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Synthetic Studies on Lytophilippine A: Synthesis of the Proposed Structure

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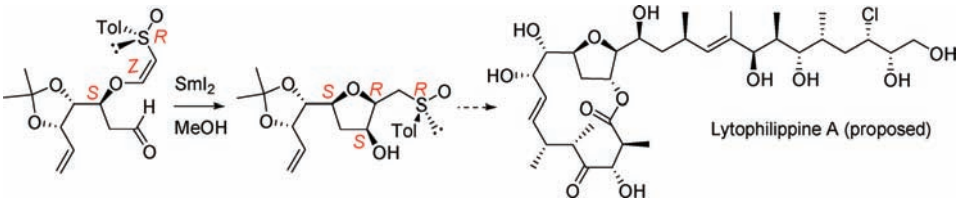
ABSTRACT

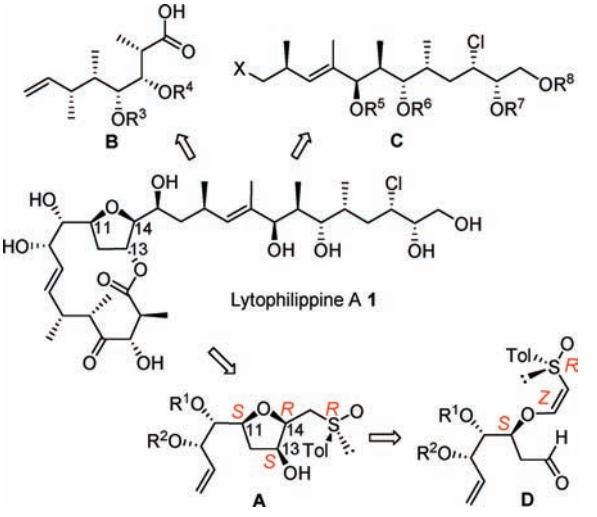


Synthesis of the proposed structure of lytophilippine A was accomplished employing SmI_2-mediated 5-*exo* cyclization of an aldehydo β-alkoxyvinyl sulfoxide and ring-closing metathesis reaction.

Lytophilippine A is a representative member of the macrolactone natural products isolated from the sea hydroid *Lytocarpus philippinus* from the Red Sea. Řezanka and coworkers proposed the structure **1** for lytophilippine A,[1] and a recent report[2] on a partial synthesis attests to the current interest in this unique natural product. The most characteristic feature in the structure of **1** is the macrolactone structure incorporating a hydroxyoxolane unit. In the retrosynthetic analysis, three major fractions appeared as viable parts in the final assemblage; the hydroxyoxolane derivative **A**, the carboxylic acid **B**, and the side chain halide **C**. We intended to obtain the key structural element **A** through 5-*exo* cyclization of an aldehydo β-alkoxyvinyl sulfoxide **D**. The stereochemical outcome of the 5-*exo* cyclizations of aldehydo (*E*)- and (*Z*)-β-alkoxyvinyl sulfoxides derived from a secondary alcohol is well established from previous studies,[3] and the synthesis of (11*S*,13*S*,14*R*)-**A** requires use of (*Z*)-(*R*)-β-alkoxyvinyl sulfoxide **D** (Scheme 1).

In practice, the known diol acetonide **3**[4] was obtained from D-ribose (**2**). TBS-protection of **3**, mesylation of the secondary hydroxyl group, TBS-deprotection, and base treatment afforded epoxide **4**. Reaction of **4** with lithiated

Scheme 1. Retrosynthetic Analysis



dithiane produced the secondary alcohol **5**. Reaction of **5** with alkynyl sulfoxide **6** in the presence of ethylmagnesium bromide and lithium chloride[3] led to aldehydo (*Z*)-β-alkoxyvinyl sulfoxide **7** after hydrolysis of the dithiane unit. Reaction of **7** with SmI_2 in THF–methanol (1:1)[5]

(1) Řezanka, T.; Hanuš, L. O.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 12191–12199.
(2) Gille, A.; Hiersemann, M. *Org. Lett.* **2010**, *12*, 5258–5261.
(3) Jung, J. H.; Kim, Y. W.; Kim, M. A.; Choi, S. Y.; Chung, Y. K.; Kim, T.-R.; Shin, S.; Lee, E. *Org. Lett.* **2007**, *9*, 3225–3228.
(4) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189–1193.

(5) A higher concentration of methanol probably prevented a retro-Michael reaction, and a higher yield of **8** was obtained.

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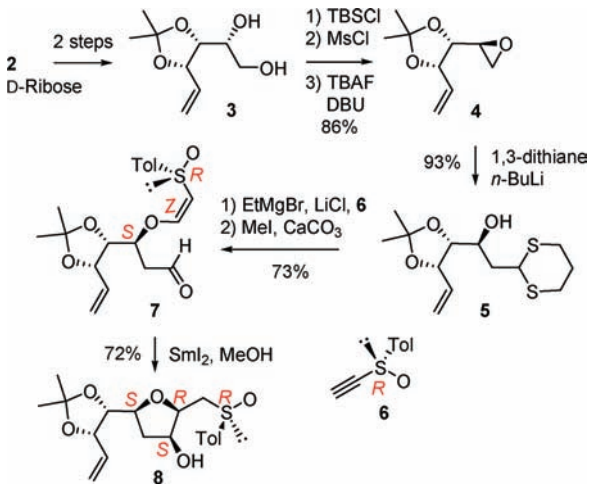
yielded mainly (dr 9:1) the 3-hydroxyoxolane product **8**, which was isolated in 72% yield (Scheme 2).

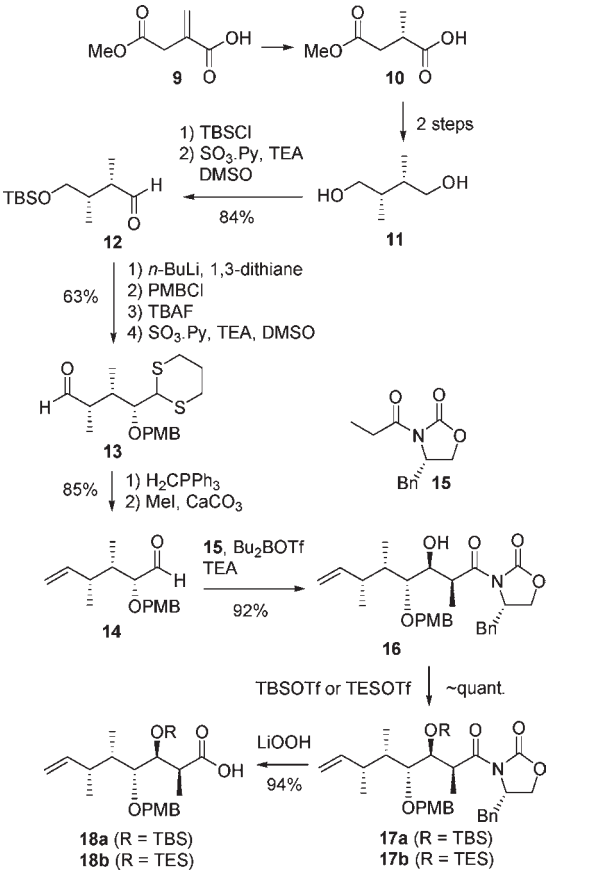
Scheme 2. Synthesis of the **A** Fragment



The known carboxylic acid **10** was prepared via asymmetric hydrogenation[6] of monomethyl itaconate (**9**), and diol **11** was obtained from **10** following the known procedures.[7] Aldehyde **12** was prepared from **11** via TBS-protection and oxidation. Addition of the lithiated dithiane to **12** proceeded under modest stereocontrol (d.r. 4.6:1), and PMB-protection, TBS-deprotection, and oxidation produced aldehyde **13**. Wittig olefination of **13** and dithiane hydrolysis led to aldehyde **14**, which reacted with the (*Z*)-boron enolate prepared from imide **15**.[8] The aldol reaction proceeded stereoselectively (dr >19:1) in high yield, and the product alcohol **16** was converted to the corresponding TBS or TES ether (**17a** and **17b**). The **B** fragment carboxylic acid **18a** and **18b** were efficiently prepared upon hydrolysis (Scheme 3).

L-Ascorbic acid (**19**) served as the starting material for the **C** fragment, and epoxide **20** was prepared following the known procedures.[9] The secondary alcohol **21** was obtained via reaction with allylmagnesium bromide in the presence of cuprous iodide. Chloride substitution of the hydroxy group in **21** proceeded smoothly to produce chloride **22**, and oxidative cleavage of the terminal double bond afforded carboxylic acid **23**.[10] Methylation of the sodium enolate of the chiral imide **25** prepared from **23** and oxazolidinone **24** was highly stereoselective, and the product was reduced by lithium borohydride to yield the primary alcohol **26**.

Scheme 3. Synthesis of the **B** Fragment



The corresponding aldehyde was obtained from **26** via Dess–Martin oxidation, which reacted under Roush crotylation conditions[11] using the chiral boronate **27** to produce the secondary alcohol **28** (dr >19:1). TMS-protection of the hydroxy group in **28** and ozonolysis produced aldehyde **29**, which reacted with the vinyllithium reagent prepared from the known vinyl iodide **30**.[12] This addition proceeded under high stereocontrol (dr 12:1), and the allylic alcohol **31** was produced in good yield. Acetonide protection on **31**, TBS-deprotection, and iodide substitution led efficiently to the **C** fragment iodide **32** (Scheme 4).

Coupling of the **A** and **B** fragments involved Mitsunobu reaction[13] between **8** and **18a**, which proceeded efficiently to produce ester **33**. Pummerer rearrangement of **33** and reductive workup followed by TBS-protection led to a new diene ester **34**. The crucial ring-closing olefin metathesis

(6) (a) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889–3890. (b) Ostermeier, M.; Brunner, B.; Korff, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 3453–3459. (c) Fürstner, A.; Bouchez, L. C.; Funel, J.-A.; Liepins, V.; Porée, F.-H.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9265–9270.

(7) Betche, H.-J.; Irdam, E. A.; Padilla, A. G.; Pearlman, B.; Perrault, W. R.; Vanalsten, J.; Franczyk, T. S. WO 2007/010387 A2.

(8) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(9) Cho, B. H.; Kim, J. H.; Jeon, H. B.; Kim, K. S. *Tetrahedron* **2005**, *61*, 4341–4346.

(10) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

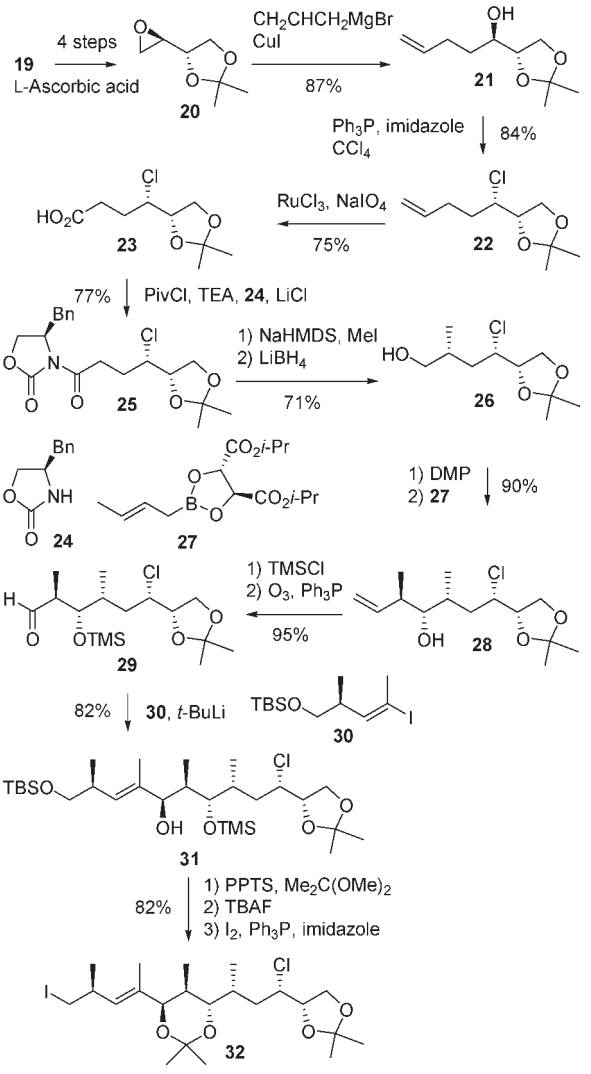
(11) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterma, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348.

(12) Kalesse, M.; Chary, K. P.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem.—Eur. J.* **2003**, *9*, 1129–1136.

(13) Mitsunobu, O.; Yamada, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.

(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

Scheme 4. Synthesis of the **C** Fragment

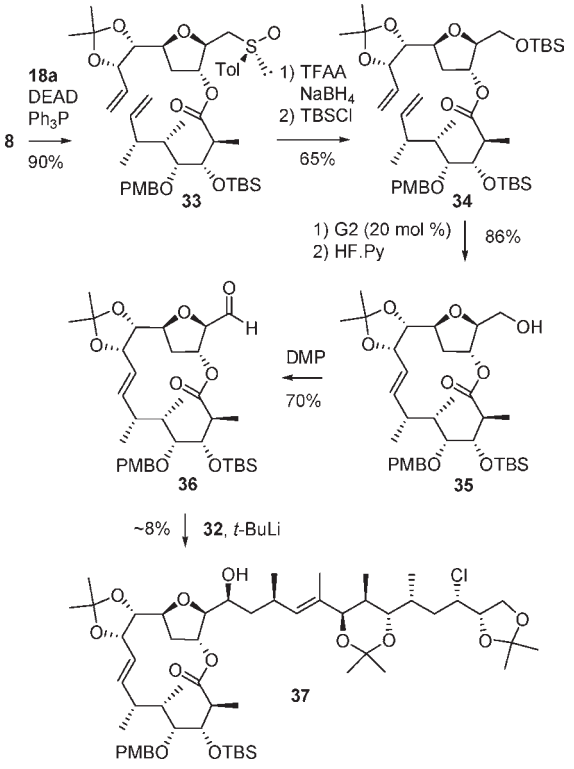


reaction in the presence of the second generation Grubbs catalyst[14] produced a single macrolactone product, and TBS-deprotection yielded macrolactone **35** efficiently. The structure of **35** was confirmed via X-ray diffraction studies.[15]

Aldehyde **36** was then prepared from **35** via Dess–Martin oxidation. Reaction of aldehyde **36** with the organolithium compound prepared from the primary iodide **32** was sluggish, producing approximately 10% of the coupling products containing the secondary alcohol **37** and the corresponding epimer (dr 4:1) (Scheme 5).

The coupling reaction was inefficient, and it was clear that adjustments should be made in the sequence of macrolactone formation and the side chain addition. Furthermore, difficulties were encountered in the deprotection steps. In particular, the TBSO-group at C-3 of **37** appeared to be the source of the problem.

Scheme 5. Synthesis of the Macrolactone Intermediates



The alternative route commenced with the inversion of stereochemistry at C-13; Mitsunobu reaction on **8** with *p*-nitrobenzoic acid and hydrolysis, TBS-protection, and Pummerer rearrangement afforded the aldehydo hydroxyoxolane intermediate **38**.[16]

Treatment of the primary iodide **32** with 2 equiv of *tert*-butyllithium and then addition of aldehyde **38** led to the efficient formation of a mixture (dr 1.6:1) of alcohols favoring **39**.[17] Stereoselectivity did not improve under different reaction conditions. TBS-deprotection of **39** led to a diol intermediate, which was converted into the diene ester **40** via reaction with **18b** and TBS-protection. The ring-forming olefin metathesis reaction of **40** proceeded efficiently (88%) to yield a single macrolactone **41**. Finally, the conversion of **41** to the target structure **1** involved PMB-deprotection of **41** using DDQ, Dess–Martin oxidation, silyl group deprotection by prolonged exposure to hydrogen fluoride–pyridine, and acetonide deprotection (Scheme 6).

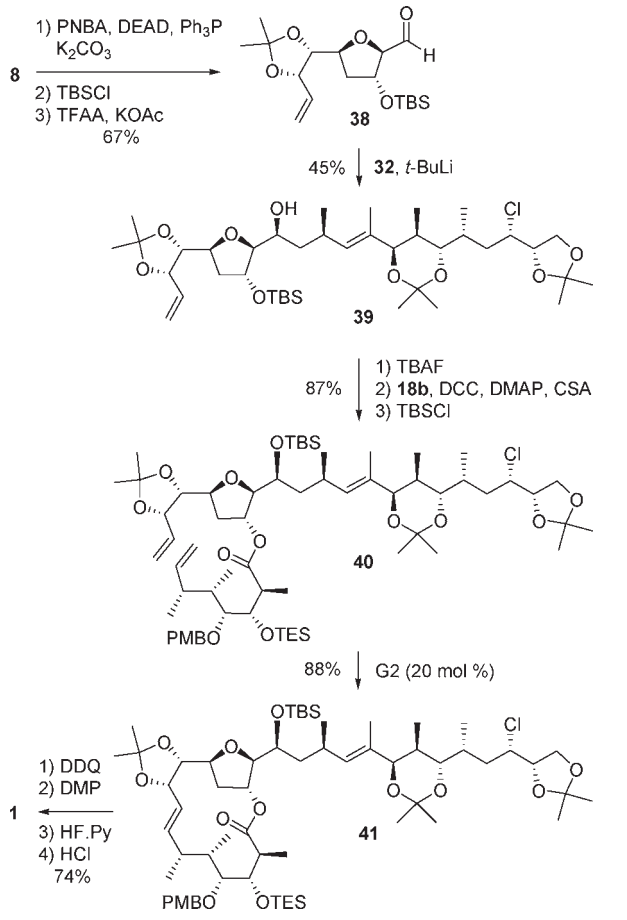
Unfortunately, physical data of the final product **1** did not match the data reported for the natural product.[1] The

(15) The structure of **35** was confirmed by X-ray diffraction studies. CCDC 812839 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) From previous studies,[3] it is known that the present sequence is more efficient overall than the direct use of (*Z*)-(*S*)-*β*-alkoxyvinyl sulfoxide.

(17) See the Supporting Information for the stereochemical assignment through the corresponding carbonates.

Scheme 6. Synthesis of the Proposed Structure of **1**



structure **1** put forward by Řezanka and co-workers appears to be in error.[18]

In summary, the key hydroxyoxolane fragment of the proposed structure of lytophilippine A (**1**) was prepared through SmI_2-mediated 5-*exo* cyclization of an aldehydo *β*-alkoxyvinyl sulfoxide. The 14-membered macrolactone was synthesized via a ring-closing olefin metathesis reaction. Correction of the structure of lytophilippine A is necessary, and future studies should focus on finding the correct structure.

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Supporting Information Available. Experimental procedures and ^1H and ^{13}C NMR spectra of the intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Comparison of NMR data was problematic, because the original report[1] by Řezanka and co-workers did not specify the NMR solvent they used. We recorded NMR spectra of **1** in methanol-d_4, acetone-d_6, THF-d_8, acetonitrile-d_3, pyridine-d_5, $CDCl_3$, DMSO-d_6, $CDCl_3$–DMSO-d_6 (4:1), and D_2O, and none matched the reported data. We did not yet find any crystalline derivative of **1**.