Letter

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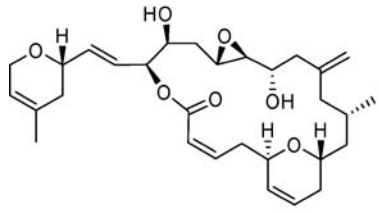
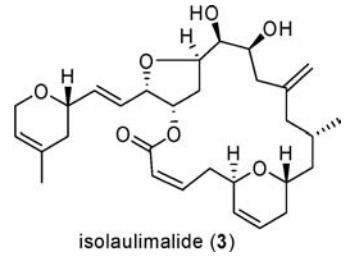


neolaulimalide (**2**)



isolaulimalide (**3**)

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Total Synthesis of Neolaulimalide and Isolaulimalide†

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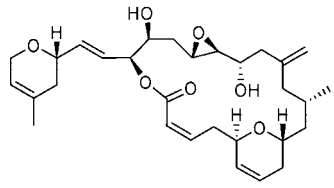
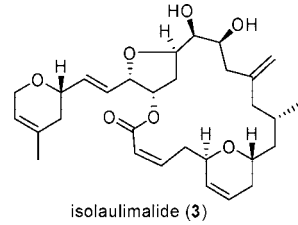
ABSTRACT



neolaulimalide (**2**)



isolaulimalide (**3**)

The first total syntheses of the potential antitumoral leads neolaulimalide (2) and isolaulimalide (3) have been achieved. Key steps in our convergent, fully stereocontrolled route are a Yamaguchi macrolactonization, a Julia−Lythgoe−Kocienski olefination, a Kulinkovich reaction, and a cyclopropyl−allyl rearrangement to install the *exo*-methylene group. Overall, we synthesized 2 in 21 linear steps (3% yield) and 3 in 24 steps (2% yield).

Laulimalide (**1**), neolaulimalide (**2**), and isolaulimalide (**3**) are isomeric polyketide macrolides which have been isolated from the marine sponge *Fasciospongia rimosa* in 1995.[1c] **1** and **3** were also found in various other sponges.[1] All three isomers stabilize microtubuli similar to paclitaxel, epothilone, discodermolide, and others.[2] **1** and **2** inhibit proliferation of several tumor cell lines with IC_{50} values in the low nanomolar range,[1c] whereas the activity of **3** is significantly lower (micromolar range).[1c,2−4]

In relation to **3** (Scheme 1), **1** is an intrinsically unstable compound. On exposure to acid, **1** rearranges to **3** within 2 h via an acid-catalyzed S_N2-type attack of the C_{20} hydroxyl group on the C_{17} position of the epoxide.[1b] **2** shows an appreciably reduced lability toward acid. First it undergoes

† Dedicated to the memory of Dr. Marion Kögl.

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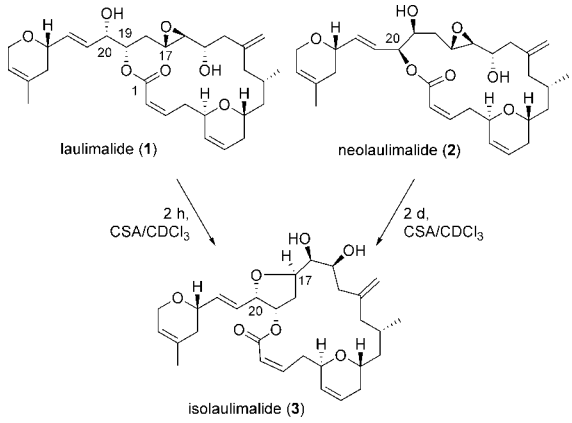
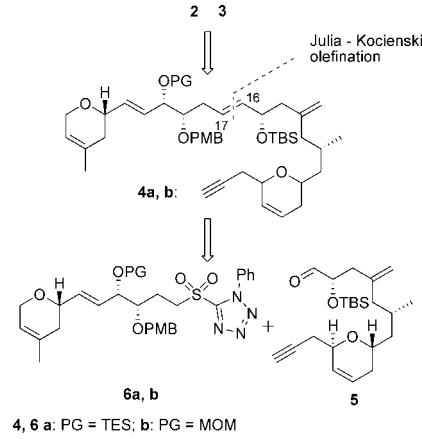
Scheme 1. Laulimalides



Scheme 2. Retrosynthetic Analysis

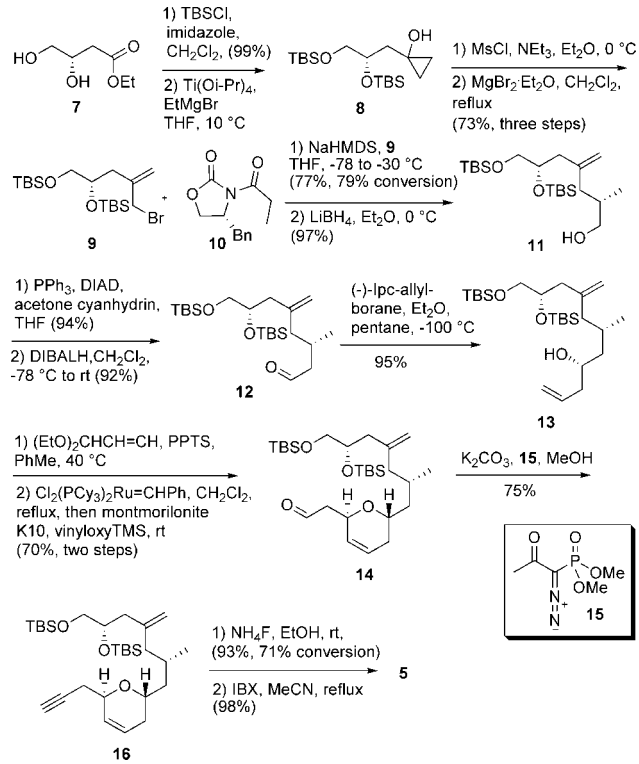


ring contraction to **1**, which then isomerizes to **3** as expected. After two days, the rearrangement is complete.[1c] The total synthesis of **1**[5] (and biologically active analogues thereof)[5k,6] has gripped the synthetic community for over a decade now. However, since acid lability has been identified as a major drawback in deleloping **1** as an anticancer drug,[6a] **2** and **3** should be considered as more promising alternative lead compounds. Compound **2** has only been isolated once, and surprisingly, no total syntheses of **2** (and/or **3**) have been reported to date. Consequently, we decided to develop efficient, flexible, stereocontrolled routes to both **2** and **3**, to enable advanced biological studies.

As shown in Scheme 2, a key step in our syntheses is the Julia−Kocienski olefination of aldehyde **5** and sulfone **6**.

The preparation of fragment **5** (Scheme 3) started from commercially available diol **7** which can be obtained from natural (*S*)-malic acid in two steps.[7] After protection of the alcohols as TBS-ethers, we used a Kulinkovich reaction[8] to generate cyclopropanol **8** which was directly used in the next step. Mesylation and treatment of the crude product with $MgBr_2{\cdot}OEt_2$ in refluxing CH_2Cl_2 resulted in a cyclopropyl−allyl rearrangement[8] furnishing allylbromide **9** in 73% yield over three steps. Evans alkylation of *N*-propionyl-oxazolidinone **10** with **9** followed by reduction with $LiBH_4$ provided alcohol **11** which was converted into the nitrile by either a Mitsunobu reaction[9] or, for a larger scale, by tosylation and S_N2 displacement with sodium cyanide. Reduction of the nitrile with DIBALH delivered aldehyde **12** which was treated with (−)-Ipc-allylborane to yield homoallylic alcohol **13** in 95% yield and 16:1 dr.[10] For streamlining the conversion of **13** into dihydropyran **14**, installation of the C-2/3 side chain

Scheme 3. Synthesis of Fragment **5**



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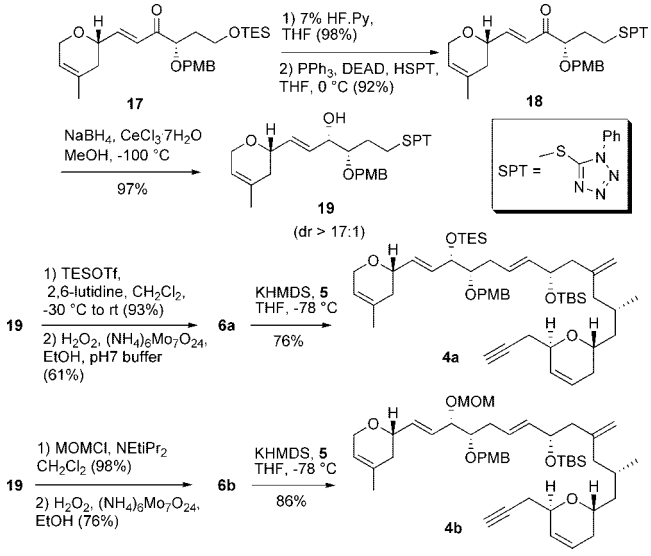
and RCM were performed successively in one pot.[5h,11] Aldehyde **14** was transformed into the terminal alkyne with the Bestmann−Ohira reagent.[12] The primary TBS ether was cleaved selectively, and the resulting alcohol was oxidized to aldehyde **5**.

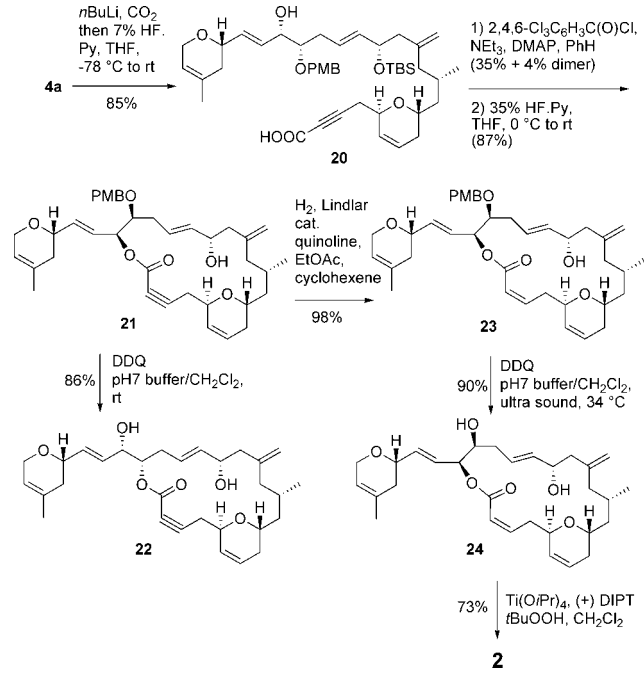
The syntheses of **6a** and **6b** (Scheme 4) started with the removal of the TES-ether from intermediate **17**[5h] with HF-pyridine to give the primary alcohol selectively which was immediately transformed into sulfide **18** (90% over two steps) by treatment with 1-phenyl-1*H*-tetrazol-5-thiol under Mitsunobu conditions. Luche reduction of **18** at low temperatures delivered the *syn*-product **19** in almost quantitative yield and good diastereoselectivity (dr > 17:1),[13] from which **6a** and **6b** were prepared by protection of the free alcohol as a TES- and MOM-ether, respectively, and oxidation to the sulfones. The Julia−Kocienski olefination[14] of aldehyde **5** with sulfones **6a**,**b** in THF at −78 °C delivered olefins **4a**,**b** with complete *E*-selectivity.

Scheme 4. Synthesis of **4a**,**b**



For the synthesis of **2** (Scheme 5), removal of the TES ether from alkyne **4a** and C-1 elongation to *seco* acid **20** were performed in one pot. Yamaguchi lactonization[15] furnished the 21-membered macrolactone in 35% yield along with 4% of the dimer.[16] The OTBS group was easily desilylated in the next step to give **21**, and what appeared a simple endgame turned out to be a highly delicate operation. For, on attempting to remove the 19-OPMB protecting group, we had not realized how strong the driving force would be to restore the more favorable 20-membered lactone. In fact, under standard conditions (excess of DDQ, phosphate buffer, pH 7), PMB removal was ensued by rapid acyl migration, and macrolactone **22** was isolated as the sole product. Model inspection, however, gave us a hint that the ring strain which obviously disfavors the larger macrolide would be much reduced in the (*Z*)-enoate. Hence, Lindlar reduction to give **23** was performed prior to the crucial oxidative PMB removal. To our delight, ultrasound treatment of **23** with DDQ under strictly neutral conditions during reaction and workup gave desoxyneolaulimalide (**24**) in excellent yield. It turned out that **24** was acid sensitive indeed; however, its trans-acylation to desoxylaulimalide was much more accelerated by base. Therefore, in the last step we used the Sharpless epoxidation (SAE) with a modified, nonbasic workup and obtained **2** in 73% yield. All analytical data of **2** were in full accord with the ones reported.[1c]

Scheme 5. Synthesis of **2**



For the synthesis of **3** (Scheme 6), TBS ether **4b** was deprotected, and SAE of the resulting allylic alcohol yielded epoxide **25**. After extensive experimentation, we found that on removing the OMOM protecting group with $BF_3{\cdot}OEt_2$ and PhSH intramolecular opening of the epoxide occurred to give the tetrahydrofuran in 70% yield. Protection of the resulting diol as TBS ethers led to compound **26**. Oxidative PMB deprotection and C-1 elongation delivered *seco* acid **27**. Model inspection indicated that macrolactonization would not be facile, due to the transannular strain exerted by the rigid tetrahydrofuran ring. Under these circumstances, we

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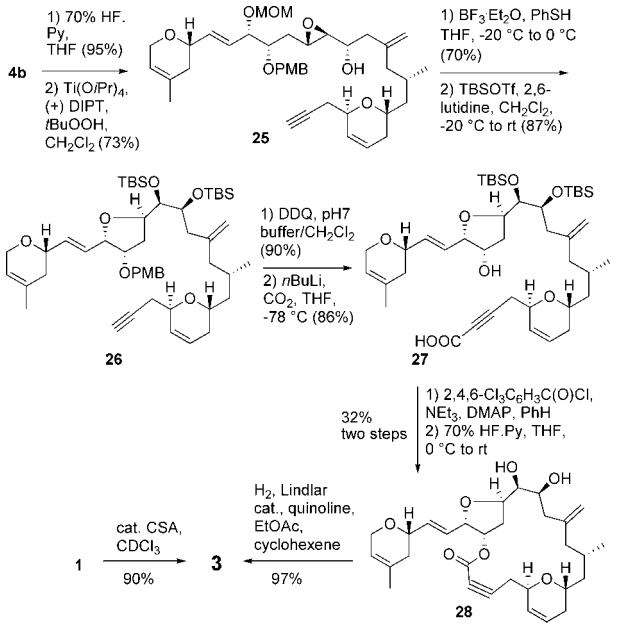
(16) Classical Yamaguchi conditions in very high dilution at rt gave best results, while "modified Yamaguchi conditions" promoted formation of the dimer. For a review see: Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911.

Scheme 6. Synthesis of **3**



were pleased to obtain, again under Yamaguchi conditions, the desired macrolactone in 38% yield, along with 9% of the dimer.[15,16] This mixture was hard to separate; however, after removal of the TBS-protecting groups the monomer **28** could be easily isolated by chromatography. Reduction of the triple bond to the (*Z*)-enoate gave **3** which was identical with the sample we obtained from **1** by treatment with a catalytic amount of acid. All analytical data of **3** matched those in the literature.[1]

In conclusion, we have described the first total syntheses of neolaulimalide (**2**) (21 steps over the longest linear sequence in 3% overall yield) and of isolaulimalide (**3**) (24 linear steps, 2% yield). The synthesis of **2** is essential for the re-evaluation of its promising biological properties since the compound has not been reisolated since its original discovery. The route to **3** could prove of value for the preparation of late-step analogues, as the polyfunctional intermediate **26** is fully stable and could be modified in many ways.

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

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