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Total and formal enantioselective synthesis of lyngbic acid and hermitamides A and B

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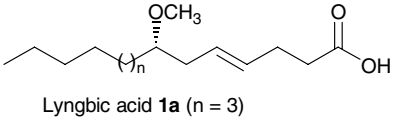
Abstract—The synthesis of lyngbic acid and both hermitamides A and B, three compounds previously isolated from *Lyngbya majuscula* has been achieved by a cross-metathesis between 4-methoxyundec-1-ene with pent-4-enoic acid or its amides. The reaction proceeds smoothly to deliver the target molecules in appreciable yields and with a very high *E* selectivity as determined by NMR experiments. Allyl transfer using a camphor derived homoallylic alcohol allowed the synthesis of enantiomerically enriched starting materials.

Lyngbic acid **1a**[1] and the related 7-methoxydocec-4-enoic acid **1b**[2] have been isolated from the marine cyanophyte *Lyngbya majuscula* (Scheme 1). They exhibit very important biological activities such as immunosuppressive activity (ED_{50} 6 μg mL^{-1} on culture cells with concanavaline K and LPS).

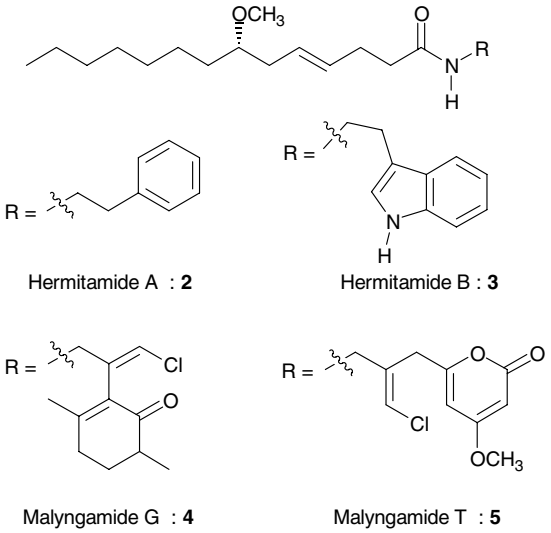
Furthermore, acid **1a** constitutes a sub-unit of hermitamides A and B, isolated in 2000 by Gerwick and coworkers,[3] but also of more elaborate structures such as malyngamides C or T[4–7] (Scheme 1). Therefore, access to acids **1a**,**b** has been the subject of numerous investigations.[1,8] The formation of the alkene moiety of lyngbic acid is usually achieved according to a Wittig reaction[1] or by reduction of an alkyne sub-unit.[8] In connection with our interest in the metathesis reaction and its application to the synthesis of natural products,[9,10] we have investigated a short access to **1a** and hermitamides A **2** and B **3** (see Scheme 2).



Lyngbic acid **1a** (n = 3)
1b (n = 1)

Scheme 1.

Our synthetic approach toward **1a** was more particularly based on a cross-metathesis (CM) between 4-pentenoic acid **6** and the readily available homoallylic ether **8**



Hermitamide A : **2**
Hermitamide B : **3**
Malyngamide G : **4**
Malyngamide T : **5**

Scheme 2.

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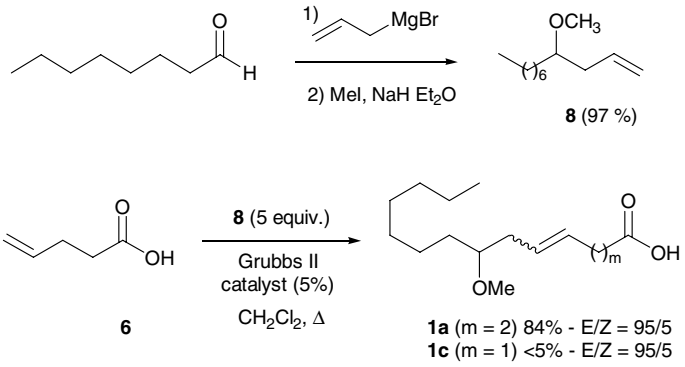


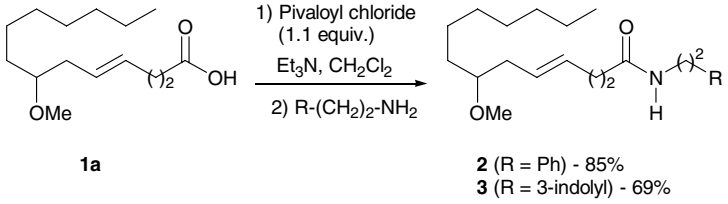
Scheme 3.

(Scheme 3). CM is a very useful procedure to functionalized terminal alkenes and has been widely applied to the synthesis of natural products.[11]

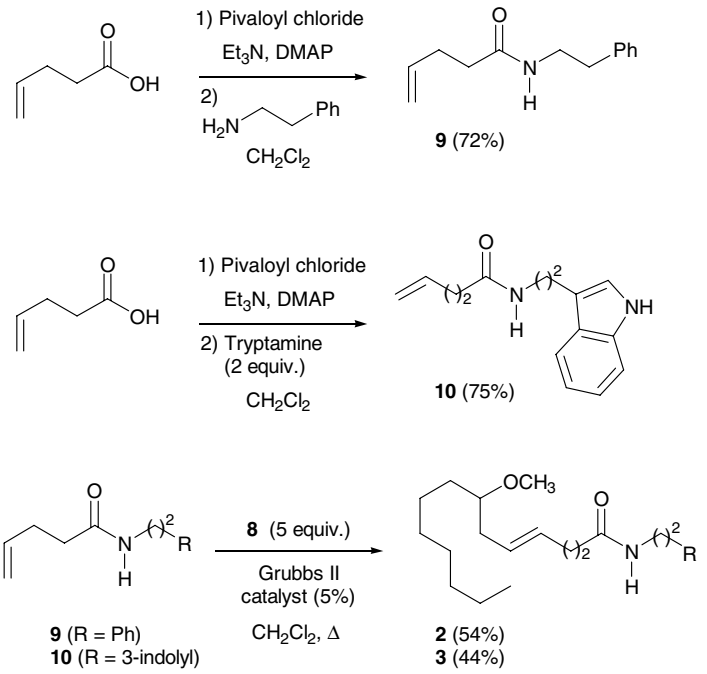
In this context, the cross-coupling metathesis was undertaken with confidence between 4-pentenoic acid and **8** in the presence of a small amount of Grubbs type II catalyst (2×2.5 mol %).[12] As expected, the corresponding 7-methoxytetradec-4-enoic acid **1a** ($m = 2$) was isolated by flash-chromatography in 84% yield and with an impressive E/Z ratio (>95/5). The E configuration of the new C=C bond was determined by NMR and this selectivity reflects the usual thermodynamic and reversible character of the cross-coupling metathesis. This determination was complicated by the very strong second-order coupling affecting the double bond sub-spectrum. However, a customized region selective HSQC experiment without ^{13}C decoupling but with homodecoupling of the two allylic CH_2, allowed a precise measurement of the ethylenic coupling constant ($J = 16.3$ Hz). Furthermore, it should also be mentioned that another unsaturated acid, identified as **1c** ($m = 1$), was formed in small amounts during the process. This compound which could be alternatively obtained by the CM of **8** with butenoic acid in 98% yield presents a characteristic signal at 2.26 ppm (d, $J = 16.3$ Hz, 2H) on the ^1H NMR spectra. Its formation results probably from the isomerization of **6** into 3-pentenoic acid before a CM with ether **8**. Similar side reactions have been widely observed in ring-closing and cross-coupling metatheses[13] and Grubbs and co-workers recently introduced the use of 1,4-paraquinone to prevent them.[14] Unfortunately, even in the presence of this additive, the yield was not improved. Finally, lyngbic acid **1a** was readily transformed into hermitamides A and B in good yields according to an amidation process promoted by the formation of an unsymmetrical anhydride intermediate[15] (Scheme 4).

An alternative synthesis of **2** and **3** was also developed by performing a CM of amide **9**[16] and **10**[17] with ether **8** (Scheme 5). In this way, the target molecules **2** and **3** were, respectively, isolated in 54% and 44% yield. While metathesis is usually sensitive to the presence of free nitrogen atom, the indole is not nucleophilic enough to alter the course of the reaction. Compared to the direct synthesis of **1a**, similar (E)-selectivities were also measured.

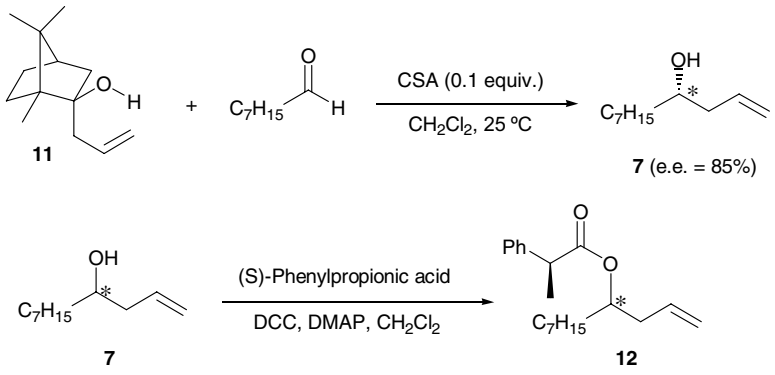
A formal enantioselective synthesis of lyngbic acid and therefore of hermitamides A and B has also been investigated which required the preparation of **8** with control of the (S) configuration of the sole stereogenic center. An astonishing number of methods to prepare enantioselectively homoallyl alcohols has been already published. For example, reaction of aldehydes with allyltitane TADOL derivatives like Hafner and Duthaler's reagents[18] or with allyltributyltin in the presence of catalytic amounts of a chiral catalyst[8e,19] affords such type of compounds in very high ee. More recently, allyl transfer processes from hindered homoallyl alcohols to aldehydes were reported in the presence of zinc, indium, tin, or zirconium salts[20] and even under metal free procedures.[21,22] In this context, we have explored the reactivity of the (+)-camphor derived homoallylic alcohol **11**[23] developed by Loh et al. toward octanal in the presence of CSA (Scheme 6).[22] The reaction proceeds smoothly and homoallylic alcohol **7** was obtained in 72% yield and 85% enantiomeric excess.[24] Attribution of (S) configuration to the newly created center was made possible by comparison of the optical rotation already reported.[20d] Finally, to secure the enantioselectivity level



Scheme 4.



Scheme 5.



Scheme 6.

especially with compounds with moderate or low $[\alpha]_D$ value, alcohol **7** was conveniently transformed into ester **12** by way of a DCC activation with commercially available (*S*)-2-phenylpropionic acid.[25] After filtration off of the urea and a filtration over a short pad of silica, the ratio of the two diastereoisomers was directly determined by ^{1}H NMR.[26,27]

In conclusion, we have reported herein a short access to racemic lyngbic acid and hermitamides A and B by using a cross-metathesis reaction performed with readily available substrates. A formal enantioselective synthesis of these three natural products has also been achieved thanks to the preparation in enantiomerically enriched form (ee = 85%) of 4-methoxyundec-1-ene, a crucial partner for the cross-metathesis. Work is now underway to apply this strategy toward the enantioselective synthesis of malyngamides and will be reported in due course.

Acknowledgements

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12. Synthesis of lyngbic acid **1a**: To a solution of 4-methoxy-undec-1-ene (460 mg, 2.5 mmol) and 4-pentenoic acid **6** (0.051 mL, 0.5 mmol) in dichloromethane (5 mL) was added second generation Grubbs' catalyst (11 mg). The mixture was heated to 40 °C for 7 h. A second portion of Grubbs' catalyst was then added and the mixture was kept warm for 16 h. The solvent was evaporated under reduced pressure and the residue was purified by flash-chromatography on silica (hexanes/AcOEt = 90/10). Acid **1a** was obtained as a colorless oil (108 mg, 84%).
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17. To a solution of pent-4-enoic acid (0.31 mL, 3 mmol), 4-dimethylaminopyridine (110 mg, 0.9 mmol), and triethylamine (0.93 mL, 6.6 mmol) in dichloromethane (30 mL) was added pivaloyl chloride (0.37 mL, 3 mmol). The solution was stirred at room temperature for 1 h. Tryptamine (529 mg, 3.3 mmol) was added and solution was stirred for additional 5 h. This solution was hydrolyzed with a 1 N solution of HCl (5 mL) and washed with a 0.1 M aqueous solution of $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$, filtered off, and concentrated under vacuo. After purification by flash-chromatography (hexanes/AcOEt, 50/50), **10** was isolated pure as a beige powder (545 mg, 75%).
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24. Preparation of (*S*)-undec-1-en-4-ol **7**: To a solution of camphor-derived allylic alcohol (9.6 g, 50 mmol) and camphor sulfonic acid (395 mg, 1.7 mmol) in dichloromethane (17 mL), was added octanal (2.13 g, 16.6 mmol). The solution was stirred at room temperature for 18 h then concentrated under reduced pressure. The residue was purified by flash-chromatography on silica (hexanes/AcOEt, 95/5) to give **7** as a colorless liquid (2.02 g, 72%, 86% ee).
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26. To a solution of (*S*)-undec-1-en-4-ol (60 mg, 0.35 mmol) in dichloromethane (3.5 mL) was added at 0 °C, (*S*)-2-phenyl propionic acid (58 mg, 0.39 mmol), 4-dimethylaminopyridine (12 mg, 0.1 mmol), and 1,3-dicyclohexylcarbodiimide (80 mg, 0.39 mmol). This solution was stirred 18 h at room temperature, filtered through cotton, and purified on silica. The desired ester was obtained as a colorless oil (103 mg, 97%).
27. Characteristic ^{1}H NMR spectra of compounds **12**: Minor diastereoisomer **12a**: $\delta = 5.71$ (m, 0.074H). Major diastereoisomer **12b**: $\delta = 5.53$ (m, 0.926H).