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(−)-Lytophilippine A: Synthesis of a C1−C18 Building Block

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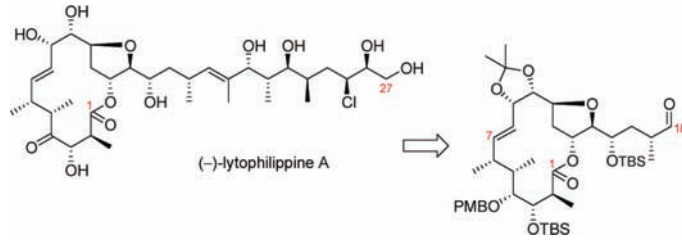
ABSTRACT



The convergent enantioselective synthesis of a protected C1−C18 building block for the total synthesis of (−)-lytophilippine A was achieved. A catalytic asymmetric Gosteli−Claisen rearrangement and an Evans aldol reaction served as key C/C-connecting transformations during the assembling of the C1−C7 subunit (10 steps from 4, 29%). The synthesis of the C8−C18 segment was achieved utilizing D-galactose as inexpensive ex-chiral-pool starting material (15 steps, 15%). The merger of the subunits was accomplished by a remarkably efficient sequence consisting of esterification and ring-closing metathesis (five steps, 56%).

Marine organisms continue to be a prolific source for structurally novel and pharmacologically active natural products.[1] Members of the macrolide family of polyketides display a wide range of biological activities and have been prominent targets for total synthesis.[2]

The isolation of the complex macrolide (−)-lytophilippine A (**1**) from the stinging hydroid *Lytocarpus philippinus* was reported in 2004 by Řezanka and co-workers (Figure 1); an in vivo antitumor activity has been suggested for **1**.[3] The gross structure of **1** was deduced from a combination of extensive NMR, IR, and mass spectroscopic techniques. The assignment of the relative configuration rests on NOESY studies as well as on empirical rules relating to chemical shifts and coupling constants. Finally, derivatization (Mosher esters, acetonides), oxidative degradation, and chemical correlation provided the basis from which the determination of the absolute configuration was accomplished. The 27-carbon atom backbone of **1** features 17 stereogenic carbon atoms and is characterized by two domains: the C1−C13 macrolactone and the C14−C27 side chain. Attracted by the architectural challenges presented by the complex structure of **1**, we devised a general retrosynthetic strategy that leads to three building blocks of comparable molecular complexity (Figure 1). In this paper, we report robust and scalable syntheses of the C1−C7 segment **2** and the C8−C18 segment **3** as well as their assembly to an orthogonally protected C1−C18 building block.

Key to our synthesis of the C1−C7 segment **2** is the enantiomerically pure α-keto ester **6** which was accessed by the catalytic asymmetric Gosteli−Claisen rearrangement[4] of the known allyl vinyl ether **4**[5] in the presence of [Cu{(*S*,*S*)-

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(2) (a) Jackson, K. L.; Henderson, J. A.; Phillips, A. J. *Chem. Rev.* **2009**, *109*, 3044–3079. (b) Roy, M.; Kalesse, M. *Nat. Prod. Rep.* **2008**, *25*, 862–870. (c) Colby, E. A.; Jamison, T. F. *Org. Biomol. Chem.* **2005**, *3*, 2675–2684. (d) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237–4313.

(3) Řezanka, T.; Hanuš, L. O.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 12191–12199.

(4) (a) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700–4703. (b) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. *Adv. Synth. Catal.* **2004**, *346*, 1281–1294.

(5) Compound **4** has been prepared on 20 g scale in five steps from commercial 2-butyn-1-ol according to the published procedure; see: Rehbein, J.; Leick, S.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1531–1540. The synthesis requires access to preparative HPLC for the separation of vinyl ether double bond isomers.

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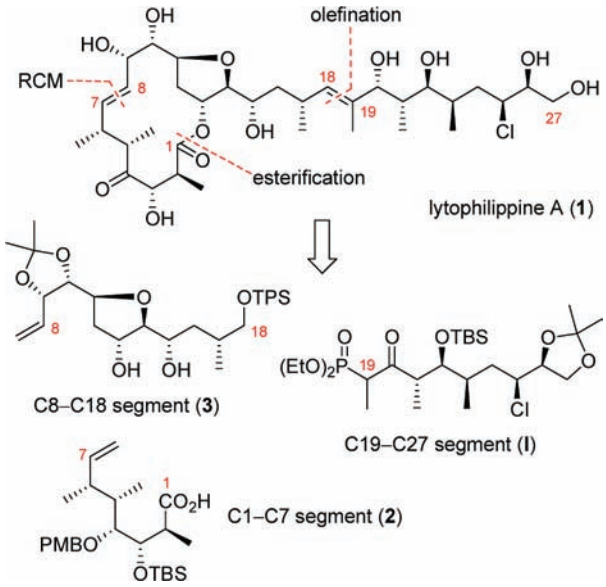
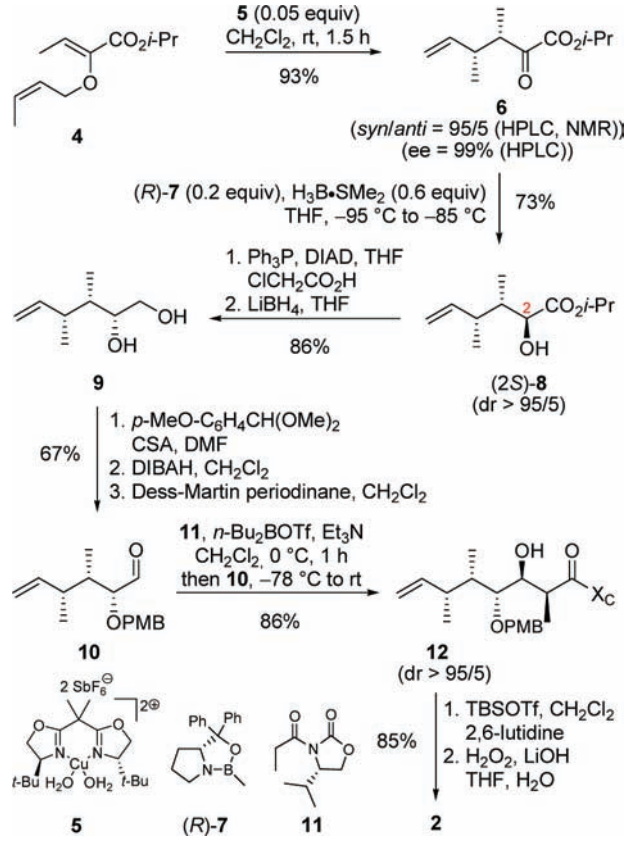


Figure 1. Synthetic strategy toward (−)-lytophilippine A **1**. TPS = *t*-BuPh$_2$Si.

t-Bu-box}(H$_2$O)$_2$](SbF$_6$)$_2$ (**5**,[6] 0.05 equiv) in CH_2Cl_2 at room temperature (Scheme 1). This operationally simple and robust procedure is amenable to multigram scale without loss of chemo- or stereoselectivity.[7]

The matched doubly diastereoselective reduction of the α-keto ester **6** employing the Me-Corey−Bakshi−Shibata (CBS) catalyst (*R*)-**7** provided the α-hydroxy ester **8** as single diastereomer after flash chromatography.[8] Inversion of the configuration at C2 was accomplished by Mitsunobu reaction,[9] and subsequent reduction with $LiBH_4$[10] delivered the diol **9**. Transacetalization of the dimethyl acetal of *p*-methoxy benzaldehyde with the diol **9** under Brønsted acid catalysis afforded the corresponding cyclic acetal, which was reductively cleaved, and the resulting primary alcohol was subsequently oxidized to provide the aldehyde **10**.[11,12] The missing stereogenic carbon atoms were then set by a matched doubly diastereoselective Evans aldol reaction between the α-chiral aldehyde **10** and the acylated Evans auxiliary **11**.[13,14] The short route to **2** finally was completed by the introduction

Scheme 1



of a TBS protecting group and the removal of the chiral auxiliary.[15,16]

We continued our synthetic endeavor with the elaboration of D-galactose (**13**) as an ex-chiral-pool building block in the context of the present purpose (Scheme 2).[17] Hence, the bis(acetonide) of **13** was prepared and the remaining hydroxyl group was subjected to the conditions of a redox condensation to afford the iodide **14**.[18] Subsequent β-elimination in the presence of Zn and catalytic amounts of vitamin B12[19] delivered a cyclic hemiacetal which was reduced to provide the diol **15**.[17] Regioselective tosylation[20] of the primary hydroxyl group introduced a capable leaving group for a Kolbe nitrile synthesis. The resulting nitrile was converted into the silyl ether **16** and then reduced[21] to afford

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(7) For selected applications of the catalytic asymmetric Gosteli−Claisen rearrangement in natural product synthesis, see: (a) Pollex, A.; Hiersemann, M. *Org. Lett.* **2005**, *7*, 5705–5708. (b) Körner, M.; Hiersemann, M. *Org. Lett.* **2007**, *9*, 4979–4982.

(8) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. Reduction in the presence of (*R*)-**7** provided (2*S*)-**8** in 87% (dr = 93:7). Treatment with K-Selectride also delivered (2*S*)-**8** (81%, dr = 85:15), albeit with limited scalability (1 g). Far inferior yields (60%) and diastereoselectivities (dr = 4:1) were obtained with (*S*)-**7**.

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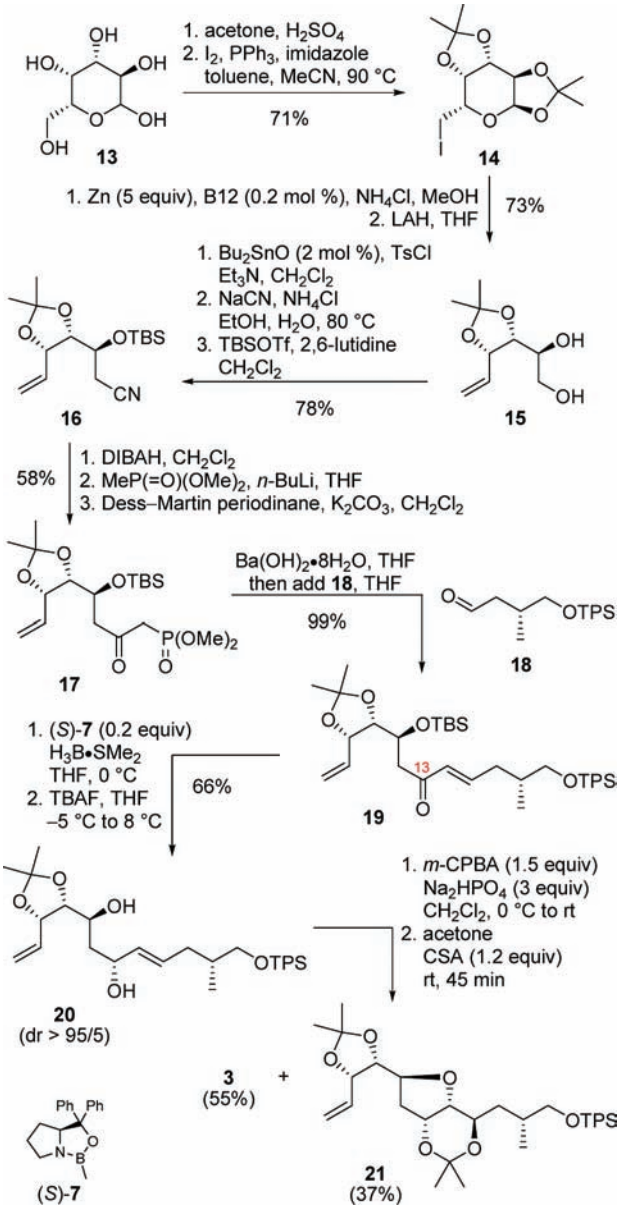
Scheme 2



the corresponding aldehyde. Using the aldehyde as an electrophile toward lithiated trimethyl phosphonate furnished a β-hydroxy phosphonate that was oxidized[12] to deliver the β-keto phosphonate **17**. Subsequent HWE reaction between **17** and the aldehyde **18**[22,23] (TPS = *t*-BuPh$_2$Si) using Paterson conditions[24] afforded the C8−C18 building block **19** in a remarkable yield.

With a concise synthesis of the carbon backbone of the C8−C18 segment **3** in place, the projected key steps for the construction of the tetrahydrofuran had to be put into practice (Scheme 2). At first, the absolute configuration at C13 was set by a CBS reduction of the enone **19** which delivered the corresponding allylic alcohol in 72% yield (dr >95/5) after chromatographic separation of the minor diastereomer (crude product dr = 9/1). Chemoselective cleavage of the TBS ether then provided the diol **20** which was epoxidized with *m*-CPBA[25] to deliver a 3/2 mixture of the corresponding diastereomeric oxiranes in 95% yield. Attempts to improve the diastereoselectivity of the substrate-directed epoxidation were unsuccessful; the VO(acac)$_2$/*t*-BuOOH epoxidation[26] favored the formation of the undesired diastereomer (dr = 15:85), and the outcome of a Katsuki−Sharpless asymmetric epoxidation (SAE)[27] (L-(+)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH) was dedicated by an unfortunate divergent interplay of substrate- and catalyst-induced diastereoselectivity (dr = 1:1). Subsequent treatment of the 3/2 diastereomeric mixture from the Prileschajew epoxidation with (+)-10-camphorsulfonic acid (CSA)[28] in acetone provided, after chromatographic separation, the desired C8−C18 segment **3** (55%) as well as the acetonide **21** (37%); **21** was formed from the diol which resulted from the S$_N$i ring-opening of the undesired diastereomer of the epoxidation. The configuration of the newly generated stereogenic carbon atoms was deduced from NOE experiments.

In order to gain insights into the reason(s) for the remarkable diastereomer-differentiating acetalization, DFT calculations using the functionals B1B95,[29] M05-2X[30] (hybrid meta-GGA), and B3LYP[31] (hybrid GGA) were performed for the model systems **II** and **III** (Figure 2).[32] Geometry optimization and harmonic vibrational frequency calculations were realized using the 6-311++G(d,p) basis set. System **II** represents a simplification of the experimentally observed acetonide **21**, and system **III** was used as a model for the inaccessible acetonide of the diol **3**; in both cases, the C8−C10 and the C16−C18 appendixes were replaced by a methyl group in order to limit the computational cost. In support of the experimental observation, the B3LYP calculations then demonstrate that the *cis*-bicyclo[4.3.0]nonane-like model **II** is 1.6 kcal/mol more stable than the *trans*-annulated model acetal **III**. Notably, our B3LYP computations predict a more pronounced dipole moment for the *cis*-annulated acetal **II** (2.4 D) compared to **III** (1.3 D); therefore, the enthalpic preference for the

(22) Prepared in four steps from **11**; see: (a) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062–9072. (b) Mulzer, J.; Langer, O. *J. Org. Chem.* **2000**, *65*, 6540–6546 (enantiomer). (c) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526. (d) Gramatica, P.; Manitto, P.; Monti, D.; Speranza, G. *Tetrahedron* **1988**, *44*, 1299–1304. Experimental details are provided in the Supporting Information.

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(32) The calculations were carried out with Gaussian03, see: Frisch, M. J. *Gaussian 03, revision E.01*; Gaussian, Inc.: Wallingford, CT, 2004. Full reference given in the Supporting Information.

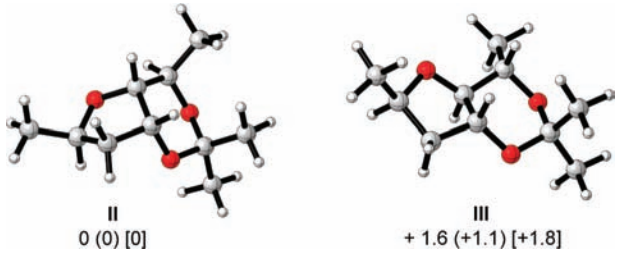

Figure 2. Structural models and relative enthalpies (kcal/mol) of model acetals predicted by DFT calculations at the B3LYP/6-311++G(d,p), (B1B95/6-311++G(d,p)), and [M05-2X/6-311++G(d,p)] level.

formation of **II** would be even more significant in the condensed phase.[33]

Having accomplished the synthesis of **2** and **3**, we were able to address the merger of the subunits to create the desired 14-membered macrolide (Scheme 3). Toward this end, we selected a sequence consisting of esterification and subsequent ring-closing metathesis. To our delight and surprise, esterification of the acid **2** with the diol **3** under the conditions reported by Shiina (MNBA = 2-methyl-6-nitrobenzoic anhydride) proceeded completely regioselective to deliver the ester **22** (94%)![34] Even more impressive was the efficiency of the subsequent ring-closing metathesis (RCM) event provided that the C15 hydroxyl group was protected first. Hence, following the uneventful introduction of a TBS protecting group, the RCM using the second-generation Grubbs precatalyst **25**[35] at elevated temperatures delivered the macrolide **23** in very good yield (90%).[36] The final obstacle was the chemoselective cleavage of the primary TPS ether in the presence of two secondary TBS ethers. After extensive experimentation we found that a large excess of NH_4F[37] (100 equiv) in hexafluoroisopropanol (HFIP) possessed the well-balanced reactivity required and subsequent oxidition of the resulting alcohol afforded the aldehyde **24** which could be purified by chromatography.

(33) Single-point self-consistent reaction field (SCRF) calculations using the PCM solvation model as implemented in Gaussian 03 (PCM, solvent = acetone) at the PCM//B3LYP/6-311++G(d,p) level support this notion and predict a free energy difference of 4.0 kcal/mol in favor of **II**.

(34) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830.

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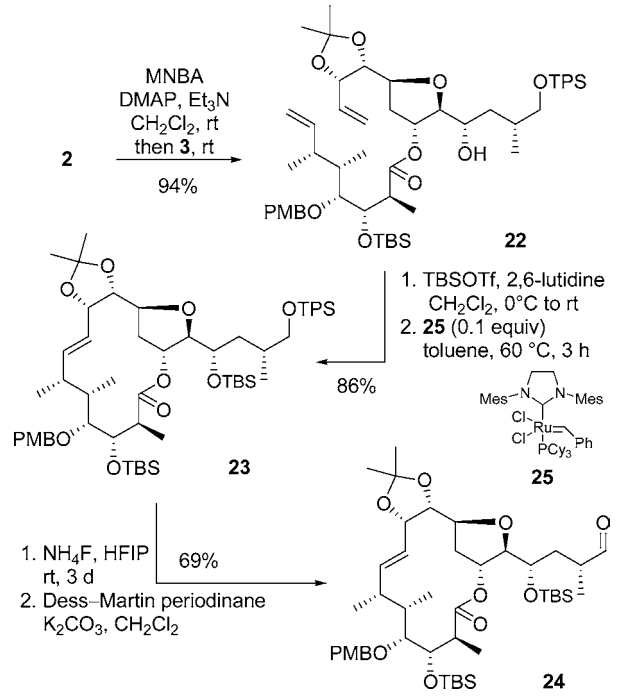
(36) The vicinal ^3J coupling constant of the vinylic protons of **23** (16.1 Hz) is in good accordanced with reported value for the natural product (15.2 Hz).

(37) NH_4F in MeOH, see: Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177–1180. However, attempts to perform the reaction in MeOH or various other alcohols, including CF_3CH_2OH, were not successful.

Scheme 3



In summary, we have established a highly convergent synthesis of the aldehyde **24** which would seem to represent a promising building block for further elaboration. We are now directing our attention to the synthesis of segment **I** and, subsequently, the completion of the total synthesis of (−)-lytophilippine A (**1**).

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Supporting Information Available: Computational details, experimental procedures, spectral and analytical data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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