA™, CH_2Cl_2, r.t., 94%; (k) isopropenyl acetate, MP-TsOH, CH_2Cl_2, 4 Å MS, r.t., 77%.

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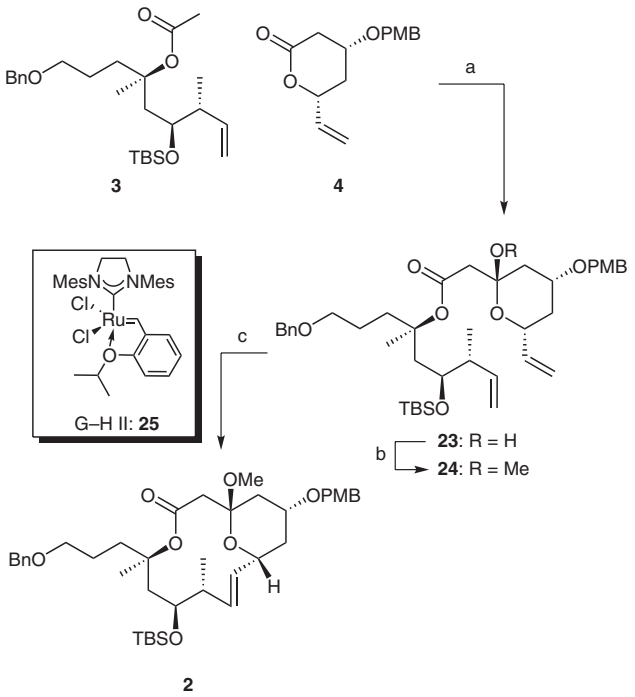
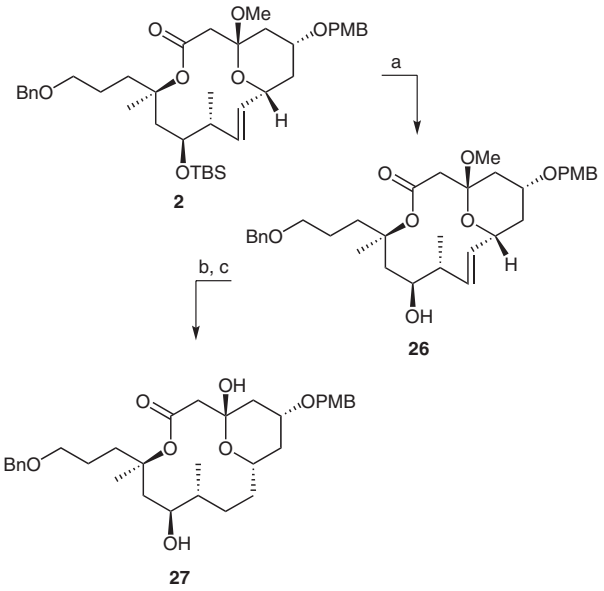
With effective routes to fragments **3** and **4** in place, attention was next turned to their successful union. Following optimization we were pleased to find that the addition of lactone **4** to 2 equivalents of the lithium enolate of **3** furnished adduct **23** (ν = 1705 cm^{-1}) in essentially quantitative yield (Scheme 4). This key bond construction could be performed on gram scale and excess **3** (required to effect full conversion) could be recovered and recycled with good efficiency. Lactol **23** was then converted into acetal **24** (ν = 1727 cm^{-1}) in preparation for the ensuing metathetic macrocyclization.[20] Spectroscopic analysis indicated that trisubstituted tetrahydropyran **24** was the 2,4,6-*cis*-configured isomer. Treatment of diene **24** with a variety of metathesis catalysts (Grubbs, Schrock, and Hoveyda types) failed to elicit detectable macrocyclization. However, following extensive model studies, we found that ring-closing metathesis of diene **24** using Grubbs–Hoveyda (G–H) catalyst **25** in the presence of 1,4-benzoquinone[21] resulted in the formation of macrocycle **2** (J = 16 Hz) in yields up to 80%.[22] The stereocontrolled synthesis of macrolactone **2** represents the first known preparation of a fully functionalized lyngbouilloside macrocycle and validates our strategy as a viable synthetic approach for the total synthesis of lyngbouilloside. It is interesting to note that recent reports on attempts to engage vinyl groups on tetrahydropyran templates in RCM-based macrocyclizations have met with considerable frustration.[23]



Scheme 4 Synthesis of macrocycle **2**. *Reagents and conditions*: (a) **3** (2 equiv), LDA, THF, –78 °C, then **4**, 99%; (b) $HC(OMe)_3$, PPTS, MeOH, r.t., 98%; (c) G–H II (**25**), 1,4-benzoquinone, toluene, reflux. 80%.

Our initial attempts into completing the total synthesis of lyngbouilloside have generated some interesting results (Scheme 5). Silyl group removal and alkene hydrogenation of **2** provides a compound whose exact spectroscopic characterization is not possible as a consequence of considerable line broadening in the ^1H NMR spectrum (the ^1H NMR spectrum of **26** did not exhibit line broadening[24]). This NMR phenomenon was unexpected as the fully resolved ^1H NMR spectrum of natural lyngbouilloside was obtained under identical experimental conditions.[25] We speculated that the presence of the methyl acetal in the macrocycle could be the cause of this unexpected spectroscopic behavior. However, mild acid hydrolysis provided **27**, a compound that again failed to correlate with the ^1H NMR and ^{13}C NMR spectra of the natural isolate. Although far from definitive, these initial observations, in conjunction with DFT-based NMR chemical shift calculations we have conducted, serve as a warning that the proposed structure of lyngbouilloside may be incorrect. A successful total synthesis of **1** is required to provide unambiguous proof of its structure.



Scheme 5 Synthesis of lyngbouilloside core **27**. *Reagents and conditions*: (a) TBAF, THF, r.t., 58%; (b) H_2, Pd/C, THF; (c) PPTS, MeCN–H_2O (3:1), r.t., quant.

In conclusion, we have designed a highly convergent synthesis of the macrocyclic core of lyngbouilloside. The formation of macrocycle **2** by an enolate–lactone coupling and ring-closing metathesis sequence provides a novel and effective entry to the challenging macrolactone core of the natural product. Particularly noteworthy is the complexity of the fragments involved in the key coupling event (**3** + **4** → **23**) and the requirement of 1,4-benzoquinone for an effective metathetic annulation. The elaboration of **2** to the proposed structure of lyngbouilloside is ongoing in our laboratories and will be reported in due course.

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(14) **Data for Compound 4**: $[\alpha]_D^{25}$ –10.6 (*c* 0.805, $CHCl_3$). IR (neat): 2932, 1734, 1612, 1513, 1355, 1302, 1245, 1172, 1075, 1031 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.25 (2 H, d, *J* = 8.5 Hz), 6.89 (2 H, d, *J* = 8.6 Hz), 5.90 (1 H, ddd, *J* = 17.2, 10.5, 6.0 Hz), 5.37 (1 H, d, *J* = 17.2 Hz), 5.26 (1 H, d, *J* = 10.5 Hz), 4.66–4.63 (1 H, m, H7), 4.50 (2 H, s), 3.97–3.93 (1 H, m), 3.81 (3 H, s), 2.90 (1 H, dd, *J* = 17.3, 6.0 Hz), 2.58 (1 H, dd, *J* = 17.3, 7.9 Hz), 2.35 (dt, 1 H, *J* = 13.8, 3.4 Hz), 1.72 (1 H, ddd, *J* = 13.8, 11.8, 9.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.8, 159.5, 135.3, 129.5, 129.3, 117.4, 114.0, 77.3, 70.1, 69.7, 55.3, 36.9, 35.3. ESI-HRMS: *m/z* calcd for $C_{15}H_{18}O_4Na$ $[M + Na]^+$: 285.1103; found: 285.1094. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.64; H, 6.97.

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(19) **Data for Compound 3**
$[\alpha]_D^{25}$ +26.5 (*c* 0.80, $CHCl_3$). IR (neat): 2958, 2930, 2857, 1732, 1639, 1364, 1246, 1101, 1075, 1041 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.33 (4 H, m), 7.29–7.27 (1 H, m), 5.74 (1 H, ddd, *J* = 17.3, 10.4, 6.8 Hz), 5.05–5.01 (2 H, m), 4.49 (2 H, s), 3.89–3.87 (1 H, m), 3.46–3.42 (2 H, m), 2.42–2.40 (1 H, m), 2.08 (1 H, dd, *J* = 14.7, 3.7 Hz), 1.96–1.93 (1 H, m), 1.95 (3 H, s), 1.87–1.84 (1 H, m), 1.63–1.56 (3 H, m), 1.45 (3 H, s), 1.00 (3 H, d, *J* = 6.9 Hz), 0.89 (9 H, s), 0.08 (3 H, s), 0.07 (3 H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.2, 140.5, 138.5, 128.3, 127.7, 127.5, 114.9, 84.0, 73.0, 72.3, 70.6, 43.9, 41.0, 35.9, 26.0, 24.2, 24.2, 22.4, 18.1, 13.4, –4.0, –4.2. ESI-HRMS: *m/z* calcd for $C_{26}H_{44}O_4SiNa$ $[M + Na]^+$: 471.2907; found: 471.2907. Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 65.59; H, 9.88. Found: C, 69.64; H, 9.85.

(20) **Data for Compound 24**
$[\alpha]_D^{25}$ –31.80 (*c* 0.47, $CHCl_3$). IR (neat): 2930, 2856, 1727, 1614, 1514, 1247, 1077, 1038 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.31 (4 H, m), 7.29–7.25 (1 H, m), 7.24 (2 H, d, *J* = 8.8 Hz), 6.85 (2 H, d, *J* = 8.8 Hz), 5.84 (1 H, ddd, *J* = 16.9, 10.5, 6.1 Hz), 5.75 (1 H, ddd, *J* = 17.3, 10.8, 6.8 Hz), 5.26 (1 H, d, *J* = 16.9 Hz), 5.12 (1 H, d, *J* = 10.5 Hz), 5.05–5.00 (2 H, m), 4.49 (1 H, d, *J* = 11.3 Hz), 4.48 (2 H, s), 4.44 (1 H, d, *J* = 11.3 Hz), 4.01 (1 H, dd, *J* = 11.3, 5.4 Hz), 3.91–3.85 (2 H, m), 3.79 (3 H, s), 3.47–3.41 (2 H, m), 3.20 (3 H, s), 2.74 (1 H, d, *J* = 13.6 Hz), 2.51 (1 H, d, *J* = 13.6 Hz), 2.48 (1 H, dd, *J* = 13.0, 3.8 Hz), 2.45–2.40 (1 H, m), 2.10 (1 H, dd, *J* = 14.8, 3.3 Hz), 2.07 (1 H, d, *J* = 12.8 Hz), 1.95 (2 H, t, *J* = 7.9 Hz), 1.70–1.55 (4 H, m), 1.49 (3 H, s), 1,33 (1 H, q, *J* = 11.9 Hz), 1.00 (2 H, d, *J* = 6.9 Hz), 0.90 (9 H, s), 0.08 (3 H, s), 0.08 (3 H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.1, 159.1, 140.4, 138.6, 138.0, 130.8, 129.1, 128.3, 127.6, 127.5, 115.5, 114.9, 113.8, 99.7, 84.9, 72.9, 72.2, 71.2, 70.5, 70.1, 69.5, 55.3, 47.9, 43.9, 43.1, 41.0, 39.7, 37.2, 36.0, 26.0, 24.1 (2 × C), 18.1, 13.3, –3.9, –4.2. ESI-HRMS: *m/z* calcd for $C_{42}H_{64}O_8NaSi$ $[M + Na]^+$: 747.4268; found: 747.4249. Anal. Calcd for $C_{42}H_{64}O_8Si$: C, 69.58; H, 8.90. Found: C, 69.53; H, 9.07.

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(22) **Data for Compound 2**
$[\alpha]_D^{25}$ –68.3 (*c* 0.925, C_6H_6). IR (neat): 2932, 2856, 1723, 1614, 1514, 1246, 1102, 1063 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.32 (4 H, m), 7.29–7.24 (3 H, m), 6.87 (2 H, d, *J* = 8.1 Hz), 5.92 (1 H, dd, *J* = 15.9, 2.7 Hz), 5.64 (1 H, dd, *J* = 16.0, 9.6 Hz), 4.51–4.46 (3 H, br s), 4.45 (2 H, s), 3.95–3.90 (1 H, m), 3.80 (4 H, br s), 3.49–3.40 (2 H, m), 3.20 (3 H, s), 2.85 (1 H, br d, *J* = 16.5 Hz), 2.82 (1 H, d, *J* = 12.9 Hz), 2.42–2.37 (1 H, m), 2.31 (1 H, d, *J* = 12.9 Hz), 2.27–2.18 (4 H, m), 1.75 (1 H, d, *J* = 16.1 Hz), 1.74–1.62 (2 H, m), 1.50–1.39 (2 H, m), 1.31 (3 H, s), 0.95 (2 H, d, *J* = 7.0 Hz), 0.86 (9 H, s), 0.03 (3 H, s), 0.01 (3 H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.8, 159.1, 138.5, 136.3, 134.4, 130.8, 129.0, 128.4, 127.7, 127.5, 113.8, 98.1, 85.8, 73.7, 73.0, 70.5, 69.7, 69.7, 69.2, 55.3, 47.7, 45.5, 44.1, 41.0, 37.4, 35.8, 32.7, 25.9, 24.3, 23.5, 18.0, 11.7, –3.8, –4.8. ESI-HRMS:

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m/z calcd for $C_{40}H_{60}O_8NaSi$ $[M + Na]^+$: 719.3955; found: 719.3945.

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(24) **Data for Compound 26**
$[\alpha]_D^{25}$ –61 (*c* 0.235, $CHCl_3$). IR (neat): 3464, 2924, 2853, 1721, 1613, 1514, 1455, 1246, 1098, 1041 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 7.33 (2 H, d, *J* = 7.8 Hz), 7.22 (2 H, d, *J* = 8.6 Hz), 7.19 (2 H, d, *J* = 7.5 Hz), 7.12–7.07 (1 H, m), 6.80 (2 H, d, *J* = 8.6 Hz), 6.04 (1 H, dd, *J* = 15.9, 3.5 Hz), 5.97 (1 H, ddd, *J* = 15.9, 8.2, 1.1 Hz), 4.36 (1 H, d, *J* = 11.6 Hz), 4.34–4.31 (4 H, m, H7), 4.01–3.96 (1 H, m), 3.74–3.70 (1 H, m), 3.35–3.27 (2 H, m), 3.29 (3 H, s), 3.02 (3 H, s), 2.88 (1 H, *J* = 12.2 Hz), 2.73 (1 H, br d, *J* = 16.1 Hz), 2.53 (1 H, dd, *J* = 13.5, 9.1 Hz), 2.54–2.46 (1 H, m), 2.31 (1 H, dd, *J* = 13.5, 7.1 Hz), 2.22–2.15 (1 H, m), 2.15 (1 H, d, *J* = 12.2 Hz), 2.14–2.08 (1 H, m), 1.75–1.66 (3 H, m), 1.63–1.54 (1 H, m), 1.47 (1 H, d, *J* = 16.1 Hz), 1.41 (3 H, s), 1.01 (3 H, d, *J* = 6.8 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ = 168.5, 159.7, 139.4, 136.9, 134.6, 131.4, 128.5, 128.3, 127.7, 127.5, 114.1, 98.9, 85.7, 73.0, 72.7, 70.7, 69.9, 69.9, 69.7, 54.7, 47.4, 45.0, 44.2, 39.8, 38.5, 36.1, 33.5, 24.8, 23.7, 11.9. ESI-HRMS: m/z calcd for $C_{34}H_{46}O_8Na$ $[M + Na]^+$: 605.3090; found: 605.3078.

(25) We have conducted our own NMR analysis of a sample of natural lyngbouilloside kindly donated to us by Professor Gerwick.

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