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Convergent Total Synthesis of (+)-Mycalamide A

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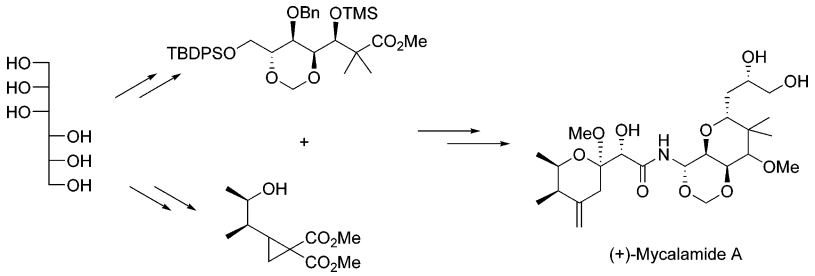

The details of a convergent total synthesis of (+)-mycalamide A are described. $Yb(OTf)_3$−TMSCl-catalyzed cross-aldol reaction conditions are used to synthesize the right segment of mycalamide A. In this reaction, an acid-sensitive aldehyde reacts with methyl trimethylsilyl dimethylketene acetal without epimerization to provide the desired aldol adduct. Additionally, a tetrahydropyran ring, which is the left segment of mycalamide A, is prepared using a novel one-pot δ-lactone formation methodology. Both segments are constructed from a common starting material, D-mannitol. These segments are then coupled in the presence of BuLi, and the functional groups are transformed to complete the synthesis of (+)-mycalamide A.

Introduction

Mycalamide A (**1a**), which was initially isolated in 1988 from a New Zealand marine sponge,[1] blocks T-cell activation and shows a more effective immunosuppressive activity than FK-506.[2] In addition, **1a** is reported to exhibit potent antitumor[3] and antiviral activities.[4] The distinctive structure of **1a** has attracted much attention because it has a trioxadecalin ring and a tetrahydropyran ring system bridged by an *N*-acyl aminal bond. As depicted in Figure 1, numerous compounds that resemble mycalamide A have been isolated. For example, in mycalamide B (**1b**), the hydroxyl group at C-17 of mycalamide A (**1a**) is replaced by a methoxy group.[5] In addition, theopederins[6] and onnamides[7] have structures similar to that of the mycalamides, except for the C-15 side chain fragments. It is noteworthy that each natural product shows a strong cytotoxic property.

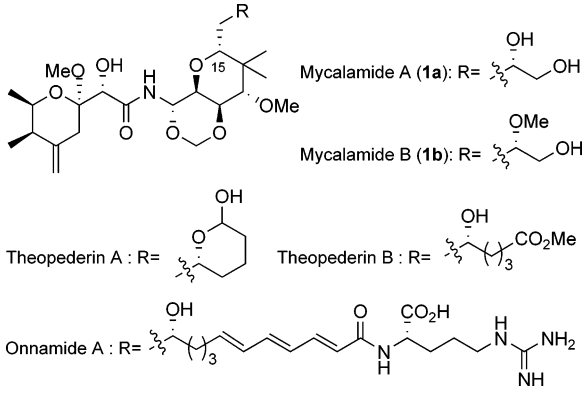

FIGURE 1. Mycalamide A (**1a**) and B (**1b**) and structurally similar natural products.

Most mycalamide families have been synthesized by convergent methodologies as shown in Figure 2. Kishi's, Nakata's,

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

(2) Garvin, F.; Freeman, G. J.; Razi-Wolf, Z.; Benacerraf, B.; Nadler, L.; Reiser, H. *Eur. J. Immunol*. **1993**, *23*, 283.

(3) (a) Burres, N. S.; Clement, J. J. *Cancer Res*. **1989**, *49*, 2935. (b) Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. *Chem. Pharm. Bull*. **1991**, *39*, 2152.

(4) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Perry, N. B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1233 and references therein.

(5) (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem*. **1990**, *55*, 223. (b) Simpson, J. S.; Garson, M. J.; Blunt, J. W.; Munro, M. H. G.; Hooper, J. N. A. *J. Nat. Prod*. **2000**, *63*, 704.

(6) (a) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem*. **1992**, *57*, 3828. (b) Tsukamoto, S.; Matsunaga, S.; Fusetani, N.; Toh-E, A. *Tetrahedron* **1999**, *55*, 13697.

(7) (a) Sakemi, S.; Ichiba, T.; Kohmoto, G.; Saucy, G.; Higa, T. *J. Am. Chem. Soc*. **1988**, *110*, 4851. (b) Matsunaga, S.; Fusetani, N.; Nakano, Y. *Tetrahedron* **1992**, *48*, 8369.

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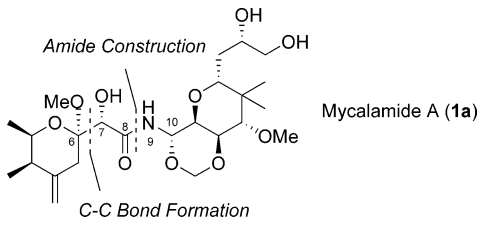


FIGURE 2. Previous convergent strategies.

Trost's and Rawal's groups have adopted a disconnection at the C-8 and N-9 positions for their total syntheses.[8] This route is useful for the mycalamide syntheses, but epimerization at the C-10 position easily occurs prior to the coupling process. On the other hand, Kocienski's[9] and Roush's[10] groups have independently demonstrated a different disconnection, which contains a coupling reaction between C-6 and C-7. The advantage of this convergent technique is that coupling proceeds without epimerization.

We recently reported the total synthesis of mycalamide A using novel $Yb(OTf)_3$–TMSCl-catalyzed cross-aldol reaction and one-pot synthesis of δ-lactone protocol.[11] However, the utility of the $Yb(OTf)_3$−TMSCl catalytic system was limited by cross-aldol reaction of methyl trimethylsilyl dimethylketene acetal and a particular aldehyde. Additionally, the function of TMSCl in the cross-aldol reaction was not clear.

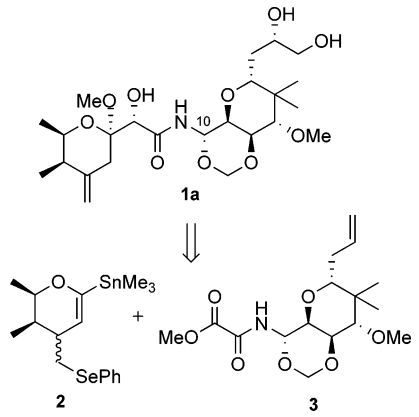
We now describe full details of the reaction mechanism related to $Yb(OTf)_3$−TMSCl-catalyzed cross-aldol reactions and the total synthesis of mycalamide A via the catalytic system.

Results and Discussion

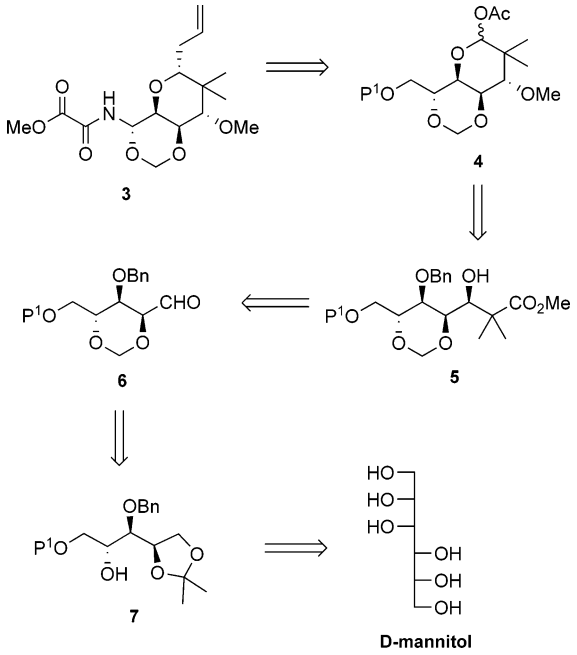
To avoid epimerization problems, Kocienski's convergent protocol is employed in the total synthesis of **1a** (Scheme 1).[11] However, our efforts have focused on the asymmetric synthesis of **2**, which contains the left segment of mycalamide A (**1a**), and trioxadecalin **3**, which is the right segment.

Right Segment Synthesis. Scheme 2 summarizes our retrosynthetic analysis of the right segment of **1a**. The sensitive aminal moiety at the C-10 position in the right segment is generated by a Curtius rearrangement of the corresponding carboxylic acid,[12] which is derived from **4**. The allyl group at C-15, which can be converted into various side chains, can be stereoselectively introduced in the presence of a Lewis acid. Compound **4** is formed by the cyclization of aldol product **5** and subsequent acetylation. It should be noted that novel cross-aldol reaction conditions without epimerization of aldehyde **6** must be created for this stage. Finally, **6** is derived from D-mannitol through alcohol **7**. Both the right and left segments are synthesized from D-mannitol because D-mannitol is a very inexpensive chiral starting material.

SCHEME 1. Retrosynthetic Analysis of Mycalamide A



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



Although the reactions of vinylmagnesium halides with (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde **8**,[13] which stems from D-mannitol, have been studied,[14] stereochemical control is still difficult. Therefore, Mulzer's protocol[15] (enzymatic resolution) is adopted to synthesize (3*R*,4*R*)-3-benzyloxy-4,5-isopropylidenedioxypentene **12**. Consequently, acetate **9** (52% yield from **8**) and alcohol **10** (41% yield from **8**) are isolated by silica gel column chromatography. Each compound is converted to alcohol **11** using the following methods. Acetate **9** is directly hydrolyzed to provide **11**. However, alcohol **10** is subjected to the Mitsunobu reaction[16] followed by hydrolysis to give **11**. Treating

(8) Total synthesis of (+)-mycalamide A: (a) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242. (b) Nakata, T.; Fukui, H.; Nakagawa, T.; Matsukura, H. *Heterocycles* **1996**, *42*, 159. (c) Sohn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290. Formal synthesis of (+)-mycalamide A: (d) Nakata, T.; Matsukura, H.; Jian, D.; Nagashima, H. *Tetrahedron Lett.* **1994**, *35*, 8229. Formal synthesis of (−)-mycalamide A: (e) Trost, B. M.; Tang, H.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48. Total synthesis of (+)-onnamide A: (f) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693.

(9) Total synthesis of mycalamide B and theopederin D: Kocienski, P.; Narquizuan, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, E. T. *J. Chem. Soc., Perkin Trans. 1.* **2000**, 2357.

(10) Total synthesis of (+)-mycalamide A: (a) Roush, W. R.; Pfeifer, L. A. *Org. Lett.* **2000**, *2*, 859. Other synthetic studies: (b) Breitfelder, S.; Schlapbach, A.; Hoffmann, R. W. *Synthesis* **1998**, 468 and references therein.

(11) As a preliminary communication: Kagawa, N.; Ihara, M.; Toyota, M. *Org. Lett.* **2006**, *8*, 875.

(12) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421.

(13) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056.

(14) Review: McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.

(15) Mulzer, J.; Greifenberg, S.; Beckstett, A.; Gottwald, M. *Liebigs Ann. Chem.* **1992**, 1131.

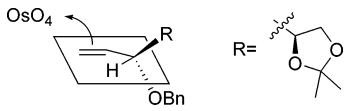
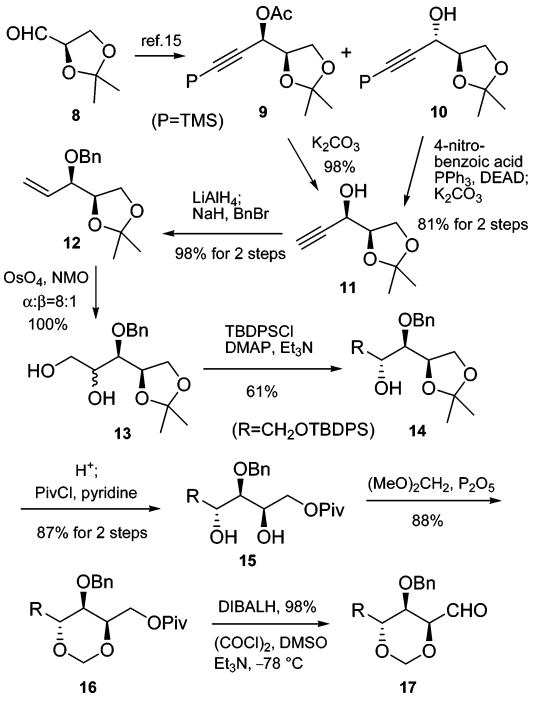


FIGURE 3. Diastereoselective dihydroxylation of alkene **12**.

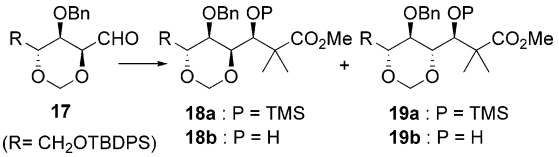
SCHEME 3. Stereoselective Synthesis of Aldehyde 17



11 with $LiAlH_4$ and benzylation of the corresponding alcohol affords benzyl ether **12**. Then the alkene moiety of **12** is diastereoselectively dihydroxylated. As expected, the major product is the desired α-diol of **13**. Applying Kishi's model for the dihydroxylation of allylic alcohols as shown in Figure 3, we find that dihydroxylation then occurs from the top.[17] The minor diastereoisomer of the diol **13** is easily separated by crystallization of the silyl ether. Deprotection of the acetonide of **14** followed by protection of the primary alcohol as the pivaloyl ester provides diol **15**, which is used to construct the 1,3-dioxane ring with dimethoxymethane and phosphorus oxide. Reduction of the pivaloyl ester of **16** with DIBALH followed by Swern oxidation produces aldehyde **17**, which is a key intermediate for the cross-aldol reaction (Scheme 3).

Table 1 shows the remarkable effects of a Lewis acid in the cross-aldol reaction. When the Lewis acid is $Yb(OTf)_3$,[18] desired compounds **18a** and **18b** are obtained in 59% total yield along with the epimers **19a** and **19b** (entry 1). Similar to using $Yb(OTf)_3$, titanium tetrachloride or indium trichloride gives the desired aldol products in moderate yields (entries 2 and 3). As shown in entry 5, a stoichiometric amount of TMSCl dramatically improves the yield of the silyl aldol product **18a** and shortens the reaction time,[19] but a catalytic amount of TMSCl does not affect the reaction (entry 4). Furthermore, a catalytic amount of TMSOTf decreases the yield of **18a** (entry 6).

TABLE 1. Lewis Acid-Promoted Cross-Aldol Reaction



entry[a]	Lewis acid (mol %)	additive (mol %)	time (h)	yield[b] 18a	18b	19a	19b
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)	TMSCl(10)	1	46	9	29	3
5	$Yb(OTf)_3$(10)	TMSCl(100)	1	79	10		
6	$Yb(OTf)_3$(10)	TMSOTf(10)	21	27	24	13	

[a] Methyl trimethylsilyl dimethylketene acetal was used as 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).

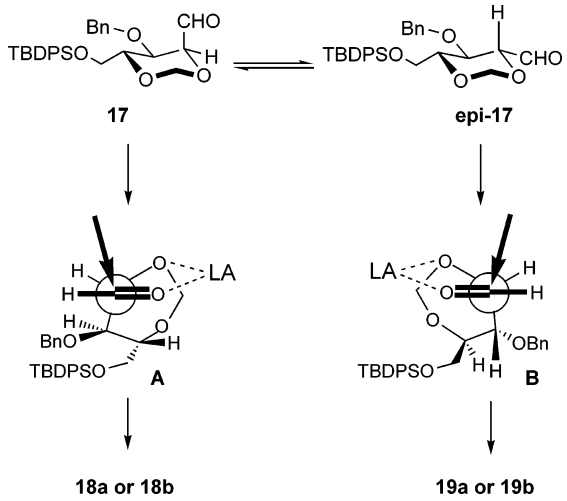


FIGURE 4. Plausible stereochemical rationale.

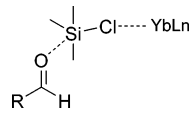


FIGURE 5. Novel combination model of $Yb(OTf)_3$ and TMSCl.

The stereochemical outcome of this aldol reaction can be rationalized as a nucleophilic attack on chelated conformation **A** from the less hindered face as depicted in Figure 4. Consequently, the major products are desired aldols **18a** and **18b**. Enolization of **17** easily occurs at this stage. Therefore, compounds **19a** and **19b** are generated from epimerized aldehyde **epi-17**. Thus, the addition of a stoichiometric amount of TMSCl to $Yb(OTf)_3$ improves the total yield of this aldol reaction by accelerating the reaction rate prior to the enolization of **17**. TMSCl probably works like a Lewis acid by combining with $Yb(OTf)_3$ through the chloride atom (Figure 5).[20] The stereochemistries of **19a** and **19b** are established after their transformation into acetonide **19c**. Namely, hydrogenolysis of **19b** followed by acetonization produces bicyclic compound **19c**.

(16) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
(17) Cha, J. K.; Christ, W. H.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
(18) Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1997**, 959.
(19) Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **2003**, *68*, 3112.
(20) (a) Fukuzawa, S.; Tsuchimoto, T.; Kanai, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2227. (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (c) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227. (d) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706.

SCHEME 4. Structure Determination of 19b

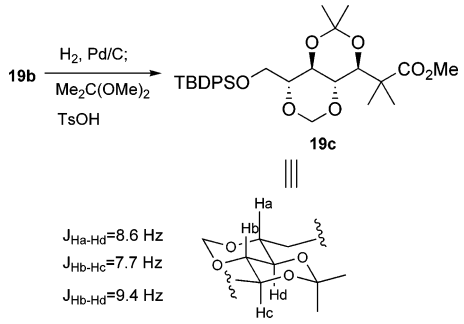
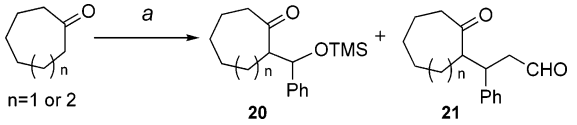


TABLE 2. Cross-Aldol Reaction Using a Combination of $Yb(OTf)_3$ and TMSCl



entry	n	time (h)	product	yield (%)	dr
1	1	36	**20**	43	62:38
			21	5	87:13
2	2	42	**20**	62	69:31
			21	5	69:31

[a] All runs were carried out using $Yb(OTf)_3$, TMSCl, and Et_3N in CH_2Cl_2. See Supporting Information for details.

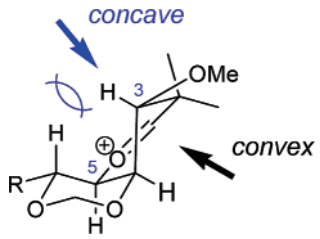
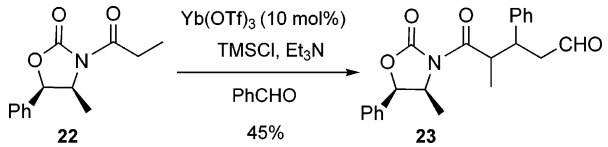


FIGURE 6. Possible explanation for stereoselective allylation.

The coupling constants in the ^1H NMR spectra suggest that **19c** has a *trans*-tetraoxadecalin ring system (Scheme 4).

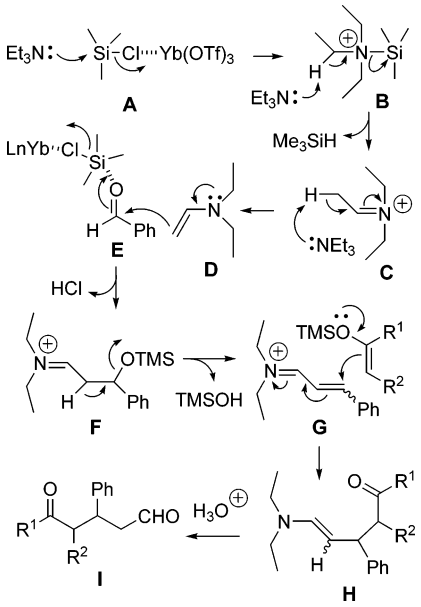
Our mechanistic speculation originally came from the unusual experimental results (Table 2). Namely, when the catalytic system is exploited to direct a cross-aldol reaction with cycloheptanone or cyclooctanone and benzaldehyde, a small amount of 3-(2-oxocycloalkyl)-3-phenylpropanal **21** is obtained along with normal aldol product **20**.[21] The best yield, 45%, is obtained when the reaction is performed on oxazolidinone **22**.



Scheme 5 rationalizes the formation of compound **21**. Initially, triethylamine attacks chlorotrimethylsilane **A**, which is activated by $Yb(OTf)_3$, and then iminium salt **C** is formed via **B**, which is easily transformed into enamine **D**. Enamine **D** reacts with benzaldehyde **E**, which is activated by $Yb(OTf)_3$ through chlorotrimethylsilane. After the resulting iminium salt

(21) Kagawa, N.; Toyota, K.; Ihara M. *Aust. J. Chem.* **2004**, *57*, 655.

SCHEME 5. Plausible Mechanism



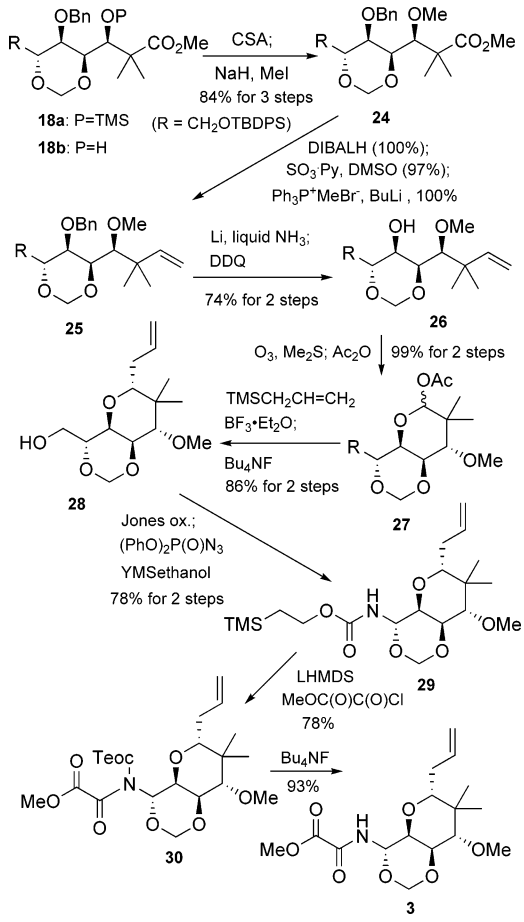
F is converted into conjugated iminium salt **G**, a Michael reaction of silyl enol ether produces enamine **H**, which is finally hydrolyzed to aldehyde **I**. This reaction series would not occur without the activation of chlorotrimethylsilane by $Yb(OTf)_3$ through the chloride atom. To obtain information about the reaction mechanism of the $Yb(OTf)_3$−TMSCl-catalyzed cross-aldol reaction, we have examined the NMR experiments and tried to isolate the reaction intermediates. Unfortunately, no direct evidence for the novel combination shown in Figure 5 was obtained. Periasamy and Bharathi proposed a mechanism similar to that shown in Scheme 5 in their transformation of benzaldehyde to cinnamaldehyde using $TiCl_4$ and Et_3N.[22] When we add our system to Et_3N and benzaldehyde, we obtain cinnamaldehyde in 35% yield. Control experiments omitting either $Yb(OTf)_3$ or TMSCl are performed, and neither result in the formation of cinnamaldehyde. This is why the reaction intermediate, which is shown in Figure 4, is proposed in the cross-aldol reaction.

Next, both **18a** and **18b** are treated with CSA in MeOH to give the corresponding alcohol, which is subsequently treated with MeI to provide methyl ether **24**. The ester moiety of **24** is converted to the olefin part of **25** in three steps. An unexpected over-reduction of the diphenyl groups on the silicon atom of **25** accompanies the removal of the benzyl ether under Birch reduction conditions. Hence, reoxidation of the crude products with DQQ provides **26**. Oxidative cleavage of the olefin moiety of **26** followed by acetylation affords acetate **27**. Treating **27** with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ followed by Bu_4NF produces alcohol **28** as a single diastereoisomer.[23] Figure 6 explains the stereochemical outcome of this reaction. In general, additions of nucleophiles to tetrahydropyran oxocarbenium ion intermediates occur through chairlike intermedi-

(22) (a) Bharathi, P.; Periasamy, M. *Org. Lett.* **1999**, *1*, 857. (b) Ram, R. N.; Charles, I. *J. Chem. Res., Synop.* **2000**, 540. (c) Our own experimental result; see Supporting Information.

(23) Breitfelder, S.; Schlapbach, A.; Hoffmann, R. W. *Synthesis* **1998**, 468.

SCHEME 6. Preparation of the Right Segment 3



ates, not twistlike intermediates.[24] However, as others have also observed,[9,23] the stereoelectronically favored concave face of the oxocarbenium ion intermediate depicted in Figure 6 is sterically crowded due to the C-3 axial hydrogen and C-5 alkyl substituent.[25] Consequently, the convex face of the oxocarbenium ion intermediate is attacked by the nucleophile with complete diastereoselectivity.

To prepare the aminal moiety, alcohol **28** is oxidized with Jones reagent to provide the corresponding carboxylic acid. A Curtius rearrangement using diphenylphosphoryl azide in the presence of TMS ethanol provides carbamate **29**, but retains the stereocenter at the C-10 position. The spectral data of **29** is identical to that reported by Kocienski et al.[9] Finally, the conditions necessary to form the remaining C_2 unit of the right segment were investigated. Treating carbamate **29** with LiN(TMS)$_2$ and methyl oxalyl chloride at a low temperature provides the desired *N*-acyl product **30**. The synthesis of the right segment **3** is completed by removing the trimethylsilylethoxycarbonyl (Teoc) group with TBAF (Scheme 6).

Left Segment Synthesis. After successfully synthesizing the right segment, the focus was shifted to preparing **2**. Scheme 7 shows the retrosynthetic analysis of left segment **2**. Vinyltin species **2** is derived from lactone **31**. The phenylselenide group is introduced by a nucleophilic ring opening of the cyclopropane unit on **32**, which is prepared using an intermolecular cyclopropanation reaction between dimethyl diazomalonate and chiral

SCHEME 7. Retrosynthetic Analysis of the Left Segment 2

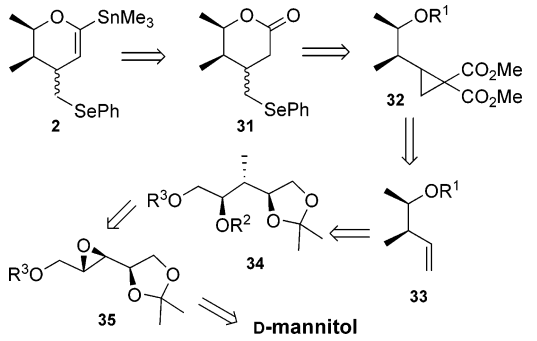
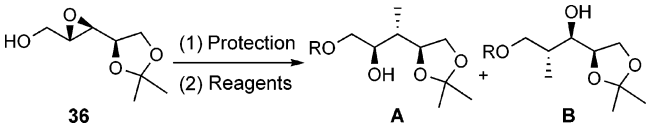


TABLE 3. Regioselective Methylation



entry	R	reagent	temp (°C)	A (%)	B (%)
1	H	Me_2CuLi	−20	16	38
2	TES	Me_2CuLi	−40	48	26
3	TBDM S	Me_2CuLi	−40	56	22
4[a]	TBDPS	Me_2CuLi	−40	77	11
5[a]	TBDPS	Me(2-Th)Cu(CN) Li_2	−50 to room temperature	23	3

[a] Two-step yield from the above alcohol. Th = thienyl.

olefin **33**. Finally, **33** is derived from D-mannitol through a regioselective reduction and regioselective methylation.

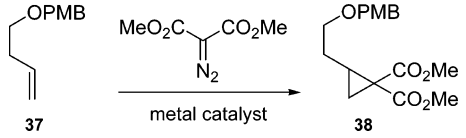
Starting with D-mannitol, α,β-unsaturated ester **39** is synthesized according to the literature.[26] Reduction of **39** with DIBALH followed by Sharpless asymmetric epoxidation[27] gives epoxy alcohol **36**, which is converted to TBDPS ether **40** via protection of the primary alcohol and regioselective methylation. The crucial methylation was attempted under various conditions, some of which are listed in Table 3. When lithium dimethylcuprate is used as the nucleophile (entries 1−4), the product ratios depend on the bulkiness of the protecting group of the hydroxyl group of **36**. Treating **36** with lithium dimethylcuprate provides alcohol **B** (38%) as the major product and alcohol **A** (16%) as the minor product. The product ratio is reversed for TES ether (entry 2), and the major product is **A**. The bulkier the silyl protective group of alcohol **36**, the higher the product ratio of **A** (entries 3 and 4). Although the mixed higher order cuprate[28] (entry 5) gives the best ratio, the conditions of entry 4 are adopted because they are suitable for a large-scale synthesis.

After mesylation of **40**, the terminal epoxide is formed by removing the TBDPS group of **41** and a subsequent basic treatment. The regioselective reduction of the epoxide produces the corresponding secondary alcohol, which is protected as the *p*-methoxybenzyl ether. Then removing the acetonide under acidic conditions affords diol **42**. Diol **42** is converted to olefin **43** by oxidative cleavage and a Wittig reaction.

We initially investigated the intramolecular cyclopropanation reactions of **37** and dimethyl diazomalonate. Table 4 shows selected results. Cu(II) catalysts are effective in the cyclopro-

(24) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−211.
(25) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641.
(26) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403.
(27) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.
(28) Lipshuts, B. H. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994; pp 105−128.

TABLE 4. Intermolecular Cyclopropanation Reaction



run	catalyst (mol %)	solvent	time (h)	yield (%)
1	$Cu(acac)_2$(1)	benzene	40	nd
2	$Cu(salycylaldimine)_2$[a](1)	toluene	24	18
3	$[Cu(MeCN)_4]PF_4$(10)	M	40	64
4	CuOTf(1)	M	90	56
5	CuOTf(10)	M	40	79
6	CuOTf(10)	toluene	40	75
7	$Rh_2(OAc)_4$	CH_2Cl_2	10	nd[b]

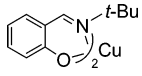
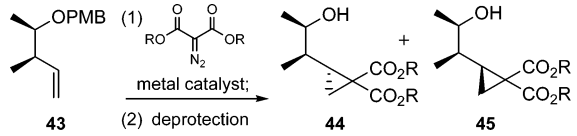
[a]  [b] Unidentifiable products were obtained. nd = not detected, M = Toluene, CH_2Cl_2 = 1:1.

TABLE 5. Diastereoselective Cyclopropanation of 43



entry	R	catalyst (mol %)	yield[a] (%)	**44:45**
1	Me	CuOTf(10)	75	3:1
2	Et	CuOTf(10)	66	5:1
3	Me	$Rh_2(cap)_4$(1)	49	7:1
4	Et	$Rh_2(cap)_4$(1)	72	1:1
5	Bu	CuOTf(10)	nd[b]	

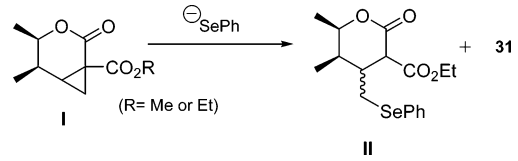
[a] Two-step yield of pure products after column chromatography. [b] A complex mixture was obtained

panation process (entries 3−6). CuOTf in CH_2Cl_2−toluene (1:1) is particularly useful in recovering alkene **37** (entry 5). Since $Rh_2(OAc)_4$ is generally a useful catalyst for cyclopropanation reactions, olefin **37** was subjected to $Rh_2(OAc)_4$-catalyzed cyclopropanation with dimethyl diazomalonate. Although dimethyl diazomalonate was consumed, only unidentifiable compounds were observed.

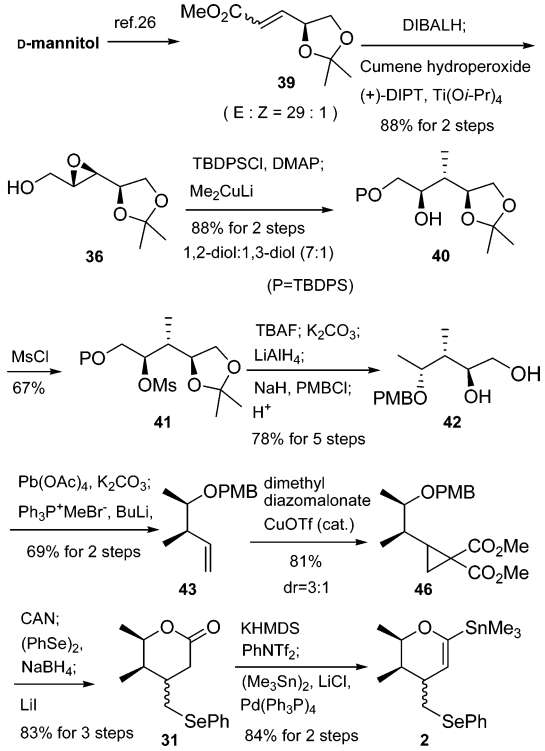
On the basis of the reaction using model compound **37**, CuOTf is adopted for the intermolecular cyclopropanation reaction of **43**. As summarized in Table 5, the epimer ratios (**44**:**45**) are affected by an alkyl group on a diazo compound and the catalyst. Isomers **44** and **45** were each transformed into the corresponding lactones to confirm their structures and to examine the effect of the stereochemistry later in the synthetic sequence. Since the stereochemistry of the phenylselenylmethyl group in *δ*-lactone **31** proved to have little influence on selectivities of the following transformations, we did not further optimize the ratios of the products.

We adopted the reaction conditions of entry 1 (Table 5) because entry 1 eventually gives 4-phenylselenomethyl lactone **31** from **46**, which is a mixture of **44** and **45**. 4-Phenylselenomethyl lactone **31** is stable and is conveniently transformed into the corresponding enol triflate.[9,29] After deprotecting the benzyl moiety, a novel *δ*-lactone generation reaction is conducted using diphenyldiselenide and $NaBH_4$ in EtOH at 80 °C. This reaction may proceed via *δ*-lactone formation **I** followed

SCHEME 8. *δ*-Lactone Generation Process



SCHEME 9. Synthesis of the Left Segment 2



by a nucleophilic addition of the phenyl selenium anion to the cyclopropane ring from the less hindered position (Scheme 8).[30] We speculate this because *p*-methoxybenzyl ether **46** produces a complex mixture under the same reaction conditions. It is noteworthy that the transesterification between ethanol and the substrate occurs easily under these reaction conditions and precursor **II** for **31** has ethyl ester moiety.

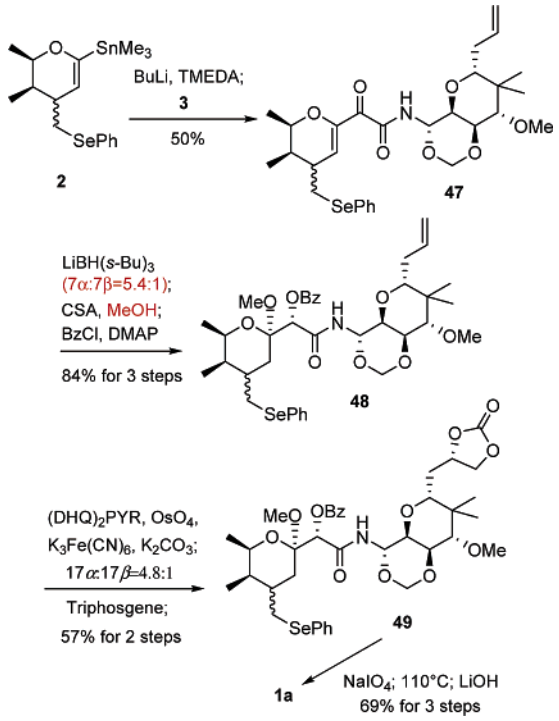
The Krapcho reaction of the mixture of **31** and ester **II** provides lactone **31**, which is transformed into the corresponding enol triflate. The enol triflate is subsequently converted to vinyltin **2** using the standard method (Scheme 9).

Total Synthesis of (+)-Mycalamide A (1a). The left and right segments are coupled by transmetalation of **2** and a subsequent regioselective nucleophilic addition of the resulting vinyl anion to the ester group of **3** to produce adduct **47** in 50% yield. After the regioselective reduction of **47** with L-Selectride at −90 °C, a methoxy group is introduced at the C-6 position under acidic conditions. Interestingly, the stereochemical outcome of the C-6 methoxy group, installed by acidic treatment in MeOH, is little affected by the stereochemistry of the C-4 substituent. In fact, the desired compound **48** was isolated in good yield. Benzoylation of the corresponding secondary alcohol yields benzoate **48**. A diol moiety is then introduced on **48** using the Sharpless asymmetric dihydroxylation protocol, and the resulting diol is transformed into

(29) Jarowicki, K.; Kocienski, P.; Marczak, S.; Willson, T. *Tetrahedron Lett.* **1990**, *31*, 3433.

(30) A representative review: Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198.

SCHEME 10. Synthesis of Mycalamide A (1a)



corresponding carbonate **49**. Finally, the exo-olefin moiety is generated through a syn elimination of the corresponding selenoxide, and subsequent hydrolysis of all the protecting groups provides (+)-mycalamide A (**1a**). The spectroscopic properties of synthetic mycalamide A (**1a**) are identical to those reported for the natural product (Scheme 10).

Conclusion

In summary, the total synthesis of (+)-mycalamide A (**1a**) has been demonstrated using Kocienski et al.'s convergent methodology. A new catalyst system, $Yb(OTf)_3$−TMSCl, was used to synthesize the right segment of **1a**, while a novel δ-lactone generation protocol formed the left segment. This convergent approach allows structural analogues of **1a** to be synthesized for further biological testing.

Experimental Section

(−)-(3*R*,4*R*)-3-Benzyloxy-4,5-isopropylidenedioxypentene (12). To a 0 °C suspension of $LiAlH_4$ (3.89 g, 0.103 mol) in Et_2O (250 mL) was added a solution of β-acetylenic alcohol **11** (14.5 g, 0.0929 mol) in Et_2O (30 mL). The mixture was stirred for 2 h at room temperature and then cooled to 0 °C, and H_2O (3.89 mL) was added slowly. After 30 min, 15% NaOH (3.89 mL) and H_2O (11.7 mL) were added, and the resulting solution was stirred for an additional 10 h at room temperature. $MgSO_4$ (4 g) was added, and the mixture was filtered through Celite and concentrated to provide the olefin (12.34 g). The crude olefin was used without further purification in the next step.

To a 0 °C suspension of NaH (3.46 g, 60% in oil, 0.0864 mmol) in DMF (180 mL) was added a solution of the crude olefin (12.34 g) in DMF (40 mL), followed by BnBr (11.2 mL, 0.0944 mmol). The mixture was stirred for 1.5 h at room temperature, and H_2O (50 mL) was added over 15 min. The phases were separated, and the aqueous phase was further extracted with Er_2O (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by flash chromatography (6% EtOAc−hexane) provided benzyl ether **12** (18.75 g, 98% for two steps) as a colorless oil.

Data for 12: $[\alpha]^{28}_D$ −27.46° (*c* 0.97, $CHCl_3$); IR (neat) 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCD_3$) δ 1.36 (s, 3 H), 1.40 (s, 3 H), 3.75 (dd, *J* = 8.5, 6.6 Hz, 1 H), 3.84 (dd, *J* = 7.4, 6.9 Hz, 1 H), 3.95 (dd, *J* = 8.5, 6.6 Hz, 1 H), 4.21 (q, *J* = 6.6 Hz, 1 H), 4.48 (d, *J* = 12.4 Hz, 1 H), 4.69 (d, *J* = 12.4 Hz, 1 H), 5.34 (ddd, *J* = 0.8, 1.4, 18.1 Hz, 1 H), 5.36 (ddd, *J* = 0.8, 1.4, 9.1 Hz, 1 H), 5.73 (ddd, *J* = 7.7, 11.0, 18.7 Hz, 1 H), 7.26−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 134.3, 128.3, 127.8, 127.6, 120.0, 109.7, 81.0, 77.4, 70.3, 65.7, 26.4, 25.3; LRMS *m*/*z* 233 (M^+ − 15); HRMS calcd for $C_{14}H_{17}O_3$: 233.1177, found: 233.1174; Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.11. Found: C, 72.60; H, 8.08.

(+)-(2*S*,3*R*,4*R*)-3-Benzyloxy-5-*tert*-butyldiphenylsilyloxy-2,4-methylenedioxypentanal (16). To a solution of diol **15** (0.340 g, 0.559 mmol) in CH_2Cl_2 (60 mL) was added freshly distilled dimethoxymethane (12 mL), followed by P_2O_5 (3.4 g). The mixture was vigorously stirred for 1.5 h and poured into saturated $NaHCO_3$ solution at 0 °C. The phases were separated, and the aqueous phase was further extracted with Et_2O (60 mL × 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by flash chromatography (9% EtOAc−hexane) provided methylene acetal **16** (0.303 g, 88%) as a colorless oil.

Data for 16: $[\alpha]^{28}_D$ +12.82° (*c* 0.95, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 1.19 (s, 9 H), 3.76 (dd, *J* = 3.8, 4.7 Hz, 1 H), 3.85−3.97 (m, 3 H), 4.17−4.24 (m, 2 H), 4.50 (dd, *J* = 9.1, 12.9 Hz, 1 H), 4.53 (d, *J* = 11.8 Hz, 1 H), 4.64 (d, *J* = 11.8 Hz, 1 H), 4.86 (d, *J* = 6.3 Hz, 1 H), 4.94 (d, *J* = 6.3 Hz, 1 H), 7.26−7.44 (m, 11 H), 7.64−7.68 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 137.7, 135.8, 135.8, 133.2, 133.1, 130.0, 128.6, 128.1, 128.1, 128.0, 88.3, 75.2, 72.4, 72.2, 70.7, 62.6, 61.6, 38.8, 27.2, 26.8, 19.2; LRMS *m*/*z* 519 (M^+ − 57); HRMS calcd for $C_{30}H_{35}O_6Si$: 519.2200, found: 519.2200; Anal. Calcd for $C_{34}H_{44}O_6Si$: C, 70.79; H, 7.68. Found: C, 70.62; H, 7.67.

(2*S*,3*R*,4*R*)-3-Benzyloxy-5-*tert*-butyldiphenylsilyloxy-2,4-methylenedioxypentanal (17). To a −78 °C solution of $(COCl)_2$ (0.080 mL, 0.917 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of DMSO (0.141 mL, 1.99 mmol) in CH_2Cl_2 (3 mL) over 10 min. The mixture was stirred for 30 min, and then a solution of the corresponding alcohol (0.377 g, 0.765 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred for 1 h at −78 °C, and then Et_3N (0.553 mL, 3.97 mmol) was added. The solution was stirred for 20 min at −78 °C and then warmed to −30 °C and quenched by H_2O (3 mL). The phases were separated, and the aqueous phase was further extracted with Et_2O (50 mL × 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to produce the crude aldehyde **17** (0.38 g). Due to the instability, aldehyde **17** was immediately used without further purification.

(+)-Methyl (3*S*,4*R*,5*R*,6*S*)-5-Benzyloxy-7-*tert*-butyldiphenylsilyloxy-2,2-dimethyl-4,6-methylenedioxy-3-trimethylsilyloxyheptanoate (18a). (−)-Methyl (3*S*,4*R*,5*R*,6*R*)-5-Benzyloxy-7-*tert*-butyldiphenylsilyloxy-2,2-dimethyl-3-hydroxy-4,6-methyl-enedioxyheptanoate (18b). To a water bath cooled suspension of $Yb(OTf)_3$ (15 mg, 0.025 mmol) and TMSCl (0.030 mL, 0.25 mmol) in CH_2Cl_2 (20 mL) was added dropwise a mixture of aldehyde **17** (0.122 g) and methyl trimethylsilyl dimethylketene acetal (0.125 mL, 0.618 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 1 h at room temperature and quenched by saturated $NaHCO_3$ solution (10 mL). The phases were separated, and the aqueous phase was further extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography. Elution with a 10:1 mixture of hexanes−EtOAc afforded ether **18a** (0.130 g, 79% for two steps) as a colorless oil. Elution with a 4:1 mixture of hexanes−EtOAc afforded aldol **18b** (15.2 mg, 10% for two steps) as a colorless oil.

Data for 18a: $[\alpha]^{27}_D$ +19.09° (*c* 0.54, $CHCl_3$); IR (neat) 1735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 9 H), 1.08 (s, 9 H), 1.13 (s, 3 H), 1.23 (s, 3 H), 3.60 (s, 3 H), 3.82 (dd, *J* = 4.4, 5.5 Hz, 1 H), 3.87 (dd, *J* = 4.8, 11.0 Hz, 1 H), 3.89 (t, *J* = 4.8 Hz, 1 H), 3.93 (dd, *J* = 5.1, 11.0 Hz, 1 H), 4.23 (q, *J* = 5.3 Hz, 1 H), 4.45 (d, *J* = 5.1 Hz, 1 H), 4.50 (d, *J* = 11.7 Hz, 1 H), 4.64 (d, *J* = 11.7 Hz, 1 H), 4.77 (d, *J* = 5.9 Hz, 1 H), 5.15 (d, *J* = 5.9 Hz, 1 H), 7.24−7.44 (m, 11 H), 7.67−7.71 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 138.2, 135.8, 135.7, 133.4, 133.2, 129.9, 128.4, 128.0, 127.9, 127.8, 127.8, 89.9, 75.9, 74.5, 74.3, 71.9, 71.9, 62.7, 51.9, 47.7, 27.0, 21.9, 21.9, 19.4, 0.9; LRMS *m*/*z* 649 (M^+ − 15); HRMS calcd for $C_{36}H_{49}O_7Si_2$: 649.3014, found: 649.3011; Anal. Calcd for $C_{37}H_{52}O_7Si_2$: C, 66.82; H, 7.88. Found: C, 66.84; H, 7.98.

Data for 18b: $[\alpha]^{27}_D$ −6.03° (*c* 1.03, $CHCl_3$); IR (neat) 3500, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9 H), 1.17 (s, 3 H), 1.19 (s, 3 H), 3.50 (d, *J* = 3.8 Hz, 1 H), 3.63 (s, 3 H), 3.74 (t, *J* = 3.3 Hz, 1 H), 3.84−3.91 (m, 4 H), 4.16−4.21 (m 1 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 4.72 (d, *J* = 11.8 Hz, 1 H), 4.86 (d, *J* = 5.8 Hz, 1 H), 5.00 (d, *J* = 5.8 Hz, 1 H), 7.27−7.48 (m, 11 H), 7.64−7.67 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 137.4, 135.7, 135.7, 133.0, 133.0, 130.0, 128.6, 128.3, 128.2, 128.0, 89.4, 76.2, 74.9, 74.5, 72.2, 71.7, 62.4, 51.9, 46.4, 26.8, 21.8, 21.6, 19.1; LRMS *m*/*z* 535 (M^+ − 57); HRMS calcd for $C_{30}H_{35}O_7Si$: 535.2150, found: 535.2147; Anal. Calcd for $C_{34}H_{44}O_7Si$: C, 68.88; H, 7.48. Found: C, 68.79; H, 7.46.

Representative Procedure for Cross-Aldol Reactions. To a suspension of $Yb(OTf)_3$ (60.0 mg, 0.0965 mmol) and chlorotrimethylsilane (0.37 mL, 2.90 mmol) in CH_2Cl_2 (8 mL) was added a solution of cyclohexanone (0.096 mL, 0.965 mmol) in CH_2Cl_2 (2 mL) followed by triethylamine (0.50 mL, 3.62 mmol). After 40 min, benzaldehyde (0.10 mL, 0.98 mmol) was added, and the resulting solution was stirred for 37 h. A solution of $NaHCO_3$ (10 mL, saturated) was added, and the biphasic solution was poured into EtOAc (20 mL). The layers were separated, and the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to provide a brown oil. The crude product was purified by flash chromatography. Elution with a 99:1 mixture of hexanes−EtOAc afforded the corresponding ether (0.187 g, 70%). Elution with a 4:1 mixture of hexanes−EtOAc afforded the alcohol (4.7 mg, 2%) as a colorless oil.

2-[Phenyl(trimethylsilyloxy)methyl]-cycloheptan-1-one (20, *n* = 1). IR (neat) 1710, 1452, 1250, 1084, 1065, 876, 841, 752, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 5.4 H), 0.03 (s, 3.6 H), 1.07−1.29 (m, 2 H), 1.39−1.48 (m, 1 H), 1.54−1.69 (m, 2 H), 1.71−1.94 (m, 3 H), 2.38−2.64 (m, 2 H), 2.92 (ddd, *J* = 4.1, 8.5, 12.4 Hz, 1 H), 4.95 (d, *J* = 8.5 Hz, 0.6 H), 5.18 (d, *J* = 4.4 Hz, 0.4 H), 7.24−7.36 (m, 5 H); LRMS *m*/*z* 290 (M^+); HRMS calcd for $C_{17}H_{26}O_2Si$: 290.1701, found: 290.1706.

3-(2-Oxocycloheptanyl)-3-phenylpropan-1-al (21, *n* = 1). IR (neat) 2855, 1722, 1693, 1495, 1452, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11−1.30 (m, 2 H), 1.37−1.50 (m, 2 H), 1.74−1.94 (m, 4 H), 2.08 (ddd, *J* = 3.2, 13.4, 15.1 Hz, 1 H), 2.22 (dddd, *J* = 1.0, 3.4, 6.3, 13.4 Hz, 0.9 H), 2.41−2.49 (m, 0.1 H), 2.54−2.60 (m, 0.1 H), 2.71 (ddd, *J* = 3.4, 5.4, 11.4 Hz, 1 H), 2.81 (ddd, *J* = 2.2, 8.8, 17.3 Hz, 1 H), 3.01 (ddd, *J* = 1.5, 6.4, 17.3 Hz, 1 H), 3.50 (ddd, *J* = 5.6, 8.6, 14.6 Hz, 0.1 H), 3.60 (ddd, *J* = 5.8, 8.5, 11.7 Hz, 0.9 H), 7.12−7.36 (m, 5 H), 9.54 (dd, *J* = 1.7, 2.0 Hz, 0.1 H), 9.65 (dd, *J* = 1.5, 2.2 Hz, 0.9 H); LRMS *m*/*z* 244 (M^+); HRMS calcd for $C_{16}H_{20}O_2$: 244.1462, found: 244.1459.

2-[Phenyl(trimethylsilyloxy)methyl]-cyclooctan-1-one (20, *n* = 2). IR (neat) 1705, 1452, 1250, 1060, 883, 843, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.10 (s, 6.3 H), −0.01 (s, 2.7 H), 1.06−2.00 (m, 10 H), 2.09−2.24 (m, 1 H), 2.34−2.50 (m, 1 H), 3.02 (ddd, *J* = 3.3, 8.1, 11.1 Hz, 0.3 H), 3.11 (ddd, *J* = 3.6, 9.6, 12.4 Hz, 0.7 H), 4.78 (d, *J* = 8.2 Hz, 0.3 H), 4.79 (d, *J* = 9.3 Hz, 0.7 H), 7.22−7.34 (m, 5 H); LRMS *m*/*z* 304 (M^+); HRMS calcd for $C_{18}H_{28}O_2Si$: 304.1857, found: 304.1856.

3-(2-Oxocyclooctanyl)-3-phenylpropan-1-al (21, *n* = 2). IR (neat) 2855, 1722, 1701, 1452, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20−1.50 (m, 5 H), 1.53−1.71 (m, 4 H), 1.83−1.94 (m, 2 H), 1.99−2.06 (m, 1 H), 2.23−2.31 (m, 0.3 H), 2.47 (ddd, *J* = 3.4, 12.4, 15.6 Hz, 0.3 H), 2.64 (ddd, *J* = 1.7, 3.9, 6.4 Hz, 0.7 H), 2.73 (ddd, *J* = 2.4, 9.5, 16.8 Hz, 0.7 H), 2.94 (ddd, *J* = 1.5, 5.4, 16.8 Hz, 1 H), 3.03 (ddd, *J* = 3.4, 9.0, 12.0 Hz, 1 H), 3.42 (ddd, *J* = 5.4, 8.8, 14.2 Hz, 0.3 H), 3.50 (ddd, *J* = 5.6, 9.3, 14.6 Hz, 0.7 H), 7.12−7.33 (m, 5 H), 9.47 (dd, *J* = 1.7, 2.2 Hz, 0.3 H), 9.60 (dd, *J* = 1.4, 2.4 Hz, 0.7 H); LRMS *m*/*z* 258 (M^+); HRMS calcd for $C_{17}H_{22}O_2$: 258.1619, found: 258.1621.

(4*S*,5*R*)-3-(1-Oxo-2-methyl-3-phenylpentan-4-alyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (23). To a mixture of oxazolidinone **22** (57.5 mg, 0.247 mmol), $Yb(OTf)_3$ (15.3 mg, 0.0247 mmol, 10 mol %), and 4 Å molecular sieves (0.30 g) in CH_2Cl_2 (2 mL) were added TMSCl (68.9 μL, 0.543 mmol) and benzaldehyde (27.6 μL, 0.271 mmol). The solution was cooled to 0 °C, and Et_3N (0.344 mL, 2.47 mmol) was added. The resulting solution was stirred for 65 h and then poured into a slurry of SiO_2 (10 mL) in hexanes−EtOAc (2:1, 15 mL). The resulting suspension was vigorously stirred for 15 min and filtered through Celite. The filtrate was concentrated to give a crude oil. Purification of the crude product by chromatography (33% EtOAc−hexane) provided aldehyde **23** (40.7 mg, 45%) as a colorless oil.

Data for a Major Isomer of 23: IR (neat) 1778, 1730, 1693, 1454, 1344, 1196, 764, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 2.64 (ddd, *J* = 1.8, 4.5, 15.9 Hz, 1 H), 2.88 (ddd, *J* = 2.4, 9.9, 15.9 Hz, 1 H), 3.55 (dt, *J* = 4.8, 10.2 Hz, 1 H), 4.21 (qd, *J* = 6.0, 9.3 Hz, 1 H), 4.80 (qd, 6.0, 7.2 Hz, 1 H), 5.68 (d, *J* = 7.4 Hz, 1 H), 7.22−7.47 (m, 10 H), 9.53 (t, *J* = 2.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 175.8, 152.7, 140.5, 132.9, 128.8, 128.7, 128.7, 128.3, 127.2, 125.5, 78.9, 55.2, 48.0, 43.4, 42.5, 16.6, 14.7; LRMS *m*/*z* 365 (M^+); HRMS calcd for $C_{22}H_{23}NO_4$: 365.1627, found: 365.1631.

Data for a Minor Isomer of 23: IR (neat) 1776, 1722, 1697, 1342, 1196, 765, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (d, *J* = 6.6 Hz, 3 H), 1.17 (d, *J* = 6.9 Hz, 3 H), 2.73−2.78 (m, 2 H), 3.55 (dt, *J* = 5.5, 9.0 Hz, 1 H), 4.28 (qd, *J* = 6.9, 9.3 Hz, 1 H), 4.51 (qd, *J* = 6.6, 7.2 Hz, 1 H), 5.45 (d, *J* = 7.4 Hz, 1 H), 7.01−7.33 (m, 10 H), 9.52 (t, *J* = 2.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 175.3, 152.5, 141.3, 133.1, 128.6, 128.5, 128.4, 128.2, 126.9, 125.5, 78.5, 54.4, 46.2, 43.0, 42.4, 15.2, 13.8; LRMS *m*/*z*: 365 (M^+); HRMS calcd for $C_{22}H_{23}NO_4$: 365.1627, found: 365.1630.

(+)-(2*R*,3*R*,4*R*,5*S*)-1-*tert*-Butyldiphenylsilyloxy-6,6-dimethyl-3-hydroxy-5-methoxy-2,4-methylenedioxyoct-7-en-3-ol (26). Liquid NH_3 (30 mL) was distilled from Na (solid) via cannula to a −78 °C flask, and Li (solid) (0.130 g, 6.92 mmol) was added, immediately producing a blue solution. A solution of benzyl ether **25** (0.199 g, 0.346 mmol) in THF (9 mL) was added dropwise over 2 min. The mixture was stirred for 20 min, and then NH_4Cl (solid) was added until the blue color disappeared. The solution was allowed to warm to room temperature, and then quenched by H_2O. The resulting solution was extracted with EtOAc (50 mL × 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a crude oil (0.176 g).

To a solution of the above product (0.176 g) in benzene (10 mL) was added DDQ (0.243 g, 1.04 mmol). The mixture was stirred for 3.5 h, and then saturated NH_4Cl was added. The resulting solution was filtered through Celite, and the filtrate was extracted with Et_2O (60 mL × 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a crude oil. Purification of the crude product by flash chromatography (13% EtOAc−hexane) provided alcohol **26** (0.124 g, 74% for two steps) as a colorless oil.

Data for 26: $[\alpha]^{22}_D$ +10.28° (*c* 0.50, $CHCl_3$); IR (neat) 3400, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.06 (s, 3 H), 1.09 (s, 3 H), 3.20 (d, *J* = 4.9 Hz, 1 H), 3.25 (d, *J* = 8.2 Hz, 1 H), 3.53 (s, 3 H), 3.82−3.94 (m, 4 H), 4.00−4.05 (m, 1 H), 4.79

(d, J = 6.0 Hz, 1 H), 4.94 (d, J = 6.0 Hz, 1 H), 4.98 (d, J = 11.3 Hz, 1 H), 4.99 (d, J = 17.0 Hz, 1 H), 5.97 (dd, J = 11.3, 17.0 Hz, 1 H), 7.37−7.46 (m, 6 H), 7.63−7.67 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 135.7, 133.0, 132.8, 130.2, 128.0, 112.0, 89.8, 87.1, 77.7, 67.1, 62.2, 61.9, 42.1, 26.8, 25.7, 21.4, 19.1; LRMS m/z 427 ($M^+ - 57$); HRMS calcd for $C_{24}H_{31}O_5Si$: 427.1939, found: 427.1940.

(+)-(1*R*,5*S*,6*S*,8*R*,10*S*)-9,9-Dimethyl-10-methoxy-8-(pro-2-enyl)-5-{*N*-[(2-trimethylsilyl)-ethoxycarbonyl]amino}-2,4,7-trioxabicyclo[4.4.0]decane (29). To a solution of alcohol **28** (5.5 mg, 0.0202 mmol) in acetone (0.5 mL) was added Jones reagent.[1] The mixture was stirred for 0.5 h, and *i*-PrOH (0.2 mL) was added. The solution was concentrated and diluted with Et_2O (3 mL). The resulting solution was washed with brine, dried ($MgSO_4$), and concentrated to afford the corresponding carboxylic acid (7.7 mg).

To a suspension of the carboxylic acid (7.7 mg) and activated 4 Å molecular sieves in THF (1.0 mL) were added Et_3N (8.5 μL, 0.0607 mmol), DPPA (4.5 μL, 0.0212 mmol), and freshly distilled trimethylsilylethanol (14 μL, 0.101 mmol). The mixture was warmed to 65 °C and stirred for 5.5 h. After filtration, the filtrate was washed with 5% citric acid solution, saturated $NaHCO_3$, and brine. The resulting solution was dried ($MgSO_4$) and concentrated. Purification of the crude product by flash chromatography (20% EtOAc−hexanes) provided carbamate **29** (6.3 mg, 78% for two steps) as a colorless oil.

Data for 29: $[\alpha]^{27}_D$ +79.83° (c 1.77, $CHCl_3$); IR (neat) 3323, 1732, 1714, 1531, 1250, 1032, 860 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9 H), 086 (s, 3 H), 0.98 (s, 3 H), 0.96−1.01 (m, 2 H), 1.98−2.06 (m, 1 H), 2.15 (ddd, J = 1.0, 6.0, 14.8 Hz, 1 H), 3.28 (d, J = 9.6 Hz, 1 H), 3.42 (d, J = 10.4 Hz, 1 H), 3.54 (s, 3 H), 3.76 (dd, J = 7.2, 10.0 Hz, 1 H), 4.16−4.21 (m, 3 H), 4.83 (d, J = 7.2 Hz, 1 H), 4.93 (d, J = 10.0 Hz, 1 H), 5.00 (dd, J = 0.8, 17.2 Hz, 1 H), 5.11 (d, J = 6.8 Hz, 1 H), 5.24 (br d, J = 8.0 Hz, 1 H), 5.50 (br t, J = 9.0 Hz, 1 H), 5.64−5.74 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 116.2, 86.6, 79.5, 78.5, 76.4, 74.7, 70.7, 63.9, 61.8, 41.6, 33.1, 23.0, 17.6, 13.3, −1.6; LRMS m/z 401 (M^+); HRMS calcd for $C_{19}H_{35}NO_6Si$: 401.2234, found: 401.2235.

(2*S*,3*S*,4*R*)-1-*tert*-Butyldiphenylsilyloxy-4,5-isopropylidenedioxy-3-methylpentan-2-ol (40) and (2*R*,3*R*,4*R*)-1-*tert*-Butyldiphenylsilyloxy-4,5-isopropylidenedioxy-2-methylpentan-3-ol. To a 0 °C solution of epoxide **36** (29.8 mg, 0.171 mmol) and Et_3N (0.119 mL, 0.856 mmol) in CH_2Cl_2 (5 mL) were added TBDPSCl (89.0 μL, 0.342 mmol) and DMAP (5.0 mg, 0.0409 mmol). The mixture was stirred for 10 h at room temperature, then cooled to 0 °C, and quenched by H_2O (10 mL). The phases were separated, and the aqueous phase was further extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by flash column chromatography (9% EtOAc−hexane) provided the corresponding silyl ether (173 mg, including any remaining silanol). To a −20 °C suspension of CuI (0.456 g, 2.40 mmol) in Et_2O (5 mL) was added dropwise MeLi (5.26 mL, 1.14 M in Et_2O, 5.99 mmol) over 5 min. When the yellow color had disappeared, the solution was cooled to −40 °C, and then the above silyl ether in Et_2O (2 mL) was added. The mixture was stirred for 1 h between −40 and −30 °C and quenched with a mixture of concentrated NH_4OH and saturated NH_4Cl (1:9, 10 mL). The resulting mixture was allowed to warm to room temperature, stirred for 20 min, and then filtered through Celite. The phases were separated, and the aqueous phase was further extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by flash chromatography (9% EtOAc−hexane) provided **40** and the isomer (64.6 mg, 0.151 mmol, 88% from **36**) as a 7:1 mixture.

Partial Data for 40 and the Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 2.6 H), 1.00 (d, J = 6.8 Hz, 0.4 H), 1.06 (s, 1.1 H), 1.07 (s, 7.9 H), 1.33 (s, 2.6 H), 1.36 (s, 0.4 H), 1.38 (s, 2.6 H), 1.44 (s, 0.4 H), 1.78−1.88 (m, 0.1 H), 1.96 (dq, J = 13.6, 6.8 Hz, 0.9 H), 2.83 (d, J = 6.4 Hz, 0.1 H), 3.12 (d, J = 2.8 Hz, 0.9 H), 3.45−3.50 (m, 0.3 H), 3.56−3.59 (m, 0.3 H), 3.56−3.59 (m, 0.1 H), 3.61−3.67 (m, 1.8 H), 3.70 (dd, J = 10.4, 4.0 Hz, 0.9 H), 3.75 (dd, J = 10.0, 3.2 Hz, 0.9 H), 3.78 (dd, J = 10.4, 4.4 Hz, 0.1 H), 3.85 (t, J = 7.6 Hz, 0.1 H), 3.99 (dd, J = 10.0, 6.4 Hz, 0.1H), 4.02 (dd, J = 8.0, 6.0 Hz, 0.9 H), 4.12 (dt, J = 6.4, 7.6 Hz, 0.9 H), 4.22−4.27 (m, 0.1 H), 7.36−7.44 (m, 6 H), 7.67 (dd, J = 3.2, 1.6 Hz, 2 H), 7.69 (dd, J = 2.8, 1.2 Hz, 2 H).

[2-(4-Methoxy)benzyloxy]ethyl-1,1-dimethyldicarboxylate (38). To a mixture of alkene **37** (6.24 g, 32.5 mmol) and dimethyl diazomalonate (0.514 g, 3.25 mmol) in toluene−CH_2Cl_2 (1:1 v/v, 120 mL) was added CuOTf·PhH (164 mg, 0.325 mmol). The mixture was heated at reflux and stirred for 40 h. After removal of the solvent, the residue was purified by column chromatography (20% EtOAc−hexane) to provide cyclopropane **38** (0.828 g, 2.57 mmol, 79%) in addition to recovered alkene **37** (5.73 g, 29.8 mmol).

Data for 38: IR (neat) 1720, 1611, 1510, 1437, 1240, 1210, 1099, 1032, 820, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (dd, J = 4.8, 8.8 Hz, 1 H), 1.43 (dd, J = 4.8, 8.8 Hz, 1 H), 1.50 (dddd, J = 6.8, 8.0, 8.0, 14.4 Hz, 1 H), 1.76 (tdd, J = 6.4, 6.4, 12.8 Hz, 1 H), 1.98−2.06 (m, 1 H), 3.51 (t, J = 6.8 Hz, 2 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 6.87 (dd, J = 2.6, 9.6 Hz, 2 H), 7.25 (dd, J = 2.4, 9.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 168.4, 159.0, 130.3, 129.1, 113.7, 72.6, 68.7, 55.2, 52.5, 52.4, 33.6, 29.1, 25.8, 21.0; LRMS m/z 322 (M^+); Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.21; H, 7.06.

(2*RS*)-2-[(1*R*,2*R*)-2-(4-Methoxybenzyl)oxy-1-methylpropyl]cyclopropane-1,1-dimethyldicarboxylate (46). To a suspension of CuOTf (31.8 mg, 63.2 μmol) in toluene−CH_2Cl_2 (1:1 v/v, 20 mL) were added alkene **43** (1.39 g, 6.32 mmol) and dimethyl diazomalonate (100 mg, 0.632 mmol). The solution was plunged into an oil bath at 110 °C, and the mixture was heated at reflux for 12 h. The solvent was removed in vacuo to afford the green oil. Purification of the crude oil by flash chromatography (20% EtOAc−hexane) provided cyclopropane **46** (179 mg, 81%, dr = 3:1) as a colorless oil.

Data for 46: IR (neat) 1728, 1514, 1437, 1300, 1248, 1213, 1132, 1035 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, J = 7.2 Hz, 0.25 × 2 H), 7.25 (d, J = 9.0 Hz, 0.75 × 2 H), 6.87 (dd, J = 1.8, 7.2 Hz, 0.25 × 2 H), 6.86 (d, J = 8.4 Hz, 0.75 × 2 H), 4.52 (d, J = 11.4 Hz, 0.25 H), 4.51 (d, J = 11.4 Hz, 0.75 H), 4.37 (d, J = 11.4 Hz, 0.25 H), 4.36 (d, J = 10.8 Hz, 0.75 H), 3.80 (s, 3 H), 3.75 (s, 0.25 × 3 H), 3.72 (s, 0.25 × 3 H), 3.72 (s, 0.75 × 3 H), 3.69 (s, 0.75 × 3 H), 3.49 (dq, J = 3.6, 6.0 Hz, 0.75 H), 3.47 (dq, J = 4.2, 6.0 Hz, 0.25 H), 2.10 (dt, J = 8.4, 8.4 Hz, 0.75 H), 1.94 (td, J = 9.0, 10.8 Hz, 0.25 H), 1.53 (dd, J = 4.8, 8.4 Hz, 0.25 H), 1.43 (dd, J = 4.8, 8.4 Hz, 0.75 H), 1.40 (dd, J = 4.2, 9.0 Hz, 0.75 H), 1.34 (dd, J = 4.2, 9.0 Hz, 0.25 H), 1.26−1.19 (m, 0.75 H), 1.18−1.12 (m, 0.25 H), 1.19 (d, J = 6.0 Hz, 0.25 × 3 H), 1.11 (d, J = 6.0 Hz, 0.75 × 3 H), 1.03 (d, J = 6.6 Hz, 0.75 × 3 H), 1.00 (d, J = 6.6 Hz, 0.25 × 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 170.6, 169.2, 169.0, 159.2, 159.2, 131.3, 131.2, 129.4, 129.4, 113.9, 113.8, 77.8, 77.4, 71.0, 70.6, 55.4, 55.4, 52.7, 52.7, 52.6, 52.5, 38.5, 38.4, 34.8, 33.5, 33.2, 32.9, 21.5, 20.3, 17.2, 16.9, 14.9, 14.4; LRMS m/z 350 (M^+); Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.85; H, 7.52.

(5*R*,6*R*)-5,6-Dimethyl-4-(phenylselenylmethyl)tetrahydropyran-2-one (31). To a suspension of $(PhSe)_2$ (1.56 g, 5.00 mmol) in EtOH (15 mL) was added $NaBH_4$ (0.36 g, 9.52 mmol). After the yellow color had dissipated, a solution of the above alcohols (0.24 g) in EtOH (5 mL) was added. The mixture was heated at reflux and stirred for 16 h. The reaction was diluted with 10% HCl (15 mL), and the resulting solution was stirred for a further 5 min and then extracted with EtOAc (3 × 80 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated. Purification of the crude product by column chromatography (33% EtOAc−hexane) provided the lactones (0.29 g, a mixture of **pre-31** and **31**). A mixture of lactones (0.29 g) and LiI (0.35 g) in DMF (5 mL) was plunged into an oil bath at 150 °C and stirred for 12 h. The solution

was diluted with H_2O (15 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Purification of the crude oil by column chromatography (33% EtOAc−hexane) provided lactone **31** (0.28 g, 83%) as a pale yellow inseparable mixture of diastereomers.

Data for pre-31: $[\alpha]^{27}_D$ +11.10° (*c* 0.82, $CHCl_3$); IR (neat) 1738, 1734, 1437, 1373, 1267, 1184, 1128, 1097, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.26 (m, 3 H), 7.53−7.48 (m, 2 H), 4.52 (dq, *J* = 3.2, 6.8 Hz, 1 H), 4.20 (qd, *J* = 7.2, 10.8 Hz, 1 H), 4.11 (qd, *J* = 7.2, 10.8, 1 H), 3.56 (d, *J* = 10.8 Hz, 1 H), 3.19 (dd, *J* = 4.0, 12.4 Hz, 1 H), 2.91 (dd, *J* = 6.4, 12.4 Hz, 1 H), 2.41 (dddd, *J* = 4.0, 4.0, 6.8, 11.2 Hz, 1 H), 1.94 (ddq, *J* = 3.2, 4.0, 8.0 Hz, 1 H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3 H), 0.98 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.1, 133.0, 129.2, 129.2, 127.4, 76.1, 61.8, 51.1, 40.7, 36.8, 33.5, 16.9, 14.2, 14.0; LRMS *m*/*z* 370 (M^+); HRMS calcd for $C_{17}H_{22}O_4Se$: 370.0683, found: 370.0687.

Data for 31 (dr = 3:2): IR (neat) 1732, 1240, 1209, 1096, 1003, 739, 692 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2 H), 7.28−7.27 (m, 3 H), 4.50 (dq, *J* = 3.6, 6.6 Hz, 0.6 H), 4.43 (dq, *J* = 2.4, 6.6 Hz, 0.4 H), 3.03 (dd, *J* = 6.0, 12.0 Hz, 0.6 H), 2.96 (dd, *J* = 7.2, 12.6 Hz, 0.6 H), 2.89 (dd, *J* = 6.6, 14.4 Hz, 0.4 H), 2.84 (dd, *J* = 7.2, 12.6 Hz, 0.4 H), 2.74 (dd, *J* = 5.4, 18.0 Hz, 0.4 H), 2.67 (dd, *J* = 6.6, 16.8 Hz, 0.6 H), 2.37 (dd, *J* = 9.6, 16.2 Hz, 0.6 H), 2.27−2.21 (m, 0.4 H), 2.17 (dd, *J* = 12.6, 18.0 Hz, 0.4 H), 2.08−2.04 (m, 0.4 H), 1.96−1.86 (m, 0.6 × 2 H), 1.33 (d, *J* = 6.6 Hz, 0.4 × 3 H), 1.28 (d, *J* = 6.6 Hz, 0.6 × 3 H), 0.95 (d, *J* = 7.2 Hz, 0.6 × 3 H), 0.83 (d, *J* = 7.2 Hz, 0.4 × 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.4, 133.2, 133.1, 133.1, 129.4, 129.3, 129.1, 127.5, 127.5, 127.4, 80.3, 75.9, 37.3, 37.2, 36.9, 34.3, 34.2, 33.8, 32.3, 31.0, 18.5, 17.0, 13.9, 4.2; LRMS *m*/*z* 298 (M^+); HRMS calcd for $C_{14}H_{18}O_2Se$: 298.0472, found: 298.0470.

(+)-(4*S*,5*R*,6*R*)-5,6-Dimethyl-4-(phenylselenylmethyl)tetrahydro-2*H*-pyran-2-one. Data for the major isomer (4α-isomer): $[\alpha]^{30}_D$ +50.00° (*c* 1.03, $CHCl_3$); IR (neat) 1732, 1578, 1479, 1437, 1385, 1254, 1205, 1123, 1094, 1074, 1022, 1001, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.46 (m, 2 H), 7.27−7.24 (m, 3 H), 4.48 (dq, *J* = 3.2, 6.4 Hz, 1 H), 3.01 (dd, *J* = 6.0, 12.0 Hz, 1 H), 2.94 (dd, *J* = 6.0, 12.4, 1 H), 2.65 (dd, *J* = 6.4, 16.4 Hz, 1 H), 2.35 (dd, *J* = 10.0, 16.8 Hz, 1 H), 1.96−1.83 (m, 2 H), 1.27 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 132.9, 129.3, 129.2, 127.3, 75.8, 37.4, 36.9, 34.3, 33.8, 17.0, 14.0; LRMS *m*/*z* 298 (M^+); Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10. Found: C, 56.48; H, 6.03.

(1*S*,5*R*,6*S*,8*R*,10*S*)-10-Methoxy-9,9-dimethyl-5-{[(2*R*,3*R*,4*RS*)-2,3-dimethyl-4-phenylselenylmethyl-3,4-dihydro-2*H*-pyran-6-yl]-oxoethanamido}-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4.4.0]decane (47). To a −78 °C solution of left segment **2** (51.6 mg, 0.116 mmol) in THF (0.65 mL) was added dropwise BuLi (0.20 mL, 0.57 M in THF, 0.12 mmol) over 10 min. After 15 min, TMEDA (0.11 mL) was added, and the solution was stirred for 30 min, and then a cold solution of right segment **3** (22.9 mg, 66.8 μmol) in THF (0.25 mL × 2) was added via cannula. The mixture was stirred for 2.5 h at the same temperature before being poured onto ice-cooled saturated NH_4Cl solution (7 mL) and stirred vigorously for 10 min. The separated aqueous phase was further extracted with CH_2Cl_2 (30 mL × 3). The combined organic extracts were dried (Na_2SO_4) and concentrated to give a crude yellow oil (71.5 mg). Purification of the crude oil by flash chromatography (33% EtOAc−hexane) provided compound **47** (19.6 mg, 50%) as a colorless oil.

Data for 47 (dr = 12.5:1): IR (neat) 3364, 2878, 1695, 1674, 1522, 1107, 1074, 1024, 739, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.47 (m, 3 H), 7.29−7.23 (m, 3 H), 7.14 (dd, *J* = 1.2, 5.0 Hz, 0.93 H), 7.07 (dd, *J* = 1.6, 2.2 Hz, 0.07 H), 5.71 (dd, *J* = 9.5, 9.5 Hz, 0.07 H), 5.70 (dd, *J* = 9.5, 9.5 Hz, 0.93 H), 5.61 (tdd, *J* = 6.8, 10.0, 16.8 Hz, 1 H), 5.16 (d, *J* = 7.1 Hz, 1 H), 4.89 (d, *J* = 6.8 Hz, 1 H), 4.86 (dd, *J* = 1.6, 9.5 Hz, 0.07 H), 4.78 (dd, *J* = 1.2, 10.0 Hz, 0.93 H), 4.25 (dd, *J* = 6.6, 10.2 Hz, 1 H), 4.09 (dq, *J* = 1.2, 6.4 Hz, 0.07 H), 4.00 (dq, *J* = 2.2, 6.3 Hz, 0.93 H), 3.92 (dd, *J* = 6.7, 9.8 Hz, 0.07 H), 3.91 (dd, *J* = 6.6, 9.8 Hz, 0.93 H), 3.57 (s, 3 H), 3.46 (d, *J* = 10.2 Hz, 0.07 H), 3.45 (d, *J* = 10.2 Hz, 0.93 H), 3.29 (dd, *J* = 2.0, 10.0 Hz, 0.07 H), 3.27 (dd, *J* = 2.0, 10.0 Hz, 0.93 H), 3.06 (dd, *J* = 5.9, 12.4 Hz, 0.93 H), 3.03−2.92 (m, 0.07 × 2 H), 2.88 (dd, *J* = 8.5, 12.7 Hz, 0.93 H), 2.89−2.81 (m, 0.07 H), 2.88 (dd, *J* = 8.5, 12.7 Hz, 0.93 H), 2.27−2.21 (m, 1 H), 2.13 (ddm, *J* = 6.6, 12.4 Hz, 1 H), 2.06−1.95 (m, 2 H), 1.38 (d, *J* = 6.6 Hz, 0.07 × 3 H), 1.31 (d, *J* = 6.6 Hz, 0.93 × 3 H), 1.01 (s, 3 H), 0.88 (s, 3 H), 0.86 (d, *J* = 7.2 Hz, 0.93 × 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer δ 179.8, 160.4, 147.5, 135.4, 133.3, 129.4, 129.1, 127.4, 124.4, 116.2, 86.7, 79.4, 78.8, 74.6, 73.8, 72.1, 70.2, 61.8, 41.7, 40.0, 34.3, 33.2, 32.8, 23.2, 17.0, 13.5, 13.2; LRMS *m*/*z* 593 (M^+); HRMS calcd for $C_{29}H_{39}NO_7Se$: 593.1892, found: 593.1891.

Mycalamide A (1a). To a solution of carbonates **49** (2.1 mg, 2.6 μmol) in MeOH−H_2O−CH_2Cl_2 (3:1:1 v/v, 1 mL) was added $NaIO_4$ (5.7 mg, 26 μmol) in one portion. The mixture was stirred for 2 h and then diluted with EtOAc (10 mL) and Et_3N (0.5 mL), washed with H_2O (2 mL × 2), dried (Na_2SO_4), and concentrated to give a white solid. The residue was dissolved in toluene (0.25 mL), and then Et_3N (0.25 mL) was added. After refluxing for 10 min, the reaction was poured onto saturated $NaHCO_3$ solution (2 mL) and extracted with Et_2O (5 mL × 3). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford a yellow oil. To a solution of the crude oil in MeOH (0.5 mL) was added a solution of LiOH (0.05 mL, 1.0 M solution in H_2O). The mixture was stirred for 2 h and concentrated to yield a white residue, which was dissolved in EtOAc (10 mL). The solution was washed with H_2O (2 mL × 2), dried (Na_2SO_4), and concentrated to give a white oil. Purification of the crude oil by pipet column chromatography provided micalamide A (**1a**) (0.9 mg, 69% for three steps).

Data for Mycalamide A (1a): $[\alpha]^{32}_D$ +98.9° (*c* 0.2, $CHCl_3$); IR (neat) 3392, 2924, 2852, 1682, 1521, 1456, 1382, 1195, 1093, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ referenced to 7.26 ppm) δ 7.49 (d, *J* = 9.7 Hz, 1 H), 5.89 (t, *J* = 9.7 Hz, 1 H), 5.16 (d, *J* = 6.9 Hz, 1 H), 4.90 (d, *J* = 6.9 Hz, 1 H), 4.87 (s, 1 H), 4.78 (s, 1 H), 4.32 (s, 1 H), 4.24 (dd, *J* = 6.4, 10.1 Hz, 1 H), 4.01 (dq, *J* = 2.7, 6.5 Hz, 1 H), 3.87 (dd, *J* = 6.9, 10.1 Hz, 1 H), 3.78 (br s, 1 H), 3.76 (m, 1 H), 3.66 (dd, *J* = 4.2, 7.8 Hz, 1 H), 3.59 (m, 1 H), 3.58 (s, 3 H), 3.48 (d, *J* = 10.1 Hz, 1 H), 3.40 (dd, *J* = 5.5, 10.6 Hz, 1 H), 3.32 (s, 3 H), 3.18 (br s, 1 H), 2.39 (m, 2 H), 2 27 (dq, *J* = 2.8, 6.9 Hz, 1 H), 2 23 (br s, 1 H), 1.56 (m, 2 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 1.02 (d, *J* = 7.3 Hz, 3 H), 1.00 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 145.5, 110.6, 99.7, 86.8, 79.0, 79.0, 74.3, 73.7, 72.8, 71.5, 71.2, 69.7, 66.4, 61.8, 48.9, 41.6, 41.3, 33.7, 31.9, 23.0, 17.8, 13.5, 12.0; LRMS *m*/*z* 502 (M − H); HRMS calcd for $C_{24}H_{40}NO_{10}$: 502.2652, found: 502.2659.

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Supporting Information Available: General experimental procedures and spectral data associated with total synthesis of (+)-mycalamide A. This material is available free of charge via the Internet at http://pubs.acs.org.

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