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Total Synthesis of (+)-Lasonolide A

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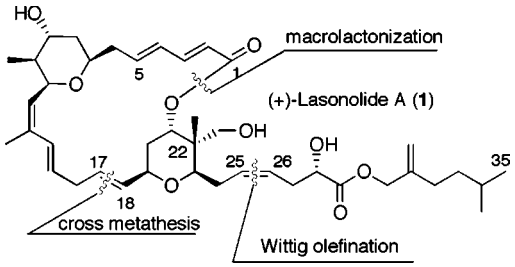
ABSTRACT



An enantiocontrolled total synthesis of (+)-lasonolide A has been accomplished by using the sequential cross metathesis and macrolactonization for the key assembly of the 20-membered polyene macrolide core of the natural product.

(+)-Lasonolide A (**1**) was isolated from an extract of the shallow water Caribbean marine sponge, *Forcepia* sp., by McConnell.[1] This compound was discovered to inhibit the in vitro proliferation of A-549 human lung carcinoma cells as well as cell adhesion in a newly developed whole cell assay that detects signal transduction agents. Because of the intriguing structural features, notable biological profiles, and limited availability, lasonolide A represents an attractive target for total synthesis. Several synthetic studies[2] have been reported, and to date, two total syntheses have been communicated.[3] In this communication, we report a novel strategy toward the synthesis of (+)-lasonolide A that is characterized by an efficient assembly of the 20-membered polyene macrolide core through sequential cross metathesis[4] and macrolactonization.

Our synthetic strategy was based on the retrosynthetic degradation of **1** into the three segments **2**−**4**. Because the introduction of the C26−C35 side chain by Wittig reaction[3a,b] of the ylide generated from **4** in the final stage of the total synthesis has been established,[3] the assembly of the 20-membered polyene macrolide core should be crucial. We envisioned that it would be constructed by a sequence consisting of the cross metathesis between the C5−C17[2f] and C18−C25 segments (**2** and **3**), carbon chain elongation, and macrolactonization. The key segment **3** would be addressed from a chiral building block **5**[5] by taking advantage of the convex nature of the molecule for the stereochemical control of the C21 and C22, particularly of the C22 quaternary center, on the pyran ring (Figure 1).

The synthesis of the C5−C17 segment (**2**) was initiated with the introduction of the skipped triene appendage at C11 of the lactone **6**, which was prepared diastereoselectively

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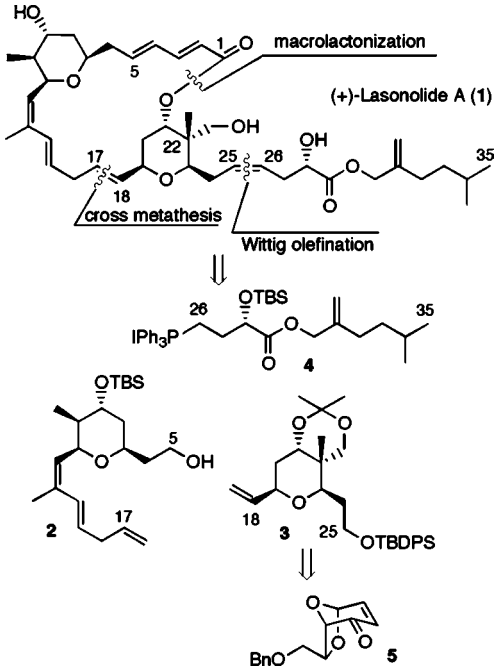
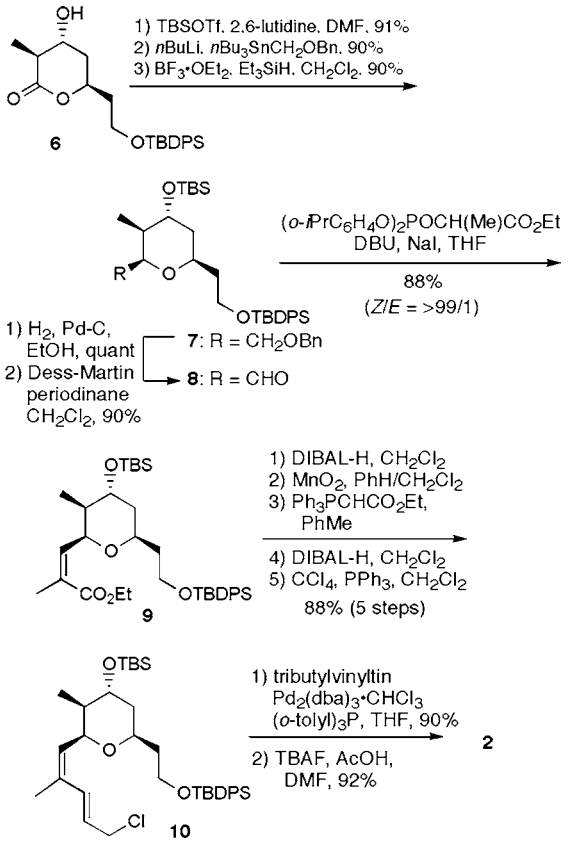


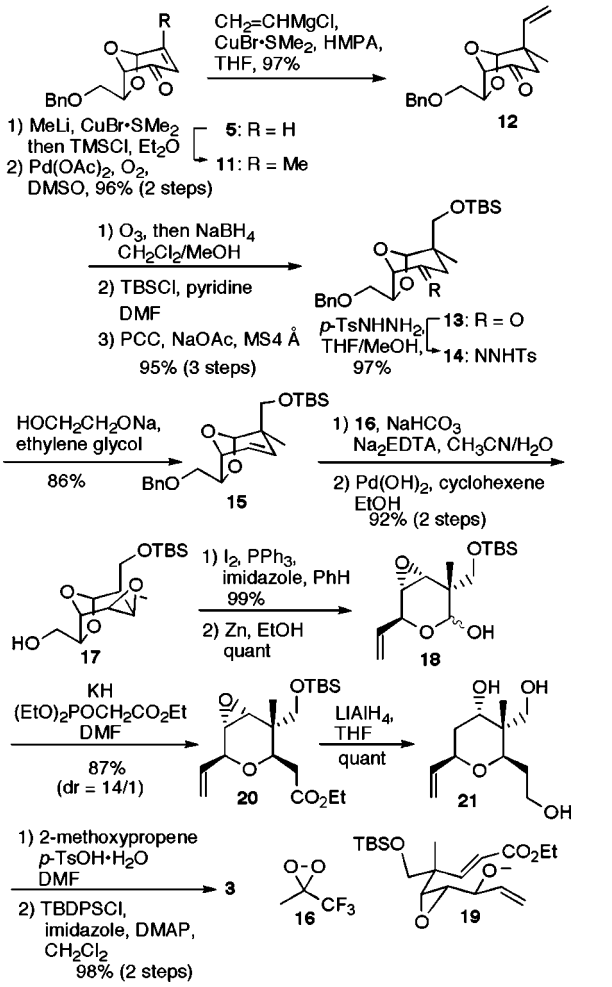
Figure 1. Structure of (+)-lasonolide A and retrosynthetic analysis.

via the Evans' aldol reaction[6] according to the previous paper.[2f] After protection of the secondary hydroxyl group as TBS ether, addition of a benzyloxymethyl anion[7] followed by reduction of the resulting lactol with boron trifluoride etherate and triethylsilane provided **7** as a single diastereomer. Debenzylation followed by Dess−Martin oxidation gave the aldehyde **8**, which was treated with ethyl 2-[di(*o*-isopropylphenyl)phosphono]propionate[8] in the presence of DBU; sodium iodide produced **9** with the *Z*-geometry, and the stereochemistries on the pyran ring were established by NOESY experiments. Carbon chain elongation to furnish the dienyl chloride **10** was carried out via a conventional five-step sequence of reactions, as shown in Scheme 1. Construction of the skipped triene employing the Stille coupling was successfully realized by treatment of **10** with tributylvinyltin in the presence of $Pd_2(dba)_3$•$CHCl_3$ and $(o\text{-tolyl})_3P$ to provide in 90% yield the triene,[9] whose primary TBDPS ether was selectively cleaved[10] to give the C5−C17 segment (**2**) in highly diastereoselective fashion (Scheme 1).

Scheme 1. Synthesis of C5−C17 Segment



Scheme 2. Synthesis of C18−C25 Segment



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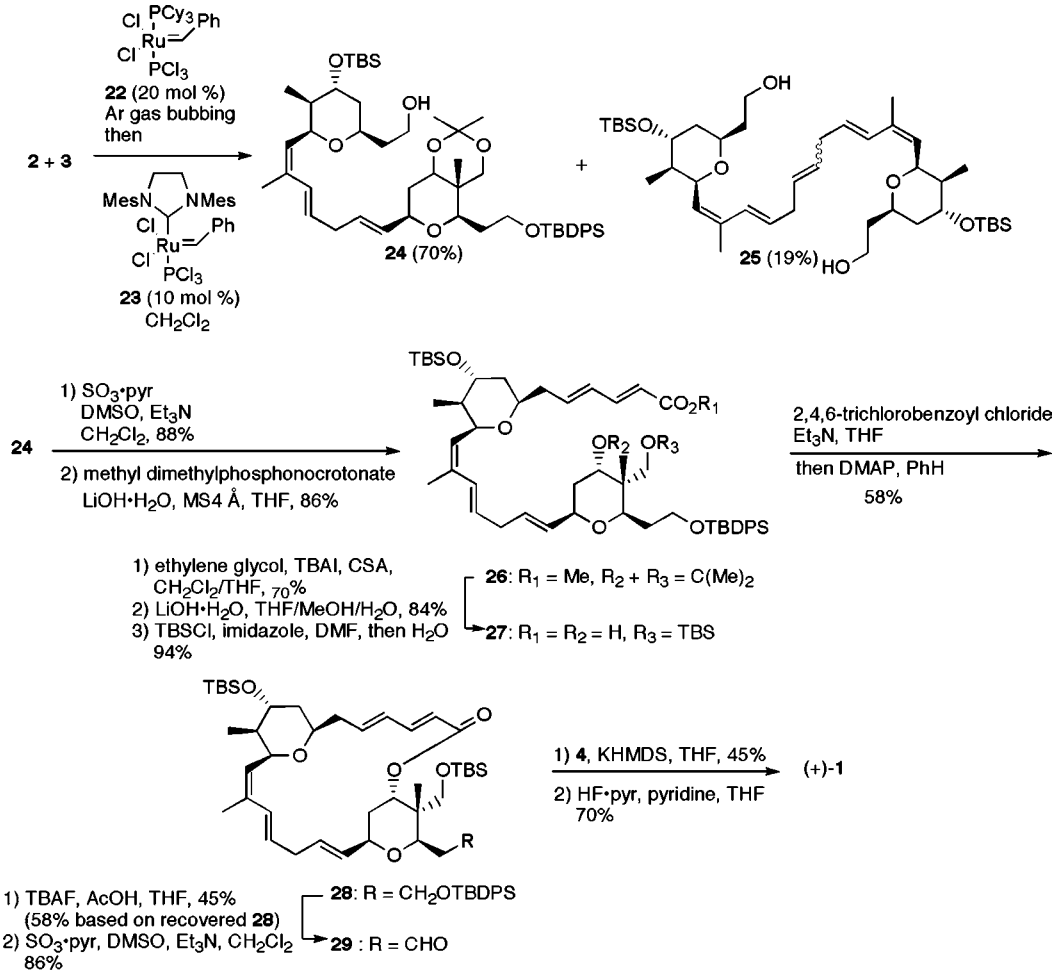
(9) When Ph_3As was used as a ligand, the isomerization of the *Z*-olefin at C12−C13 was observed in a ratio of 4.3:1 (*Z*/*E*).

Scheme 3. Total Synthesis of (+)-Lasonolide A



The optically pure enone **5**,[5] prepared from 2-furfural via the six-step sequence, with a bicyclo[3.2.1]octane framework served as the starting material for the synthesis of the C18−C25 segment (**3**). The reaction of **5** with methyllithium in the presence of $CuBr•SMe_2$ and TMSCl followed by oxidation[11] of the resulting silyl enol ether gave the enone **11**, and on subsequent 1,4-addition of the vinyl group, the ketone **12** having a crucial quaternary stereogenic center at the C22 was obtained diastereoselectively. Conversion of **12** to **13** was achieved by a three-step sequence involving ozonolysis, selective protection of a primary alcohol moiety, and oxidation. The ketone **13** was then treated with *p*-toluenesulfonylhydrazine to give the hydrazone **14**, which was subjected to the Bamford−Stevens reaction[12] to afford cleanly the olefin **15**. Although the epoxidation of **15** with *m*CPBA resulted in the formation of the requisite epoxide only in 46% yield, the use of methyl(trifluoromethyl)-dioxirane **16**[13] in aqueous acetonitrile provided **17** in 92% yield with 90% diastereomeric excess (de) after debenzylation. The optically and diastereomerically pure **17**, purified by a recrystallization, was iodinated and reduced by zinc in refluxing ethanol to produce **18**. Introduction of the two-carbon unit into the C23 position with *R*-configuration was carried out efficiently by treatment of **18** with triethyl phosphonoacetate in the presence of potassium hydride as a base in DME to provide **20** as a chromatographically separable mixture of diastereoisomers in a ratio of 14:1 in 87% yield. The configuration at C23 of the major isomer proved to be the desired *R* by the NOESY experiment. The selective formation of the desired *R*-isomer can be explained by considering the conformation of the transition state in the intramolecular Michael reaction, in which the conformation **19** would be sterically favored over the other conformer which gives rise to the C23 *S*-isomer. Reduction of **20** with lithium aluminum hydride in refluxing THF furnished the triol **21**, whose 1,3-diol and primary alcohol moieties were sequentially protected as acetonide and TBDPS ether to give the C18−C25 segment (**3**) (Scheme 2).

The C26−C35 segment (**4**) was prepared from 5-methylhexan-1-ol[14] by Swern oxidation followed by one-pot methylenation[15] and immediate DIBAL-H reduction to give

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5-methyl-2-methylenehexanol. This was then converted to the phosphonium iodide **4** according to the procedure reported by Lee.[3b]

With the desired three segments in hand, the stage was now set for crucial construction of the 20-membered polyene macrolide core. The key installation of the C17−C18 *E*-olefin by cross metathesis[16] between **2** and **3** proved to be difficult; however, after numerous trials, it was found that sequential treatment of a mixture of **2** and **3** with the Grubbs type I catalyst **22** in CH_2Cl_2 for 24 h under bubbling argon gas and then with the Grubbs type II catalyst **23** for an additional 24 h[17] provided the desired coupled product **24** with the C17−C18 *E*-olefin (from ^{1}H NMR) and the homodimer **25** in 70% and 19% yield, respectively. The dimer can be converted[18] to **24** by treatment with **3** in the presence of **23** in 27% (57% based on the recovered **25**) yield. Oxidation of the primary hydroxy group in **24** and the vinylogous Horner−Emmons reaction gave the ester **26**, which was subjected to sequential deacetalization, alkaline hydrolysis, and selective protection of a primary alcohol to afford the hydroxy carboxylic acid **27**. The macrolactonization was achieved by employing the pocedure of Yamaguchi[19] to provide **28** in 58% yield. Selective desilylation followed by oxidation of the resulting primary alcohol afforded the aldehyde **29**. Finally, a Wittig reaction[3a,b] between the ylide, prepared from **4** with KHMSD, and the aldehyde **29** led to (+)-lasonolide A (**1**) after subsequent TBS deprotection (Scheme 3). Spectroscopic properties and the optical rotation of the synthetic **1** were identical to those reported for the natural product.[1]

In summary, we have completed an enantiocontrolled total synthesis of (+)-lasonolide A using the sequential cross metathesis between the two highly functionalized segments, which were prepared efficiently, and macrolactonization for the key assembly of the 20-membered macrolide backbone of the natural product. The synthetic route that we developed here is general and efficient and can also be applied to the synthesis of the other related natural products.

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

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