Facile Synthesis of the C1–C13 Fragment of Lyngbouilloside

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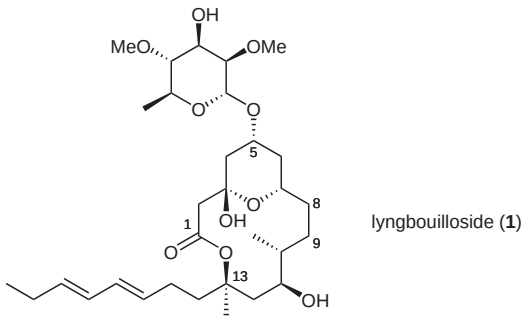
Received 7 December 2007

Abstract: A highly efficient synthesis of the C1–C13 fragment of the marine macrolide lyngbouilloside is presented starting from commercial (*S*)-citramalic acid.

Key words: lyngbouilloside, cross-metathesis, crotyltitanation

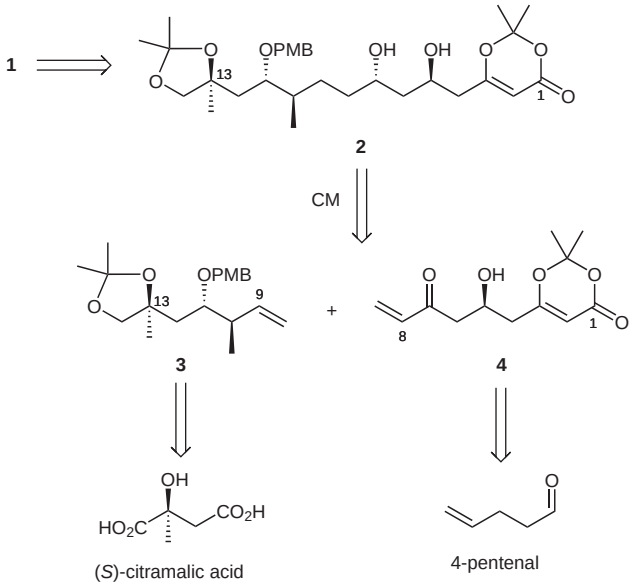
Marine cyanobacteria are an exceptionally rich source of bioactive mainly nitrogenous secondary metabolites.[1] Isolated from the filamentous species *Lyngbya bouillonii* (*Oscillatoriaceae*) collected off the coast of Papua New Guinea, lyngbouilloside (**1**) represents one of the first glycosidic macrolides of cyanobacterial origin and its structure was determined as a 14-membered lactone containing a six-membered hemiacetal, a pendant dienyl side chain and a rhamnose derivative attached at C5 (Figure 1).[2] While **1** shares these structural features with the related callipeltosides[3a] or the aurisides,[3b] the presence of an unusual tertiary methyl carbinol at C13 is in common only with lyngbyaloside B, a brominated analogue from *Lyngbya* sp.[4]

Despite its interesting cytotoxic activity against neuro-2a tumor cells (IC_{50} = 17 μM) and its challenging chemical structure no total synthesis of **1** has been reported to date. In the course of our ongoing efforts towards a first total synthesis of **1**, we herein wish to present a rapid access to the linear carbon backbone **2** containing the complete stereochemical information of the macrocyclic core (Scheme 1). As the key step in our convergent approach we envisioned a selective cross-metathesis (CM) of the fully functionalized C1–C8 and C9–C13 fragments **3** and **4** which are easily derived from commercial (*S*)-citramalic acid and 4-pentenal, respectively. Subsequent protecting-group manipulations in fragment **2** followed by introduction of the side chain and thermal macrolactonization via intramolecular ketene trapping[5] should then give rise to the aglycon of lyngbouilloside in a few steps.



lyngbouilloside (**1**)

Figure 1 Proposed structure of lyngbouilloside



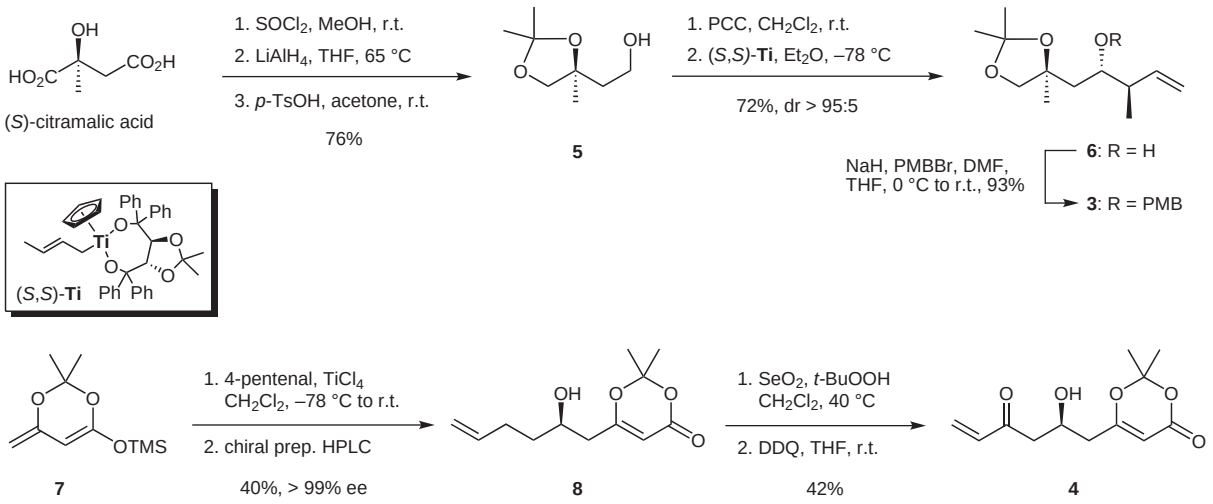
Scheme 1 Retrosynthetic analysis of the C1–C13 fragment **2**

While the C5 stereocenter in the eastern fragment **4** was planned to be introduced via an asymmetric vinylogous aldol reaction, the 1,2-*anti* relationship found in the western fragment **3** at C10 and C11 should be installed by an enantioselective crotyltitanation of the corresponding aldehyde.

Thus, the synthesis of **3** began with an esterification of (*S*)-citramalic acid using $SOCl_2$ in MeOH followed by $LiAlH_4$ reduction of the resulting dimethyl citramalate (Scheme 2). Selective 1,2-diol protection with acetone in the presence of PTSA then gave the known acetal **5** in 76% overall yield (three steps).[6] Treatment of the crude aldehyde obtained upon PCC oxidation of **5** with the highly face-selective crotyltitanium complex (*S*,*S*)-**Ti**[7] produced the homoallylic alcohol **6** with excellent diastereoselectivity (dr >95:5) in 72% overall yield. The latter was then protected as a PMB ether (NaH, PMBBr, DMF–THF) to efficiently afford the desired CM partner **3**.[8]

Whereas various examples for the asymmetric aldol reaction of silyl dienol ethers of type **7** with aromatic or olefinic aldehydes are known, efficient and highly enantioselective methods for the conversion of aliphatic

SYNLETT 2008, No. 5, pp 0712–0714
Advanced online publication: 26.02.2008
DOI: 10.1055/s-2008-1042805; Art ID: G40307ST

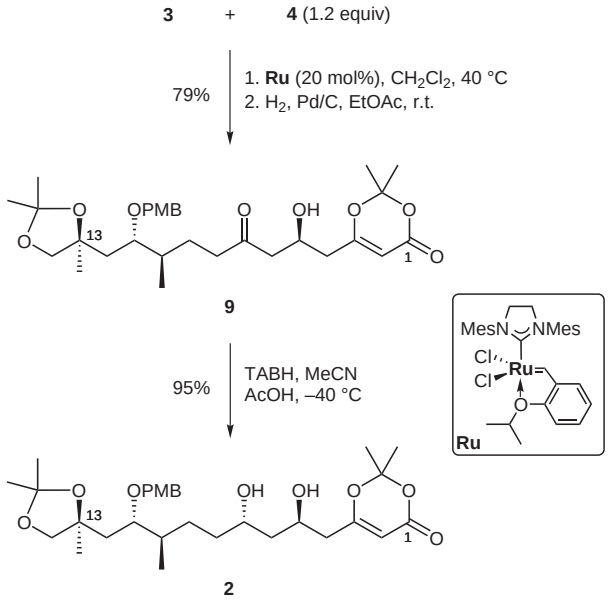


Scheme 2 Synthesis of the CM partners **3** and **4**

aldehydes are rare and the availability of the required catalyst systems is usually low.[9] As initial attempts to control the C5 stereocenter in **8** by reaction of **7** with 4-pentenal using conditions described by Sato[10] and Denmark et al.[11] were rather unsatisfying, we decided to separate the racemate of **8** by preparative chiral HPLC.[12]

Fortunately, the pure *R*-enantiomer **8** could be obtained in 40% overall yield from commercial 4-pentenal.[13] In course of the subsequent allylic oxidation we were pleased to find that a sequential treatment of alkene **8** with SeO_2 and *t*-BuOOH in refluxing CH_2Cl_2 and DDQ in THF regioselectively furnished the desired enone **4** in an acceptable yield of 42% (two steps).[14]

With both fragments available, CM of **3** with a slight excess (1.2 equiv) of **4** in the presence of 20 mol% of the Hoveyda–Grubbs catalyst **Ru**[15] followed by direct catalytic hydrogenation (1 atm H_2, Pd/C, EtOAc) of the crude enone gave rise to the entire carbon backbone of **1** in 79% (Scheme 3).[16] Finally 1,3-*anti* reduction of **9** with tetramethylammonium triacetoxyborohydride (TABH)[17] then afforded the C1–C13 fragment **2** as the only product (dr >95:5) in almost quantitative yield.[18]



Scheme 3 Synthesis of the C1–C13 fragment **2**

In conclusion, we have described a facile stereoselective access to the fully functionalized C1–C13 fragment **2** of lyngbouilloside (**1**), which was obtained in nine steps and 38% overall yield starting from commercially available (*S*)-citramalic acid. The completion of the total synthesis of lyngbouilloside (**1**) will be reported in due course.

Acknowledgement

We would like to thank Johnson & Johnson Pharmaceutical Research & Development (division of Janssen-Cilag France), particularly David Speybrouck and Jérome Guillemont, for the separation of compound **8**. J.G. thanks the CNRS for a grant.

References and Notes

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(8) Compound **3**: $[\alpha]_D^{20}$ –26.2 (*c* 1.0, $CHCl_3$). ^1H NMR (C_6D_6): δ = 7.29 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 5.92–5.83 (m, 1 H), 5.19–5.14 (m, 2 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 4.25 (d, *J* = 11.0 Hz, 1 H), 3.96 (d, *J* = 8.5 Hz, 1 H), 3.77 (d, *J* = 8.5 Hz, 1 H), 3.69 (m, 1 H), 3.41 (s, 3 H), 2.74 (m, 1 H), 1.92 (dd, *J* = 14.3, 3.0 Hz, 1 H), 1.85 (dd, *J* = 14.3, 9.3 Hz, 1 H), 1.54 (s, 3 H), 1.50 (s, 3 H), 1.40 (s, 3 H), 1.15 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (C_6D_6): δ = 159.7 (C_q), 141.0 (CH), 131.2 (C_q), 129.5 (CH), 114.9 (CH_2), 114.1 (CH), 108.6 (C_q), 80.8 (C_q), 79.3 (CH), 75.8 (CH_2), 70.7 (CH_2), 54.8

(CH_3), 40.5 (CH_2), 39.5 (CH), 27.6 (CH_3), 27.4 (CH_3), 25.0 (CH_3), 12.8 (CH_3). ESI-HRMS: *m/z* calcd for $C_{20}H_{30}NaO_4$: 357.2036; found 357.2035.

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(12) CHIRALPAK AD-H (SFC), MeOH/CO_2 = 8:92.

(13) The absolute configuration of alcohol **8** was determined by hydrogenation of the terminal double bond and comparison of the optical rotation {$[\alpha]_D^{20}$ –21.0 (*c* 1.0, $CHCl_3$)} with the literature {$[\alpha]_D^{20}$ +19.8 ($CHCl_3$) for the enantiomer}.[10]

(14) Compound **4**: $[\alpha]_D^{20}$ +19.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 6.30 (dd, *J* = 17.8, 10.3 Hz, 1 H), 6.19 (d, *J* = 17.8 Hz, 1 H), 5.88 (d, *J* = 10.3 Hz, 1 H), 5.29 (s, 1 H), 4.34 (m, 1 H), 2.80–2.67 (m, 2 H), 2.44–2.29 (m, 2 H), 1.64 (s, 3 H), 1.63 (s, 3 H), 1.50 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 200.3 (C_q), 168.3 (C_q), 161.0 (C_q), 136.4 (CH), 129.8 (CH_2), 106.7 (C_q), 95.5 (CH), 64.7 (CH), 45.1 (CH_2), 40.5 (CH_2), 25.5 (CH_3), 24.6 (CH_3). ESI-HRMS: *m/z* calcd for $C_{12}H_{16}NaO_5$: 263.0890; found 263.0885.

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(16) Compound **9**: $[\alpha]_D^{20}$ –11.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (C_6D_6): δ = 7.34 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.42 (s, 1 H), 4.52 (d, *J* = 11.0 Hz, 1 H), 4.34 (d, *J* = 11.0 Hz, 1 H), 4.27 (m, 1 H), 3.97 (d, *J* = 8.5 Hz, 1 H), 3.70 (d, *J* = 8.5 Hz, 1 H), 3.65 (m, 1 H), 3.44 (s, 3 H), 3.17 (br s, 1 H), 2.26–2.11 (m, 5 H), 2.03–1.94 (m, 3 H), 1.84 (m, 2 H), 1.66 (m, 1 H), 1.55 (s, 3 H), 1.52 (s, 3 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.42 (s, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (C_6D_6): δ = 209.7 (C_q), 168.0 (C_q), 160.1 (C_q), 159.7 (C_q), 131.2 (C_q), 129.5 (CH), 114.1 (CH_2), 108.6 (C_q), 106.3 (C_q), 96.1 (CH), 80.8 (C_q), 79.2 (CH), 75.9 (CH_2), 70.6 (CH_2), 64.9 (CH_2), 54.8 (CH_3), 48.4 (CH_2), 41.5 (CH_2), 40.7 (CH_2), 40.2 (CH_2), 34.1 (CH), 27.7 (CH_3), 27.4 (CH_3), 26.9 (CH_2), 25.2 (CH_3), 25.0 (CH_3), 24.4 (CH_3), 13.6 (CH_3). ESI-HRMS: *m/z* calcd for $C_{30}H_{44}NaO_9$: 571.2878; found: 571.2870.

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(18) Compound **2**: $[\alpha]_D^{20}$ –21.8 (*c* 0.15, $CHCl_3$). ^{1}H NMR (C_6D_6): δ = 7.34 (d, *J* = 8.8, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.42 (s, 1 H), 4.52 (d, *J* = 11.0 Hz, 1 H), 4.34 (d, *J* = 11.0 Hz, 1 H), 4.28 (m, 1 H), 3.97 (d, *J* = 8.5 Hz, 1 H), 3.81 (d, *J* = 8.5 Hz, 1 H), 3.65 (m, 1 H), 3.44 (s, 3 H), 3.17 (br s, 1 H), 2.25–2.10 (m, 5 H), 2.03–1.90 (m, 3 H), 1.84 (m, 2 H), 1.67 (m, 1 H), 1.55 (s, 3 H), 1.52 (s, 3 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.42 (s, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (C_6D_6): δ = 209.7 (C_q), 168.0 (C_q), 160.1 (C_q), 159.7 (C_q), 131.2 (C_q), 129.5 (CH), 114.1 (CH), 108.6 (C_q), 106.3 (C_q), 96.1 (CH), 80.8 (C_q), 79.2 (CH), 75.9 (CH_2), 70.6 (CH_2), 65.0 (CH), 54.8 (CH_3), 48.4 (CH_2), 41.5 (CH_2), 40.7 (CH_2), 40.2 (CH_2), 34.1 (CH), 27.7 (CH_3), 27.4 (CH_3), 26.9 (CH_2), 25.2 (CH_3), 25.0 (CH_3), 24.4 (CH_3), 13.6 (CH_3). ESI-HRMS: *m/z* calcd for $C_{30}H_{46}NaO_9$: 573.3034; found: 573.3024.