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Total Synthesis of (+)-Mycalamide A

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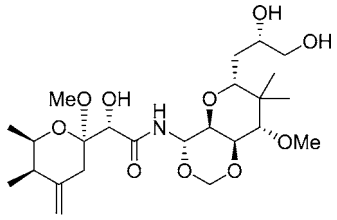
ABSTRACT



Mycalamide A

A convergent total synthesis of (+)-mycalamide A is described. A $Yb(OTf)_3$–TMSCl catalytic system is used to synthesize a trioxadecalin ring system, which contains the right segment of mycalamide A. In addition, a tetrahydropyran ring, which is the left segment, is constructed with use of a novel one-pot δ-lactonization protocol. Both segments are prepared from a common starting material, D-mannitol. These segments are then coupled and the functional groups are transformed to synthesize (+)-mycalamide A.

Mycalamide A (**1a**) was initially isolated from a New Zealand marine sponge in 1988.[1] This natural product blocks T-cell activation and exhibits a more effective immunosuppressive activity than FK-506.[2] Additionally, **1a** is reported to show potent antitumor and antiviral activities. The unique structure of **1a** has attracted the attention of synthetic chemists since it has a tetrahydropyran ring and a trioxadecalin ring system bridged by an *N*-acyl aminal bond.[3] Numerous compounds which resemble mycalamide A (**1a**) have been isolated. For example, the hydroxyl group at C-17 of mycalamide A (**1a**) is replaced by a methoxy group in mycalamide B (**1b**).[4] Also, theopederins[5] and onnamides[6] have structures similar to the mycalamides, except for the C-15 side chain fragments. Interestingly, each natural product shows a strong cytotoxic property. Kocienski's convergent protocol[7] is adopted in our total synthesis of mycalamide A (**1a**). However, our efforts have focused on the asymmetric synthesis of both right and left segments of mycalamide A (**1a**). Scheme 1 summarizes our retrosynthetic analysis of the right segment of **1a**. The stereochemistry of the aminal

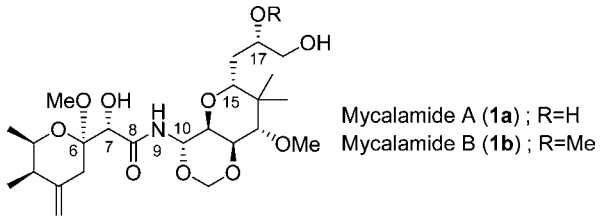


Figure 1. Structures of mycalamides A (**1a**) and B (**1b**).

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[‡] Tohoku University.

(1) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Am. Chem. Soc.* **1988**, *110*, 4850−4851.

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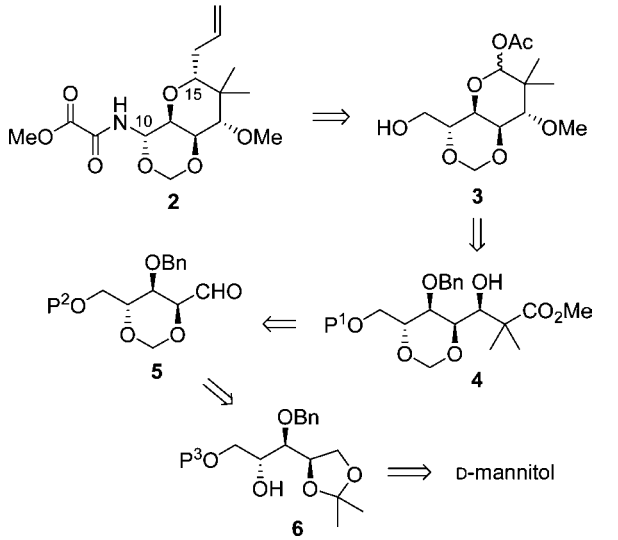
Scheme 1. Retrosynthetic Analysis of the Right Segment **2** of Mycalamide A (**1a**)

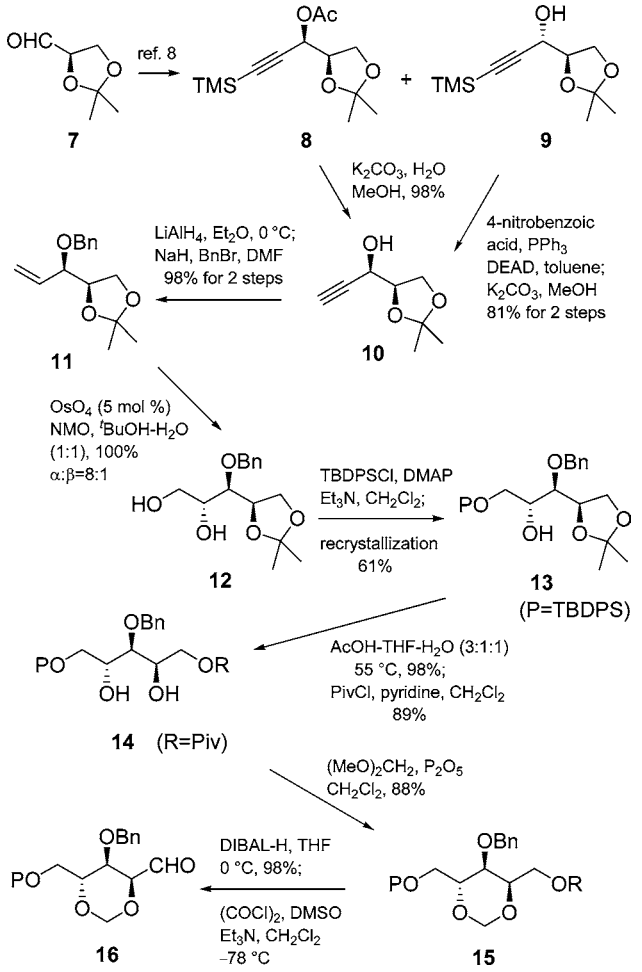


at the C-10 position in the right segment **2** is due to a Curtius rearrangement of the corresponding carboxylic acid, which is derived from alcohol **3**. The allyl group at C-15 can be stereoselectively introduced in the presence of a Lewis acid. Compound **3** is formed by the cyclization of aldol product **4** and subsequent acetylation. It should be noted that novel cross-aldol reaction conditions without epimerization of the aldehyde **5** must be created for this stage. Finally, **5** is derived from D-mannitol through alcohol **6**. Both the right and left segments are synthesized from D-mannitol since it is a very inexpensive chiral starting material.

Mulzer's protocol[8] is adopted to synthesize (3*R*,4*R*)-3-benzyloxy-4,5-isopropylidenedioxypentene **11**. Consequently, acetate **8** (52% yield from **7**) and alcohol **9** (41% yield from **7**) are respectively isolated by silica gel column chromatography. Each compound is converted to alcohol **10** by using the following methods. Acetate **8** is directly hydrolyzed to provide **10** in 98% yield. On the other hand, alcohol **9** (41% yield from **7**) is subjected to the Mitsunobu reaction followed by hydrolysis to give **10** (2 steps, 81% yield). Treating **10** with $LiAlH_4$ and benzylation of the corresponding alcohol afforded benzyl ether **11** in 98% overall yield. Then the olefin moiety of **11** is diastereoselectively dihydroxylated. As expected, the major product is desired diol **12**.[9] Compound **12** is converted to **15** through alcohol **13** and diol **14**.

Reduction of **15** with DIBAL-H (98% yield) followed by Swern oxidation produces aldehyde **16**, which is a key intermediate for the cross-aldol reaction. Table 1 shows the

Scheme 2. Stereoselective Synthesis of Aldehyde **16**



remarkable effects of a Lewis acid in the cross-aldol reaction. When $Yb(OTf)_3$ is used as the Lewis acid, desired compounds **17a** and **17b** are obtained in 59% total yield along with the epimers **18a** and **18b** (entry 1). Using titanium tetrachloride or indium trichloride gives the desired aldol products in moderate yields (entries 2 and 3), which is similar to the results with $Yb(OTf)_3$. As shown in entry 5, a stoichiometric amount of TMSCl dramatically improves the yield of the silyl aldol product **17a**, while shortening the reaction time. Interestingly, a catalytic amount of TMSCl does not affect the reaction (entry 4). Furthermore, a catalytic amount of TMSOTf decreases the yield of **17a** (entry 6).

The stereochemical outcome of this aldol reaction can be rationalized as a nucleophilic attack on the chelated conformation **A** from the less hindered face as depicted in Figure 2. Consequently, the major products are the desired aldols **17a** and **17b**. Enolization of **16** easily occurs at this stage. Therefore, compounds **18a** and **18b** are generated from the epimerized aldehyde *epi*-**16**. Thus, the addition of a stoichiometric amount of TMSCl to $Yb(OTf)_3$ improves the total

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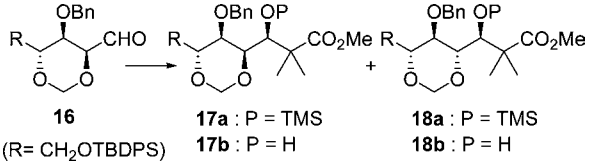
Table 1. Lewis Acid-Promoted Cross-Aldol Reaction[a]



entry	Lewis acid (mol %)	additive (mol %)	time (h)	yield (%)[b] 17a	17b	18a	18b
1	$Yb(OTf)_3$ (10)	none	48	51	8	25	5
2[c]	$TiCl_4$ (150)	none	1		63		
3	$InCl_3$ (10)	none	43	41	21		
4	$Yb(OTf)_3$ (10)	TMSCI (10)	1	46	9	29	3
5	**$Yb(OTf)_3$ (10)**	**TMSCI (100)**	**1**	**79**	**10**		
6	$Yb(OTf)_3$ (10)	TMSOTf (10)	21	27	24	13	

[a] Methyl trimethylsilyl dimethylketene acetal was used as a nucleophile. [b] Two-step yield from the corresponding alcohol. [c] All reactions were carried out at room temperature in CH_2Cl_2 except entry 2 (−78 °C).

yield of this aldol reaction by accelerating the reaction rate prior to the enolization of **16**.[10]

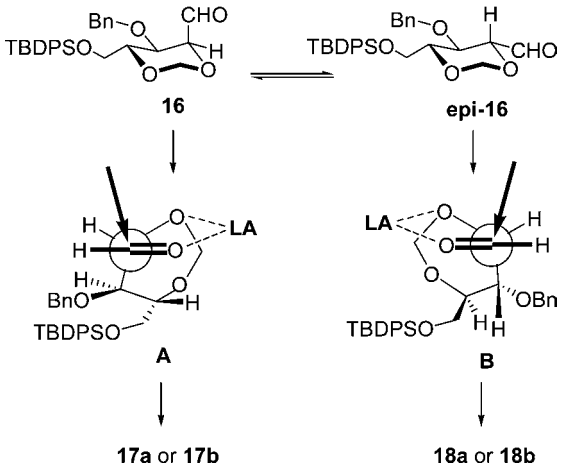
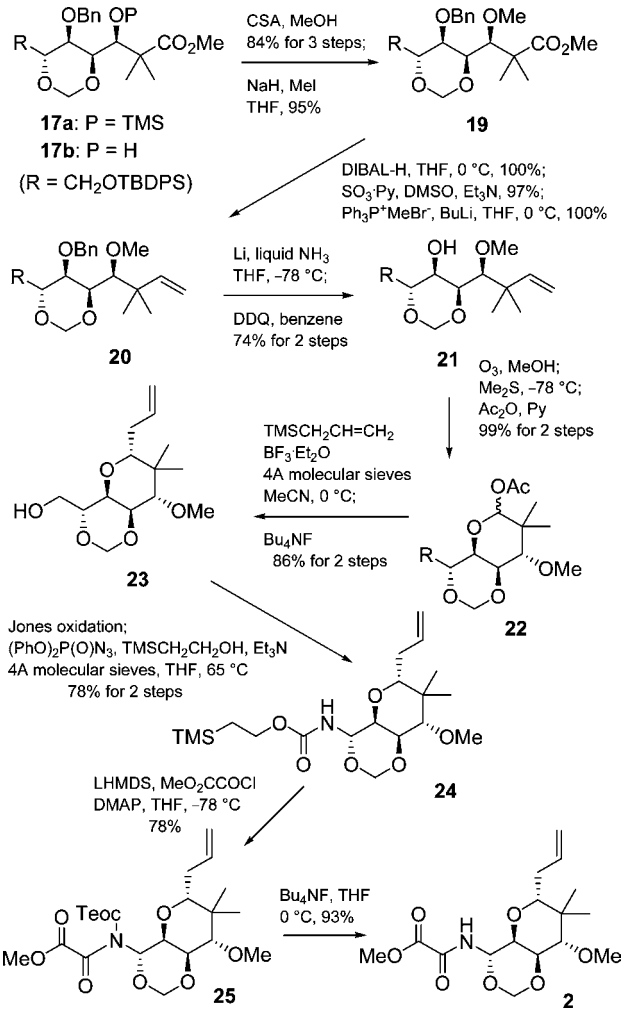


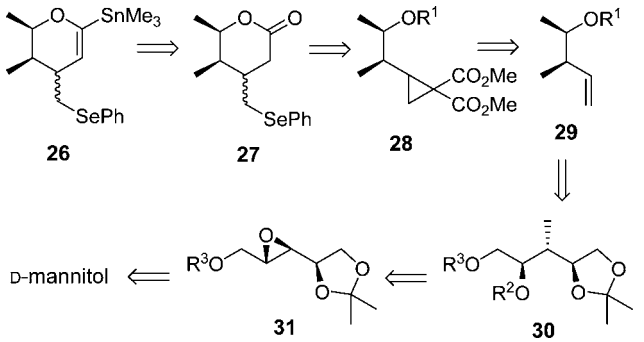
Figure 2. Plausible stereochemical rationale.

Both **17a** and **17b** are treated with CSA in MeOH to give the corresponding alcohol (3 steps, 84% yield), which is subsequently treated with MeI in the presence of NaH to provide methyl ether **19** (95% yield). Ester **19** is converted to **20** in three steps. An unexpected overreduction of the diphenyl groups on the silicon atom of **20** accompanies the removal of the benzyl ether under Birch reduction conditions. Hence, reoxidation of the crude products with DDQ provides **21** (2 steps, 74% yield). Oxidative cleavage of the olefin moiety of **21** followed by acetylation affords acetate **22** (2 steps, 99% yield). Treating **22** with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ produces the corresponding allyl product as a single diastereoisomer. To prepare the aminal moiety, alcohol **23**, which is obtained from **22** in 86% overall yield, is oxidized with Jones' reagent to provide the corresponding carboxylic acid. A Curtius rearrangement[11]

Scheme 3. Preparation of the Right Segment **2**



Scheme 4. Retrosynthetic Analysis of the Left Segment **26** of Mycalamide A (**1a**)



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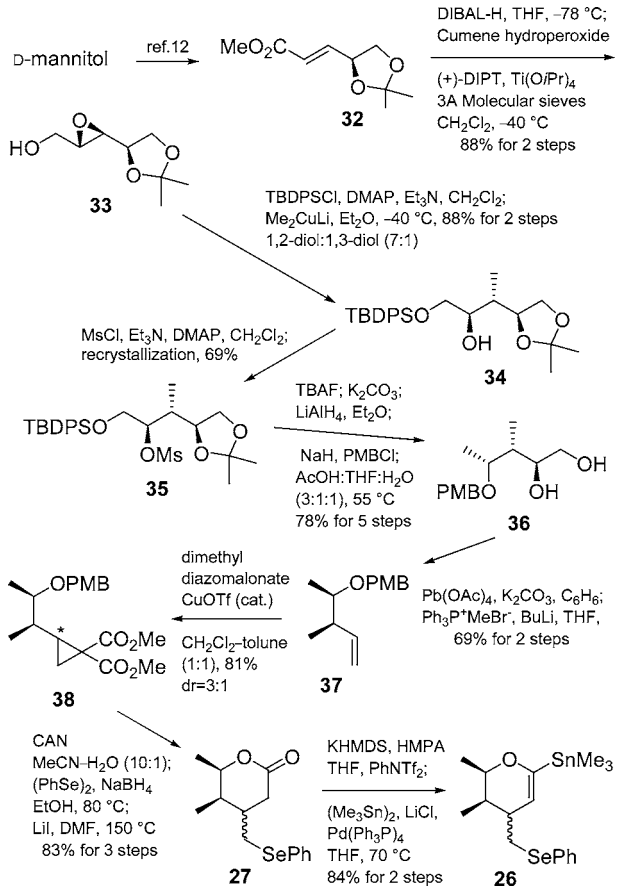
Scheme 5. Synthesis of the Left Segment **26**



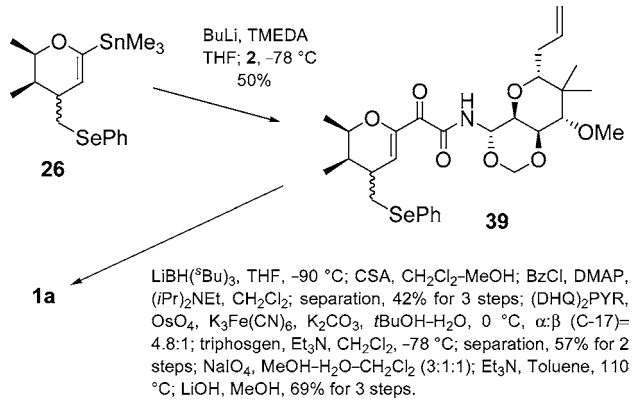
with diphenylphosphoryl azide in the presence of TMS ethanol provides carbamate **24** (2 steps, 78% yield). The spectral data of **24** are identical with those reported by Kocienski.[7] Carbamate **24** is transformed into the desired *N*-acyl product **25** in 78% yield. The synthesis of the right segment **2** is completed by removing the trimethylsilylethoxycarbonyl (Teoc) group with TBAF (93% yield) (Scheme 3).

Scheme 4 shows the retrosynthetic analysis for the left segment **26**. Vinyltin species **26** is derived from lactone **27**. The phenylselenide group is introduced by a nucleophilic ring opening of the cyclopropane unit of **28**, which is prepared by using an intermolecular cyclopropanation reaction between dimethyl diazomalonate and chiral olefin **29**. Finally, **29** is derived from D-mannitol through a regioselective reduction and regioselective methylation.

Starting with D-mannitol, α,β-unsaturated ester **32** is synthesized as described in the literature.[12] The reduction of **32** with DIBAL-H followed by Sharpless' asymmetric epoxidation gives epoxy alcohol **33** (2 steps, 88% yield), which is converted to TBDPS ether **34** via protection of the primary alcohol and regioselective methylation. Alcohol **34** is converted to diol **36** through mesylate **35**. Diol **36** is transformed into olefin **37** by oxidative cleavage and a Wittig reaction (2 steps, 69% yield). Finally, CuOTf is used to conduct an intermolecular cyclopropanation reaction to give cyclopropane derivative **38** as a 3:1 mixture of the diastereoisomers in 81% yield. After deprotection of the benzyl moiety, a novel δ-lactone generation reaction is conducted with diphenyldiselenide and $NaBH_4$ in EtOH at 80 °C.[13] The Krapcho reaction[14] of the crude product provides lactone **27**, which is then transformed into the corresponding enol triflate. The enol triflate is subsequently converted to vinyltin **26** by using the standard method[15] (Scheme 5).

The left and right segments are coupled by transmetalation of **26** followed by regioselective nucleophilic addition of the resulting vinyl anion to the ester group of **2** and produce adduct **39** in 50% yield. Functional group manipulations of **39**, as shown in Scheme 6, provide (+)-mycalamide A (**1a**).

Scheme 6. Synthesis of Mycalamide A (**1a**)



The spectroscopic properties of synthetic mycalamide A (**1a**) are identical with those reported for the natural product.

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Supporting Information Available: Experimental conditions and spectral data for compounds reported in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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