ORGANIC LETTERS

2012
Vol. 14, No. 1
314–317

# Total Synthesis of Nominal Lyngbouilloside Aglycon

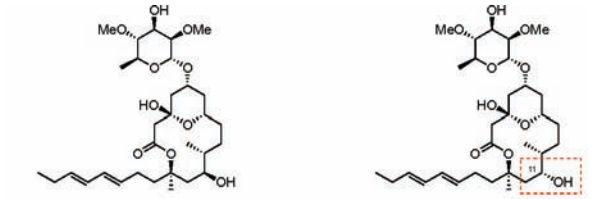
**Abdelatif ElMarrouni, Raphael Lebeuf, Julian Gebauer, Montserrat Heras,‡ Stellios Arseniyadis,* and Janine Cossy***

*Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France*

*stellios.arseniyadis@espci.fr; janine.cossy@espci.fr*

**Received November 14, 2011**

## ABSTRACT




**The first enantioselective total synthesis of the originally assigned structure of lyngbouilloside aglycon has been achieved using a particularly flexible route featuring an acylketene macrolactonization of a tertiary methyl carbinol as the key step. Comparison of the C13 chemical shifts of our synthetic aglycon with the ones pertaining to natural lyngbouilloside and lyngbyaloside C resulted in a possible stereochemical reassignment of the C11 stereogenic center.**

In 2002, two closely related 14-membered lactones, namely lyngbouilloside **1**[1] and lyngbyaloside B **2**,[2] were isolated from two different marine cyanobacteria of the genus *Lyngbya* (*Oscillatoria*). Belonging to the interesting class of antitumoral glycosyl macrolides,[3] **1** and **2** were found to exhibit moderate activity against neuroblastoma and KB cells with $IC_{50}$ values of 17 and 4.3 $\mu$M, respectively. In addition, **1** and **2** were also found to possess unique structural elements including more than 10 stereogenic centers, a six-membered ring hemiketal, and an (*E*,*E*)-octadienyl side chain (Figure 1). However, the most characteristic and synthetically challenging feature remains to be the unusual tertiary methyl carbinol at C13, as macrolactonizations of sterically encumbered alcohols are particularly rare and, more importantly, low yielding.[4] Hence, due to its challenging molecular architecture, its natural scarcity, and the fact that the absolute configuration of both the sugar and the aglycon fragments is still unknown, lyngbouilloside **1** presents a unique opportunity for chemical synthesis. We herein present a general and highly flexible synthetic approach toward this intriguing natural product which resulted in the first total synthesis of the originally assigned structure of lyngbouilloside aglycon **4**.

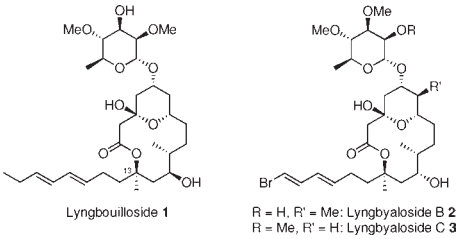



**Figure 1.** Proposed structures of lyngbouilloside[1] and lyngbyaloside B[2] and C.

In 2008, we initially reported the stereoselective synthesis of the fully functionalized carbon backbone of **1** featuring

‡ Present address: Department of Chemistry, Faculty of Sciences, University of Girona, Campus de Montilivi, E-17071 Girona, Spain.

(1) Tan, L. T.; Márquez, B. L.; Gerwick, W. H. *J. Nat. Prod.* **2002**, *65*, 925–928.

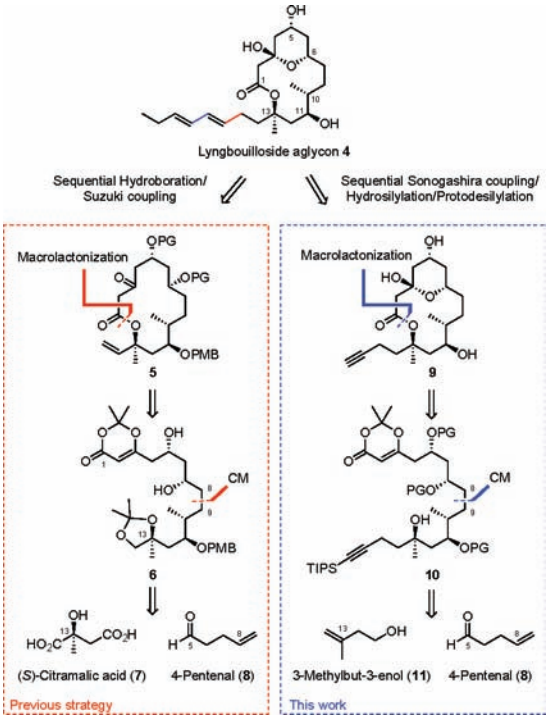
(2) Luesch, H.; Yoshida, W. Y.; Harrigan, G. G.; Doom, J. P.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 1945–1948.

(3) La Ferla, B.; Airoldi, C.; Zona, C.; Orsato, A.; Cardona, F.; Merlo, S.; Sironi, E.; D'Orazio, G.; Nicotra, F. *Nat. Prod. Rep.* **2011**, *28*, 630–648.

(4) (a) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9743–9746. (b) Booth, P. M.; Fox, C. M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 121–129. (c) Clyne, D. S.; Weiler, L. *Tetrahedron* **1999**, *55*, 13659–13682.

10.1021/ol203064r 
**Published on Web 12/07/2011**

**Scheme 1.** First and Second Generation Approach to Lyngbouilloside Aglycon **4**

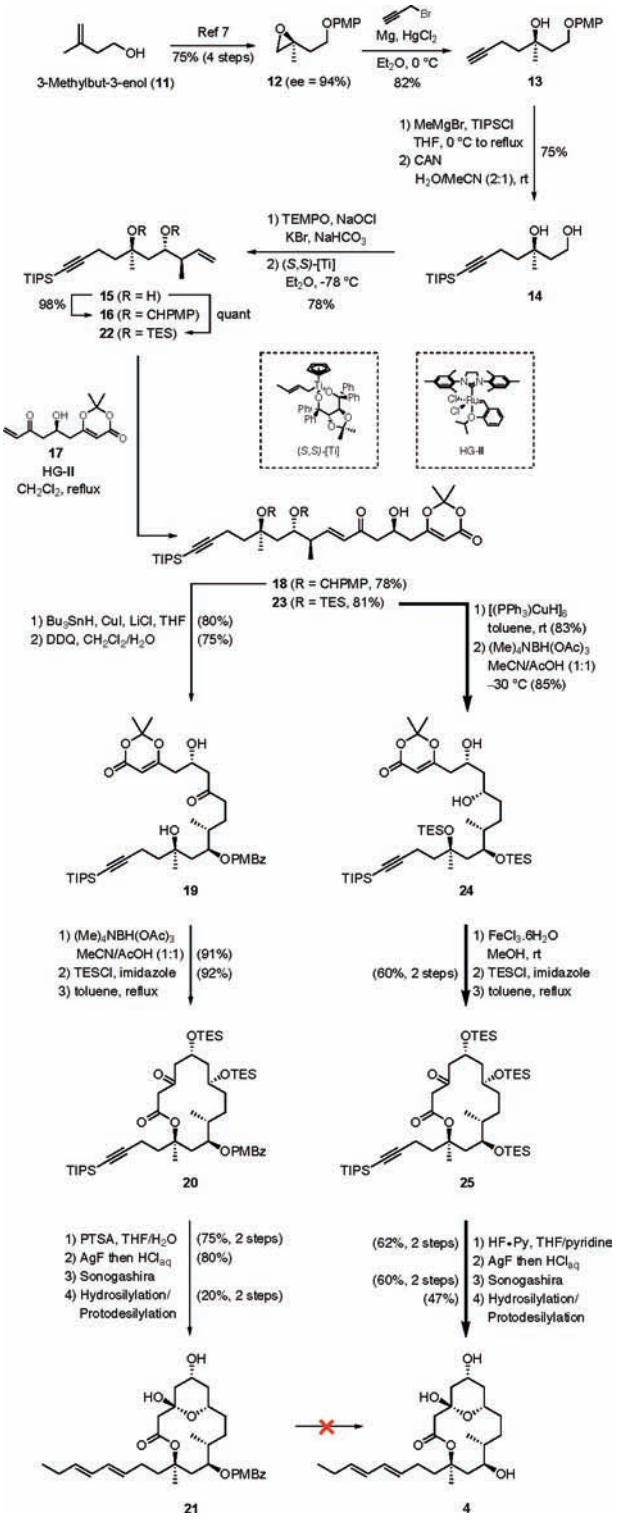



a cross-metathesis (CM) between a C1−C8 and a C9−C13 fragment, the latter being derived from (*S*)-citramalic acid **7**.[5] Albeit we were in the following able to cyclize the advanced intermediate **6** *via* the intended intramolecular acylketene-trapping,[4a,6] the synthesis of the desired methyl vinyl carbinol from the corresponding hydroxy aldehyde and the attempted side chain introduction *via* a sequential hydroboration/Suzuki coupling proved to be rather low yielding (Scheme 1).

Encouraged by this overall proof-of-concept, we finally decided to adapt our strategy by already installing half of the side chain early in the synthesis thus avoiding the delicate late-stage aldehyde methylenation (Scheme 1). In practice, the synthesis of the C9−C17 fragment began by converting commercially available 3-methylbut-3-enol (**11**) to the known isoprenol-derived (*R*)-epoxide **12** following a reported procedure,[7] which consists of a Mitsunobu etherification,[8] a Sharpless dihydroxylation[9] using AD-mix α (ee = 94%), and an epoxidation of the resulting

(5) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Synlett* **2008**, 712–714.
(6) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022–3034.
(7) (a) Anikin, A.; Maslov, M.; Siele, J.; Blaurock, S.; Baldamus, J.; Hennig, L.; Findeisen, M.; Reinhardt, G.; Oehme, R.; Welzel, P. *Tetrahedron* **2003**, *59*, 5295–5306. (b) Sparks, S. M.; Chen, C.; Martin, S. F. *Tetrahedron* **2007**, *63*, 8619–8635.
(8) (a) Mitsunobu, O.; Yamada, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(9) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

**Scheme 2.** Second and Third Generation Approach to Lyngbouilloside Aglycon **4**




1,2-diol,[10] to afford the title compound in 75% overall yield (Scheme 2). Ring opening of the latter with a propargyl Grignard[11] reagent gave alkynol **13** as an adequate

(10) Tietze, L. F.; Görlitzer, J. *Synthesis* **1998**, 873–878.

substrate for subsequent side chain elongation. Triisopropylsilyl (TIPS)-protection of the terminal alkyne and PMP-deprotection with cerium ammonium nitrate (CAN) then provided 1,3-diol **14** which, after sequential TEMPO oxidation/asymmetric crotyltitanation (dr > 95:5),[12] furnished the alternative CM precursor **15** in nine steps and 36% overall yield starting from 3-methylbut-3-enol (**11**).

While attempted CM between diol **15** and the previously reported enantiopure $\beta$-hydroxy dioxinone fragment **17**[5] was accompanied by pyrane formation *via* intramolecular oxa-Michael addition,[13] cross-coupling with the corresponding PMP-acetal **16** employing 20 mol % of the Hoveyda−Grubbs second generation catalyst proceeded smoothly to afford enone **18** in both high yield (78% over two steps) and excellent *E*-selectivity ($E/Z$ > 95:5). Conjugate reduction using an *in situ* generated hydridocuprate[14] and treatment with DDQ then gave hydroxy ketone **19** in 60% overall yield. Tetramethylammonium triacetoxyborohydride (TABH)-mediated reduction (dr > 95:5),[15] bis-triethylsilyl (TES)-protection of the resulting 1,3-*anti*-diol (84% over two steps), and thermolysis in refluxing toluene eventually afforded the desired orthogonally protected macrolactone **20** along with trace amounts of the corresponding methyl ketone derivative resulting from keto-acid decarboxylation. After removal of the silyl protecting groups (60% over three steps),[16] the stereoselective introduction of the (*E*,*E*)-octadienyl side chain was best achieved *via* a Sonogashira coupling with (*E*)-1-iodo-1-butene [$PdCl_2(PPh_3)_2$, CuI, $Et_3N$, DMF] followed by a one-pot hydrosilylation/protodesilylation[17] sequence [$HSi(OEt)_3$, $Cp^*Ru(MeCN)_3]PF_6$, $CH_2Cl_2$, 0 °C to rt, then Agf, THF/MeOH, rt followed by an aqueous HCl workup] thus giving rise to the *para*-methoxybenzoyl (PMBz)-protected aglycon **21** in an acceptable 20% overall yield. Unfortunately, despite the wide range of reaction conditions tested, the final cleavage of the PMBz protecting group met with no success most likely due to an intramolecular hydrogen bonding between the carbonyl of the PMBz and the hydroxyl of the hemiketal rendering the former particularly congested and therefore nonaccessible. To overcome this unexpected drawback without significantly altering the synthesis and with the idea that a selective glycosylation of the less hindered C5 hydroxyl would be favored in the final steps of the synthesis, we decided to simplify our protecting group strategy by choosing a silyl protecting group instead of an ester derivative. Diol **15** was thus converted to the corresponding

**Table 1.** C1 to C13 Chemical Shifts ($\delta$, ppm) for Lyngbouilloside **1**, Lyngbyaloside C **3**, and Our Synthetic Aglycon **4**, and the Differences ($\Delta\delta$, ppm) with Lyngbouilloside **1**[a]

| carbon | $\delta$ for (**1**)[a] | $\delta$ for (**4**)[a] ($\Delta\delta$) | $\delta$ for (**3**)[b] ($\Delta\delta$) |
|---|---|---|---|
| 1 | 172.9 | 172.3 (+0.6) | 172.3 (+0.6) |
| 2 | 47.5 | 47.1 (+0.4) | 46.9 (+0.6) |
| 3 | 97.2 | 96.3 (+0.9) | 96.6 (+0.6) |
| 4 | 41.9 | 43.4 (−1.5) | 41.5 (+0.4) |
| 5 | 69.8 | 64.9 (+4.9) | 69.2 (+0.6) |
| 6 | 38.4 | 40.7 (−2.3) | 37.7 (+0.7) |
| 7 | 70.2 | 68.9 (+1.3) | 69.8 (+0.4) |
| 8 | 31.9 | 33.5 (−1.6) | 31.4 (+0.5) |
| 9 | 33.0 | 31.5[c] (+1.5) | 32.4 (+0.6) |
| 10 | 37.5 | 37.6 (−0.1) | 37.0 (+0.5) |
| 11 | 66.0 | 67.4 (−1.4) | 65.5 (+0.5) |
| 12 | 44.7 | 45.8[c] (−1.1) | 44.1 (+0.6) |
| 13 | 86.9 | 86.4 (+0.5) | 86.2 (+0.7) |

[a] 150 MHz. [b] 100 MHz. [c] Chemical shifts determined by HMQC correlation.

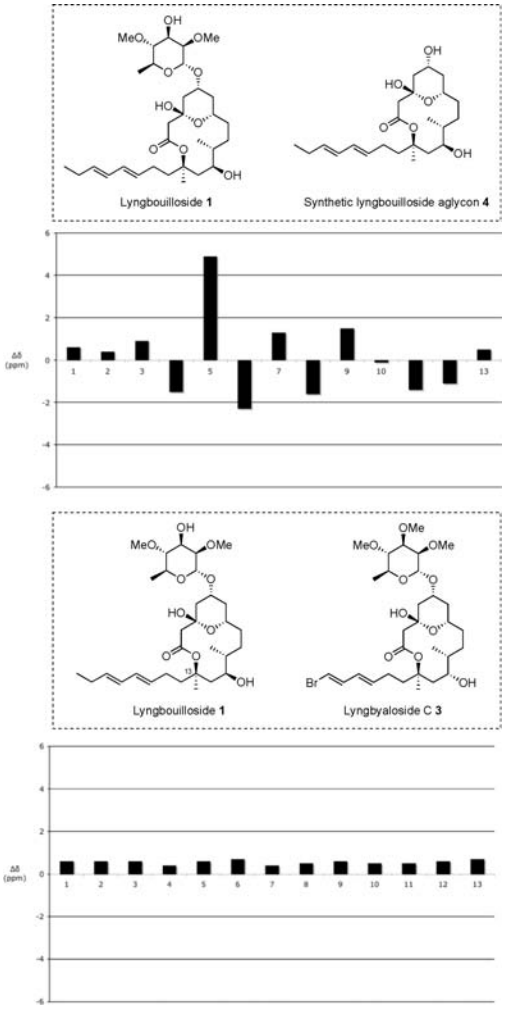



**Figure 2.** Graphically depicted $^{13}C$ chemical shift differences ($\Delta\delta$, ppm) for each carbon between C1 and C13 of lyngbouilloside **1** and our synthetic aglycon **4** (top), and lyngbouilloside **1** and lyngbyaloside C **3** (bottom).

(11) (a) Nakayama, Y.; Kumar, G. B.; Kobayashi, Y. *J. Org. Chem.* **2000**, *65*, 707–715. (b) Dimitrieva, L. L.; Nikitina, L. P.; Albanov, A. I.; Nedolya, N. A. *Russ. J. Org. Chem.* **2005**, *41*, 1583–1593.

(12) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. (b) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807–832.

(13) Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* **2010**, *12*, 1636–1639.

(14) Lipshutz, B. H.; Ung, C. S.; Sengupta, S. *Synlett* **1989**, 64–66.

(15) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *11*, 3560–3578.

(16) Kim, S.; Kim, B.; In, J. *Synthesis* **2009**, *12*, 1963–1968.

(17) (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726–12727. (b) Bressy, C.; Bargiggia, F.; Guyonnet, M.; Arseniyadis, S.; Cossy, J. *Synlett* **2008**, *4*, 565–568. (c) Bressy, C.; Vors, J.-P.; Hillebrand, S.; Arseniyadis, S.; Cossy, J. *Angew. Chem, Int. Ed.* **2008**, *47*, 10137–10140.

bis-triethylsilyl ether **22**, and the resulting product was engaged in the same Hoveyda−Grubbs second generation catalyst-mediated CM as mentioned previously (**16**→**18**). Next, as reduction of the enone under the hydrostannylation conditions afforded slightly lower yields compared to those previously obtained (**18**→**19**), compound **23** was treated with Stryker's reagent[18] instead, and the resulting hydroxy ketone was subjected to the approved Evans TABH-mediated 1,3-*anti* reduction to furnish the 1,3-*anti* diol **24** as a single diastereoisomer (dr > 95/5) in 71% overall yield. After removal of the TES protecting groups under mild conditions using a catalytic amount of $FeCl_3 \cdot 6H_2O$ in methanol,[19] the three secondary alcohols were selectively reprotected (TESCl, imidazole) to complete the synthesis of the key macrocyclization precursor in 60% yield over two steps. Thermolysis of the dioxinone under rigorously anhydrous conditions then resulted in the generation of the corresponding acylketene which was efficiently trapped intramolecularly by the remaining free alcohol thus allowing us to isolate the 14-membered macrocyclic lactone **25**. The TES groups were eventually removed with HF·Py, resulting in the concomitant formation of the pyrane ring, while treatment with AgF gave the terminal alkyne. Finally, Sonogashira coupling followed by the approved one-pot hydrosilylation/protodesilylation sequence completed the synthesis, leading to the desired lyngbouilloside aglycon **4** in 18% yield over four steps.

Interestingly, comparison of the NMR chemical shifts of our synthetic aglycon with the ones reported for the natural lyngbouilloside (Table 1, Figure 2, top), particularly in the C9−C13 region, strongly suggests that the structure of the natural product may have been originally misassigned. This observation, which was also made by Ley and co-workers after spectroscopical analysis and DFT chemical shift calculations of a closely related PMB-protected macrolactone,[20] is also supported by the fact that the $^{13}C$ NMR data of both lyngbouilloside and the more recently reported lyngbyaloside C, **3** (Figure 1),[21] are virtually identical within the region of the macrocycle (Figure 2, bottom) while the proposed structures of the two natural products differ at C11.

In summary, we have completed the first total synthesis of the originally assigned structure of lyngbouilloside aglycon **4** in 20 steps and 2.1% overall yield starting from commercially available 3-methylbut-3-enol (**11**) and suggested a stereochemical reassignment at C11. This straightforward and particularly flexible approach featuring an acylketene macrolactonization and a late stage side chain introduction and glycosylation provides an expedient entry into the lyngbouilloside framework as well as to the various lyngbyalosides.

**Acknowledgment.** We would like to thank Generalitat de Catalunya for financial support to A.E.

**Supporting Information Available.** Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293. (b) Paterson, I.; Blakey, S. B.; Cowden, C. J. *Tetrahedron Lett.* **2002**, *43*, 6005–6008.

(19) Yang, Y.-Q.; Cui, J.-R.; Zhu, L.-G.; Sun, Y.-P.; Wu, Y. *Synlett* **2006**, 1260–1262.

(20) Webb, D.; Van den Heuvel, A.; Kögel, M.; Ley, S. V. *Synlett* **2009**, 2320–2324.

(21) Matthew, S.; Salvador, L.; Schupp, P. J.; Paul, V. J.; Luesch, H. *J. Nat. Prod.* **2010**, *73*, 1544–1552.