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Stereoselective Synthesis of the C9−C19 Fragment of Lyngbyaloside B and C via Ether Transfer

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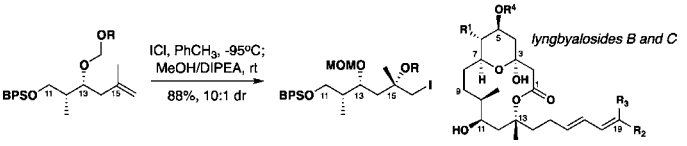
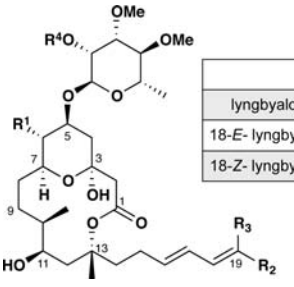
ABSTRACT



A stereoselective synthesis of the C9−C19 fragment of lyngbyaloside B and C highlighted, by an extension of our ether transfer methodology, enables the formation of tertiary ethers. 2-Naphthylmethyl ethers have been shown to proceed efficiently through ether transfer with high stereoselectivity and are easily deprotected by DDQ oxidation. Variation of the workup conditions results in the stereoselective formation of *syn*-1,3-diol mono- or diethers.

Polyketide metabolites of marine cyanobacteria are increasingly attracting the attention of synthetic groups due to their unique structural features and diverse biological activity. These compounds have demonstrated a broad spectrum of biological activities, including antiviral, antibiotic, antifungal, anticancer, and protein synthesis inhibition. For example, investigations of *L. bouillonii* collections from the Ulong Channel in Palau led to the discovery of lyngbyaloside B by Moore (Figure 1).[1] More recently, Luesch and co-workers isolated congeners, 18*E*- and 18*Z*-lyngbyaloside C, from Papua New Guinea.[2]

Many polyketides from marine cyanobacteria have been shown to possess β-branching, methyl substituents at odd numbered carbons, resulting from an HMG-CoA synthase (HCS) cassette within the polyketide synthase.[3] The lyngbyalosides are structurally interesting due to a lactone



	R1	R2	R3	R4
lyngbyaloside B	-Me	-Br	-H	-H
18-*E*- lyngbyaloside C	-H	-Br	-H	-Me
18-*Z*- lyngbyaloside C	-H	-H	-Br	-Me

Figure 1. Structure of Lyngbyalosides B and C from *L. bouillonii*.

generated by acylation of a tertiary alcohol. Despite initial efforts, lyngbyaloside B and C have yet to be synthesized.[4]

We have recently developed a novel approach to the formation of *syn*-1,3-diol mono- and diethers through electrophilic activation of homoallylic alkoxymethyl ethers.[5] As shown in Scheme 1, activation of alkene **1a** with iodine monochloride, in toluene at low temperature, initiates a stereoselective cyclization to form oxonium ion **2a** through a chairlike transition state. NMR evidence supported the ultimate generation of chloromethyl ether

(1) Luesch, H.; Yoshida, W. Y.; Harrigan, G. G.; Doom, J. P.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 1945–1948.
(2) Matthew, S; Salvador, L. A.; Schupp, P. J.; Paul, V. J.; Luesch, H. *J. Nat. Prod.* **2010**, *73*, 1544–1552.
(3) Kerr, J.-C.; Gatte Picchi, D.; Dittmann, E. *Beilstein J. Org. Chem.* **2011**, *7*, 1622–1635.
(4) (a) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9743–9746. (b) For a recent synthesis of the aglycone of the structurally related polyketide, lyngbouilloside, see: El Marrouni, A.; Lebeuf, R.; Gebauer, J.; Heras, M.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2012**, *14*, 314–317.

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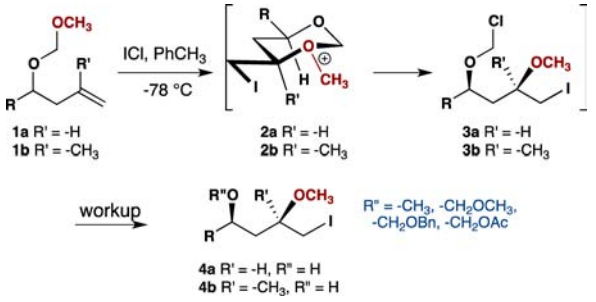
3a, which can be selectively functionalized with a variety of nucleophiles. Hydrolytic workup directly generates a 1,3-*syn*-diol monoether **4a** with excellent stereocontrol.

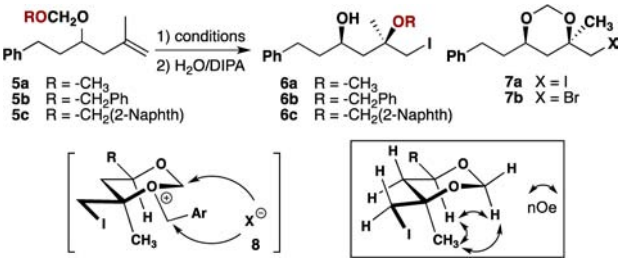
Scheme 1. *Syn*-1,3-Diol Mono- and Diethers via Ether Transfer



More recently, we envisaged extension of this methodology to the preparation of tertiary ether **4b** from 1,1-disubstituted alkene **1b**. The effect of an axial methyl substituent (R′) in **2b** on the stereoselectivity of the cyclization was an important question. However, good diastereoselectivities were observed in related iodine-induced carbonate cyclization previously demonstrated by Cardillo.[6]

The homoallylic methoxymethyl ether **5a** was readily obtained as a racemate from ring opening of the corresponding terminal epoxide with isopropenyl magnesium bromide followed by protection with commercially available methoxymethyl chloride. Initial studies focused on subjecting **5a** to a variety of electrophilic activation conditions followed by a hydrolytic workup, and the results are listed in Table 1. The choice of activating agent and solvent proved critical for high yield and diastereoselectivity of the desired methyl ether transfer product and suppression of side reactions. As in our previous study,[5a] iodine monochloride and toluene at low temperature were found to be the best activation conditions (entry 1) and increased diastereoselectivity was observed by lowering the temperature to −95 °C (entry 6). With favorable reaction conditions in hand, the analogous benzyloxymethyl ether **5b** was investigated. Benzyl ether transfer provides access to orthogonally protected *syn*-1,3-diol units since benzyl groups can typically be removed by hydrogenolysis. The choice of the activating agents and solvents were again critical in the formation of the ether transfer product **6b** over acetal **7a** which results from benzyl cleavage of intermediate **8**.[5a] The use of ICl in toluene provided predominantly the ether transfer product **6b** (entry 8), while activation in DCM led to preferential formation of the 1,3-dioxane **7a** as the major product (entry 10). Interestingly, the use of IBr in toluene (entry 9) also resulted in benzyl cleavage although rationale for the sensitivity of the reaction to the halide counterion and solvent is currently unclear.

Table 1. Electrophile-Induced Methoxy Transfer



	sm	conditions	yield (dr)[a]	yield **7a** (dr)
1	**5a**	ICl, $PhCH_3$, −78 °C	**6a** 78% (5:1)	not obs.
2	**5a**	IBr, $PhCH_3$, −78 °C	**6a** 62% (1.1:1)	not obs.
3	**5a**	I_2, $PhCH_3$, −78 °C	trace	not obs.
4	**5a**	IPy_2BF_4, $PhCH_3$, −78 °C	NR	not obs.
5	**5a**	ICl, CH_2Cl_2, −78 °C	**6a** 63% (2.4:1)	not obs.
6	**5a**	ICl, $PhCH_3$, −95 °C	**6a** 75% (8.5:1)	not obs.
7	**5a**	ICl, pentane, −115 °C	**6a** 53% (7.5:1)	not obs.
8	**5b**	ICl, $PhCH_3$, −78 °C	**6b** 63% (8.5:1)	15%
9	**5b**	IBr, $PhCH_3$, −78 °C	**6b** 5%	71% (5:1)
10	**5b**	ICl, CH_2Cl_2, −78 °C	trace	60% (3:1)
11	**5b**	ICl, CH_3CN, −78 °C	**6b** 50% (2.5:1)	trace
12	**5b**	ICl, $PhCH_3$, −95 °C	**6b** 60% (10:1)	not obs.
13	**5c**	ICl, $PhCH_3$, −95 °C	**6c** 65% (11:1)	not obs.
14	**5c**	IBr, $PhCH_3$, −78 °C	**6c** 51% (20:1)	20%

[a] Diastereomeric ratio was determined by ^1H and ^{13}C NMR.

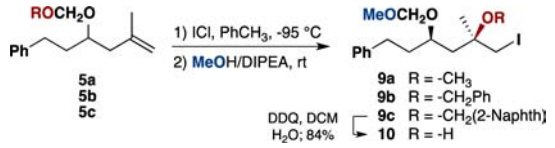
The use of an alternative arylmethyl ether in the transfer, a 2-naphthylmethyl group, improved the selectivity for ether transfer product **6c** over dioxane **7a** even under the IBr activation conditions (entries 13 and 14). The stereochemistry of ether transfer products **6a**−**c** were all inferred from **7a**, unambiguously assigned by ROESY (Rotating-frame Overhauser Effect Spectroscopy) experiments, since each of these compounds arise from intermediate **8**.

Our original publication on ether transfer provided in situ NMR evidence to support the intermediacy of chloromethyl ether intermediate **3** prior to aqueous workup and loss of the acetal methylene as formaldehyde.[5a] This enabled the development of a number of nucleophilic workup conditions to provide *syn*-1,3-diethers.[5] Of particular interest was the regeneration of the methoxymethyl ether through a basic methanol quench. As shown in Table 2, ICl-induced ether transfer followed by a basic methanol quench provided orthogonally protected diethers **9a**−**c** from **5a**−**c** in high yields and stereoselectivities. The 2-naphthylmethyl ether was found to be a particularly useful transferable group as the resulting product could be easily deprotected with aqueous DDQ providing **10** in 84% yield.

(5) (a) Liu, K.; Taylor, R. E.; Kartika, R. *Org. Lett.* **2006**, *8*, 5393–5395. For applications of the ether transfer, see: (b) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047–5050. (c) Kartika, R.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 6874–6877. (d) Kartika, R.; Taylor, R. E. *Heterocycles* **2007**, *74*, 447–459. (e) Liu, K.; Arico, J. W.; Taylor, R. E. *J. Org. Chem.* **2010**, *75*, 3953–3975. (f) Kartika, R.; Frein, J. D.; Taylor, R. E. *J. Org. Chem.* **2008**, *73*, 5592–5594.

(6) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626–4633.

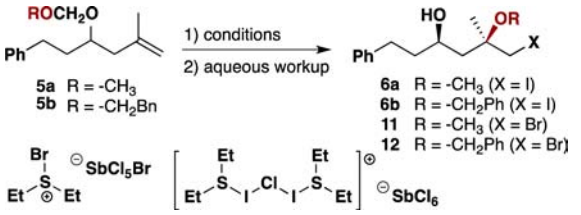
Table 2. Ether Transfer–Methanol Quench



	sm	R	product	yield (dr)
1	**5a**	$-CH_3$	**9a**	88% (7:1)
2	**5b**	$-CH_2Ph$	**9b**	65% (12:1)
3	**5c**	$-CH_2$(2-Naphth)	**9c**	74% (12:1)

Despite its critical role in the ether transfer, the use of iodine monochloride has also shown some limitations. With some substrates, an appreciable amount of ICl addition products have been observed leading to low yields of the desired ether transfer. Recently, Snyder reported polyene cyclizations affected by new electrophilic halogen sources such as bromodiethylsulfoniumbromopentachloroantimonate (BDSB) as well as the iodine version (IDSI).[7] These new conditions were successfully applied to the ether transfer, Table 3, to provide methoxy and benzyloxy transfer products in higher yield (entries 11 and 12) but, unfortunately, at the expense of the diastereomeric ratio.

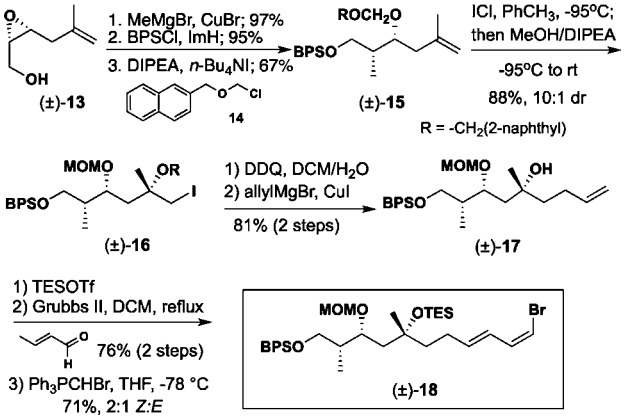
Table 3. New Activating Conditions



	sm	conditions	yield (dr)
1	**5a**	BDSB, CH_3NO_2, −29 °C	**11** 75% (4:1)
2	**5a**	BDSB, $CH_3CH_2NO_2$, −78 °C	**11** 72% (6.1:1)
3	**5a**	BDSB, CH_3CN, −45 °C	**11** 62% (7.4:1)
4	**5a**	BDSB, CH_3CH_2CN, −78 °C	**11** 46% (17:1)
5	**5b**	BDSB, CH_3NO_2, −29 °C	**12** 71% (4.3:1)
6	**5b**	BDSB, $CH_3CH_2NO_2$, −78 °C	**7b** only
7	**5b**	BDSB, CH_3CN, −45 °C	**12** 52% (6.3:1)
8	**5b**	BDSB, CH_3CH_2CN, −78 °C	**7b** only
9	**5a**	IDSI, CH_3NO_2, −29 °C	**6a** 78% (3.2:1)
10	**5a**	IDSI, $CH_3CH_2NO_2$, −78 °C	**6a** 76% (3.3:1)
11	**5a**	IDSI, CH_3CH_2CN, −78 °C	**6a** 95% (2.8:1)
12	**5b**	IDSI, CH_3NO_2, −29 °C	**6b** 75% (4:1)
13	**5b**	IDSI, CH_3CH_2CN, −78 °C	**6b** 67% (5:1)

The oxygenation pattern found in ether transfer products such as **6a**–**c** and **9a**–**c** is of significant utility in the synthesis of polyketides with unique patterns of methylation such as those derived from cyanobacterial PKS biosynthetic pathways. Having accomplished the development of a reliable ether transfer protocol to stereochemically defined tertiary ethers, we next focused our efforts on an application to the synthesis of the C9–C19 fragment of lyngbyaloside B and C, Scheme 2. The epoxy alcohol **13**, obtained in three steps from propargyl alcohol and 2-methyl-2-propen-1-ol,[8] was regioselectively opened with methylmagnesium bromide in the presence of a copper bromide dimethyl sulfide complex.[9] BPS protection of the primary alcohol followed by incorporation of the transferable naphthylmethyloxymethyl group provided **15**.

Scheme 2. Application to the C9–C19 Fragment Synthesis



Upon treatment with our optimized conditions followed by the methanolic quench, the MOM protected **16** was obtained in 88% yield as a 10:1 mixture of diastereomers. Mild oxidative deprotection, which selectively liberated the tertiary alcohol, was followed by coupling to allylmagnesium bromide in the presence of copper iodide. Carbon–carbon bond formation and generation of **17** likely occurs through nucleophilic addition to an in situ generated epoxide. Confirmation of the 1,3-syn-stereochemical assignment was obtained by conversion of MOM ether **17** to the corresponding methylene acetal under acidic conditions (see Supporting Information). Toward our natural product target, the tertiary alcohol was protected as a triethylsilyl ether and subjected to an *E*-selective cross-metathesis homologation. Finally, Wittig olefination with (bromomethyl)triphenylphosphonium bromide gave the C9–C19 fragment of lyngbyaloside **18** as a 1:2 mixture of *E*/*Z* isomers.

In summary we have successfully applied our ether transfer conditions to the stereoselective formation of tertiary ethers. Electrophilic activation of homoallylic alkoxymethyl ethers enabled the formation of *syn*-1,3-diol mono- and orthogonally protected diethers through ether transfer. As an additional advancement of our previously described method, 2-naphthylmethyl ethers have been

(7) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314.

(8) Alegret, C.; Santacana, F.; Riera, A. *J. Org. Chem.* **2007**, *72*, 7688–7692.

(9) Hodgson, D. M.; Arif, T. *Org. Lett.* **2010**, *12*, 4204–4207.

shown to proceed efficiently through ether transfer with high stereoselectivity and are easily deprotected by DDQ oxidation. This new, stereoselective route to structural units containing tertiary ethers has found application in the synthesis of the C9–C19 fragment of lyngbyaloside B and C. Additional efforts toward the total synthesis of these cyanobacteria-derived polyketides are currently underway in our laboratories and will be reported in due course.

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

The authors declare no competing financial interest.