

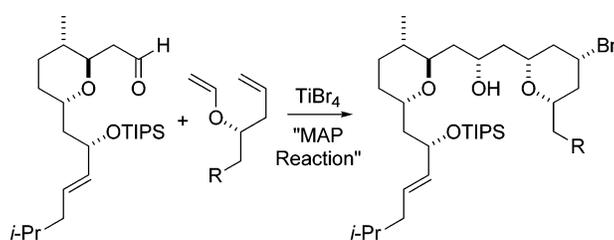
## Total Synthesis of Leucascandrolide A: A New Application of the Mukaiyama Aldol–Prins Reaction

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A total synthesis of the marine natural product leucascandrolide A has been completed. The titanium tetrabromide-mediated Mukaiyama aldol–Prins (MAP) reaction with aldehydes developed in our group provided a highly convergent and stereoselective method for assembling the core of the molecule. A new class of MAP reactions with acetals is introduced, and mechanistic considerations for both MAP methods are described. The total synthesis was completed by coupling of the side chain through two avenues: a known Still–Gennari olefination and a new *Z*-selective aldol/dehydroseleation reaction. Both procedures were highly selective and provided the natural product.

### Introduction

In 1989, Pietra and co-workers first isolated leucascandrolide A off the coast of New Caledonia from a new genus of calcareous sponges called *L. caveolata* (Figure 1).<sup>1</sup> Leucascandrolide A has an unusual 18-membered macrolide ring with an alternating oxygenation pattern and a disubstituted oxazole-containing side chain. These structural features are not characteristic of the other metabolites isolated from this class of sponges.<sup>2</sup> This structurally interesting macrolide is also the most active metabolite isolated from calcareous sponges, with high cytotoxicity in vitro against human KB tumor cell lines ( $IC_{50} = 50$  ng/mL) and P388 leukemia cell lines ( $IC_{50} = 250$  ng/mL) as well as potent antifungal inhibition against *Candida albicans*. The biological and medicinal interest in leucascandrolide A prompted unsuccessful attempts to reisolate it, and its actual origin is now believed to be from an opportunistic microbial colony.<sup>1</sup>

Currently, the only reliable source of leucascandrolide A is through chemical synthesis. In 2000, Leighton reported the first total synthesis, confirming the stereochemical assignments made

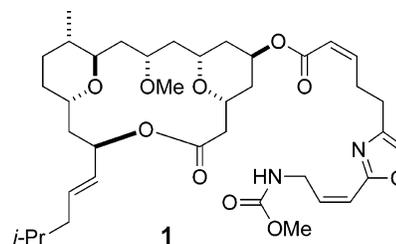


FIGURE 1. Leucascandrolide A.

by Pietra's group.<sup>3</sup> Since then, there have been elegant total syntheses reported by Paterson,<sup>4</sup> Kozmin,<sup>5</sup> and most recently by Panek.<sup>6</sup> In addition to these projects, many formal syntheses have been reported including ones by Carreira,<sup>7</sup> Crimmins,<sup>8</sup> Wipf,<sup>9</sup> and Williams.<sup>10</sup> Our group also has reported a formal

(3) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894–12895.

(4) (a) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343–347. (b) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833–6849.

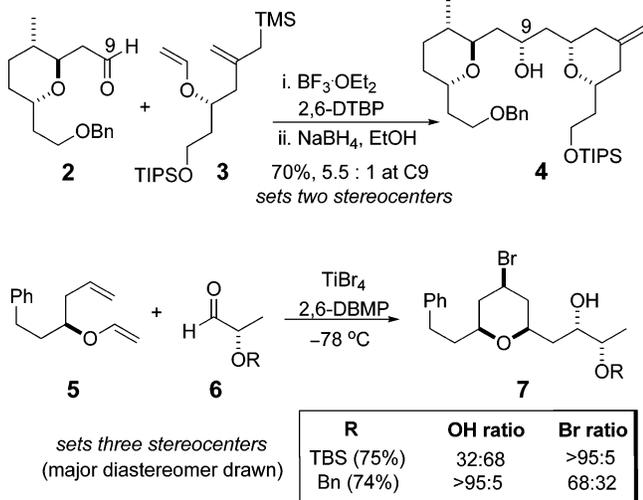
(5) (a) Wang, Y.; Janjic, J.; Kozmin, S. A. *Pure Appl. Chem.* **2005**, *77*, 1161–1169. (b) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670–13671.

(6) (a) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2006**, *72*, 2–24. (b) Su, Q.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223–1224.

(1) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51–60.

(2) This particular class of sponges typically produces compounds consisting of 2-amino imidazoles. See ref 1.

## SCHEME 1. Two Variants of the Mukaiyama Aldol–Prins Reactions



synthesis, which introduced the Mukaiyama aldol–Prins (MAP) cyclization as an effective method for generating 2,6-*cis*-tetrahydropyran (THP) rings in complex systems (Scheme 1, top).<sup>11</sup> The lengthy sequence required to synthesize the requisite enol ether allylsilane precursor, as well as subsequent elaboration of the core (**4**) for the completion of the macrocycle, made the overall synthetic strategy inefficient.

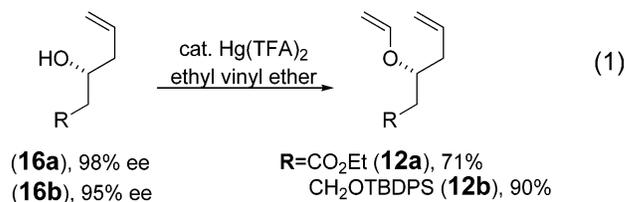
Methodology recently developed in our group has shown potential for streamlining the synthesis of the 2,6-*cis*-THP of leucascandrolide A. A titanium tetrabromide-promoted MAP cyclization of simple homoallylic enol ethers and  $\alpha$ -oxygenated aldehydes was reported to provide 2,4,6-*cis*-THP rings with good stereoselectivity (Scheme 1, bottom).<sup>12</sup> This modified approach allowed accessible cyclization precursors to be used and also afforded more highly functionalized products with three new stereocenters set in a single transformation.

Our new retrosynthetic plan for leucascandrolide A was designed around the new methodology and is detailed below (Figure 2). A cesium carboxylate side chain<sup>13</sup> displacement of the macrocyclic secondary bromide **8** would afford the natural product. A late-stage titanium tetrabromide-promoted MAP cyclization of aldehyde **11** and one of the homoallylic enol ethers **12** was anticipated to provide the desired 2,4,6-*cis*-THP. The precedent in Scheme 1 suggested that an aldehyde with a chelatable  $\alpha$ -alkoxy functional group would provide good selectivity at the alcohol center and moderate selectivity for the equatorial bromide in the MAP reaction. Because our proposed aldehyde coupling partner has a  $\beta$ -alkoxy group from the 2,6-*trans*-THP, we would expect to see results similar to that of the  $\alpha$ -benzyloxy model system. Enol ethers **12** could be accessed

through transvinylations of the corresponding alcohols, which have been previously synthesized by many methods.<sup>14</sup> The approach envisioned for aldehyde **11** involved silyl enol ether (**14**)<sup>4</sup> addition to  $\alpha$ -acetoxy ether **13**, which would be obtained from a sequence of steps involving a ring closing metathesis of a homoallylic ether **15** derivative. This alcohol (**15**) would be accessed from an asymmetric crotylation of the TIPS-protected aldehyde from 1,3-propanediol.<sup>15</sup>

## Results

**Synthesis of the MAP Coupling Partners.** The enol ether coupling partners **16a** and **16b** were accessed in a single step by mercuric trifluoroacetate-catalyzed transvinylation of their corresponding homoallylic alcohols (eq 1).<sup>16</sup> A lower yield is reported for ester-substituted enol ether **16a** due to a shorter reaction time, which was necessary to prevent decomposition of the product under the reaction conditions.



Synthesis of the 2,6-*trans*-THP of leucascandrolide A was initiated from homoallylic alcohol **15**.<sup>15</sup> Acylation with acryloyl chloride provided acrylate **17**, which was subjected to ring closing metathesis (RCM) conditions (Scheme 2). Although there are several protocols for such metatheses,<sup>17</sup> we were most interested in a recent report by Grubbs of a one-pot tandem RCM/hydrogenation procedure.<sup>18</sup> In the first few attempts, the acrylate was subjected to the ruthenium catalyst in one portion (5 mol %) and the solution was heated at reflux for 5 h. Following the olefin reduction at 23 °C, lactone **18** was isolated in only 65% yield along with the reduced acrylate as a major byproduct. Presumably, the ruthenium catalyst was undergoing slow decomposition at elevated temperatures,<sup>19</sup> leaving unreacted starting material to be reduced in the hydrogenation step. A modification was made to the procedure in which the catalyst was added in two portions. This improved the RCM efficiency to afford **18** in 91% yield. Subsequent reductive acetylation, using conditions developed in our group, provided  $\alpha$ -acetoxy ether **13**.<sup>20</sup> Silyl enol ether **14**, which was synthesized from the corresponding enone,<sup>21</sup> was then coupled with **18** in the presence of catalytic zinc bromide to generate **19** in 92% yield.<sup>22</sup> Axial

(14) (a) Preparation of **12a**: Bennett, F.; Knight, D. W.; Fenton, G. J. *Chem. Soc., Perkin Trans. 1* **1991**, 133–140. (b) Preparation of **12b**: Keck, G. E.; Truong, A. P. *Org. Lett.* **2005**, 7, 2153–2156.

(15) La Cruz, T. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, 7, 1873–1875.

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(17) For a recent comprehensive review, see: Grubbs, R. H. *Tetrahedron* **2004**, 60, 7117–7140.

(18) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, 123, 11312–11313.

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(21) Kourouli, T.; Kefalas, P.; Ragoussis, N.; Ragoussis, V. *J. Org. Chem.* **2002**, 67, 4615–4618.

(22) A similar approach was used by Paterson to assemble the C11–C15 THP ring (ref 4).

(7) (a) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, 68, 9274–9283. (b) Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, 41, 4098–4101.

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(10) (a) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, 42, 3934–3938. (b) Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* **2003**, 5, 5035–5038.

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(12) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, 5, 3163–3166.

(13) At this stage, we planned to use the combined procedures of Leighton and Kozmin (cf. refs 3 and 5) to access the side chain.

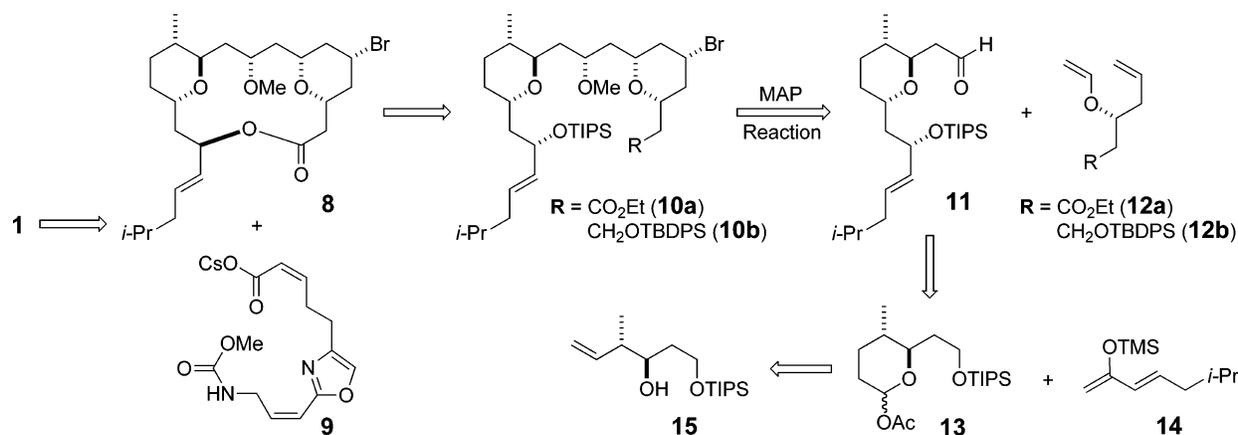
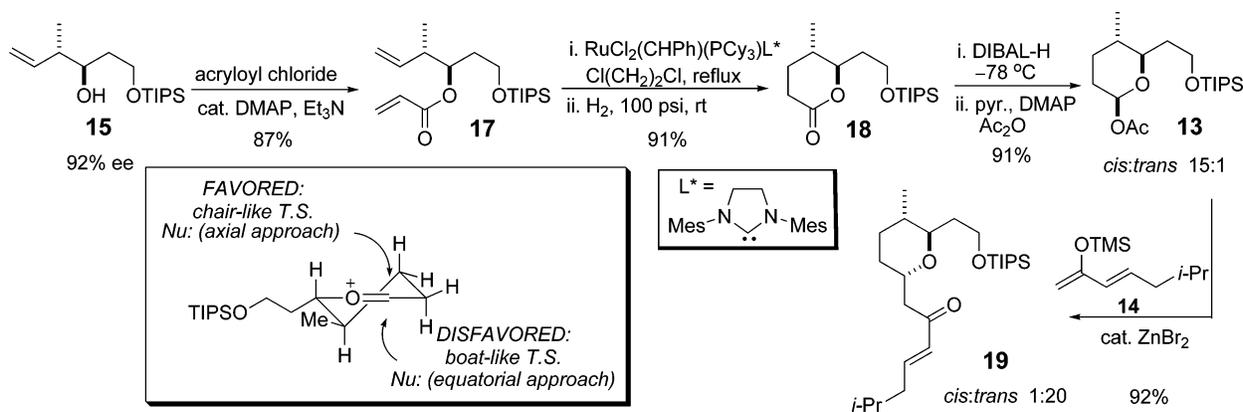


FIGURE 2. Second generation retrosynthesis of leucascandrolide A.

### SCHEME 2. Synthesis of the 2,6-*trans*-THP



approach of the nucleophile to the oxocarbenium ion intermediate shown afforded the *trans*-THP in high diastereoselectivity (20:1).<sup>23</sup>

Based on precedence from Paterson's synthesis of leucascandrolide A, we intended to set the C17 stereocenter through a regioselective and highly diastereoselective reduction of enone **19**.<sup>4</sup> Formation of either the (*R*)- or the (*S*)-configuration at C17 would be tolerated as the macrocyclization could proceed with either a Yamaguchi macrolactonization<sup>7,8,10,11</sup> or a Mitsunobu reaction,<sup>4,9</sup> both of which have precedent. Paterson found that LiAl(OBu)<sup>t</sup><sub>3</sub> reduction of an enone, which is different from **19** only at remote stereocenters, led to the *R*-allylic alcohol with 32:1 stereoselectivity. Applying these reduction conditions to our enone, however, provided primarily ketone **22** as a result of 1,4-reduction (Table 1, entry 1). The selectivity in Paterson's system was attributed to either a highly lithium-coordinated intermediate, which would have directed the reduction through a lowest energy conformation, or an Evans-type polar addition.<sup>4</sup> Although no modeling studies have been done to investigate the differences between **19** and Paterson's substrate, it is likely that enhanced lithium chelation was responsible for the reported regioselective and stereoselective hydride addition. Luche reduction conditions and DIBAL-H provided the correct 1,2-regiochemistry for the reduction but offered no stereoselectivity

TABLE 1. 1,2-Reduction of the Unsaturated Ketone **19**

entry	reducing agent	temp (°C)	yields (%)	
			20:21	22
1	LiAl(OBu) <sup>t</sup> <sub>3</sub>	-78 to -10	3:4	70
2	DIBAL-H	-78	43:43	
3	NaBH <sub>4</sub> /CeCl <sub>3</sub> ·7H <sub>2</sub> O	0 or -78	35:35	
4	( <i>R</i> )-CBS/BH <sub>3</sub> ·DMS	-78	trace <sup>b</sup>	
5	( <i>R</i> )-CBS/BH <sub>3</sub> ·DMS	-40	60:6	
6	( <i>R</i> )-CBS/BH <sub>3</sub> ·DMS	0	83:0	
7	( <i>S</i> )-CBS/BH <sub>3</sub> ·DMS	0 <sup>c</sup>	26:62	

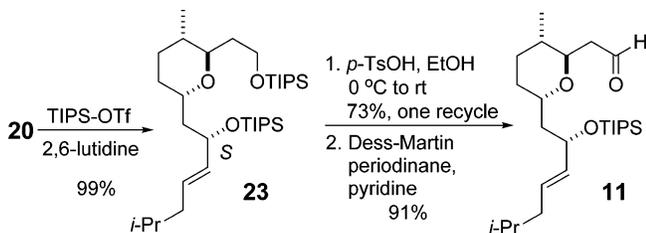
<sup>a</sup> All CBS catalysts were freshly prepared according to the reported procedure (ref 25). <sup>b</sup> Starting ketone recovered. <sup>c</sup> Lower temperatures provided lower conversions and less selectivity.

(entries 2 and 3). Corey's oxaborolidine (CBS) catalyst, which is typically used for enantioselective reductions of ketones and enones,<sup>24,25</sup> showed promise for the diastereoselective reduction of enone **19**. Although only starting material was recovered from

(23) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209–221. (b) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032–7035. (c) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289–296. (d) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.

(24) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

### SCHEME 3. Completion of the Aldehyde MAP Coupling Partner



CBS reductions at  $-78\text{ }^{\circ}\text{C}$  (entry 4), the reaction proceeded smoothly to approximately 75% conversion at  $-45\text{ }^{\circ}\text{C}$  (entry 5). Increasing the temperature to  $0\text{ }^{\circ}\text{C}$  gave optimal results for the reduction, with the (*R*)-CBS catalyst generating **20** in an 83% yield as a single diastereomer (entry 6). The reduction selectivity manifested from the (*S*)-CBS catalyst was inferior, providing a diastereomeric mixture of alcohols favoring **21** in a ratio of 2.5:1 (entry 7).

With all four stereocenters in the C9–C24 fragment of leucascandrolide A established, three additional transformations provided the aldehyde coupling partner for the anticipated MAP cyclization (Scheme 3). Protection of secondary alcohol **20** with triisopropylsilyl trifluoromethanesulfonate (TIPS-OTf) afforded bis-protected diol **23** in quantitative yield. Various conditions were surveyed to achieve selective deprotection of the primary TIPS-ether. Initial attempts utilizing tetrabutylammonium fluoride readily removed both TIPS groups, but a milder *p*-toluenesulfonic acid (*p*-TsOH)-mediated deprotection was selective. Although subjecting **23** to stoichiometric *p*-TsOH afforded primarily the bis-deprotected diol, catalytic acid (20 mol %) provided the desired alcohol in reasonable yields (55–60%). The recovered bis-protected starting material was recycled to supply an overall yield of 73%. Aldehyde **11** was then prepared in 91% yield by Dess-Martin oxidation.

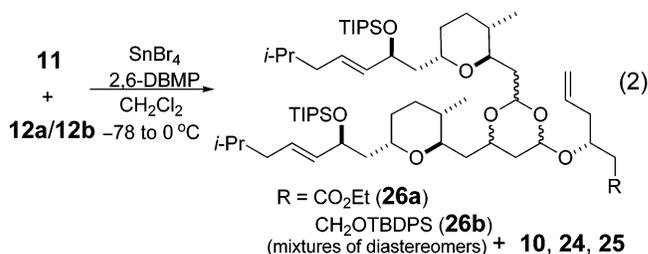
**The Mukaiyama Aldol–Prins Reaction with Aldehydes.** The key MAP reaction between aldehyde **11** and enol ether **12a** or **12b** was anticipated to provide the 2,4,6-*cis*-THP of leucascandrolide A. Subjection of aldehyde **11** and enol ether **12a** or **12b** to cyclization conditions (titanium tetrabromide and 2,6-di-*tert*-butyl-4-methylpyridine (2,6-DBMP)), however, provided undesired adduct **25** as the major product (Table 2, entries 1 and 5). It was presumed that titanium tetrabromide, in addition to mediating the desired MAP reaction, also complexed to and activated the siloxy group, facilitating an allylic displacement by bromide. An aluminum tribromide/trimethyl aluminum mixed Lewis acid system provided similar results (entries 2 and 6).<sup>26</sup> Attenuation of the titanium tetrabromide with 50% titanium tetraisopropoxide resulted in only starting materials (entries 3 and 7), but a 9:1 mixture of the two Lewis acids circumvented the side reaction and provided desired products **10** and **24**, each as a mixture of diastereomers at the alcohol center (entries 4 and 8).

(25) Synthesis of the pyrrolidinol ligands: (a) Nikolic, N. A.; Beak, P. *Organic Syntheses*; Wiley & Sons: New York, 1998; Collect. Vol. 9, pp 391–397. (b) Xavier, L. C.; Mohan, J. J.; Mathre, D. J.; Thompson, A. S.; Carroll, J. D.; Corley, E. G.; Desmond, R. *Organic Syntheses*; Wiley & Sons: New York, 1998; Collect. Vol. 9, pp 676–689. Synthesis of the catalyst: (c) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner Jones, E. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751–762. (d) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880–2888.

(26) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649–1651.

As shown in the retrosynthetic analysis (Figure 2), enol ether **12a** would have been the ideal coupling partner for our key MAP cyclization because the ethyl ester would be at the correct oxidation state for leucascandrolide A. The undesired axial diastereomer, however, was shown to be favored in a 2:1 ratio for this MAP reaction, and only modest yields were observed. These results supported those obtained in the segment-coupling Prins reaction: electron-withdrawing groups were shown to diminish the yield and to favor axial selectivity for nucleophilic trapping at the C4 position of the THP.<sup>27</sup>

MAP reactions with the corresponding TBDPS ether (**12b**) were consistently high yielding (97%) and slightly favored the desired equatorial bromide **10b**. The axial and equatorial bromide adducts (**10b** and **24b**), which were separable by chromatography, were individually methylated with methyl trifluoromethanesulfonate. The diastereomeric ratios of the methoxy epimers were determined to be approximately 7.8:1 for the axial bromide diastereomer and 4.5:1 for the equatorial bromide diastereomer. Although no studies were done to determine the absolute configuration of the C9 center, we presumed that the major diastereomers formed (as shown in Table 2) were those that would arise from a preferred 1,3-*anti* aldol addition (see Discussion).<sup>28</sup> Subsequent spectroscopic correlation with authentic leucascandrolide A substantiated this assumption.



As an interesting observation, tin tetrabromide, which is a popular Lewis acid for initiating Mukaiyama aldol reactions, failed to provide good conversion to the desired products in any of the MAP reactions investigated (eq 2). These conditions afforded acetals **26** as the major products. MAP reactions require a Lewis acid that can serve as a source of bromide ion to trap the cyclized THP carbenium ion after the initial aldol reaction. If the Lewis acid is not reactive enough or cannot provide a sufficiently nucleophilic bromide source, the intermediate oxocarbenium ion will be trapped with an extra equivalent of aldehyde. Model studies demonstrated that titanium tetrabromide was active enough to convert acetals similar to **26** to the corresponding Prins products, but that tin tetrabromide was not.<sup>29</sup>

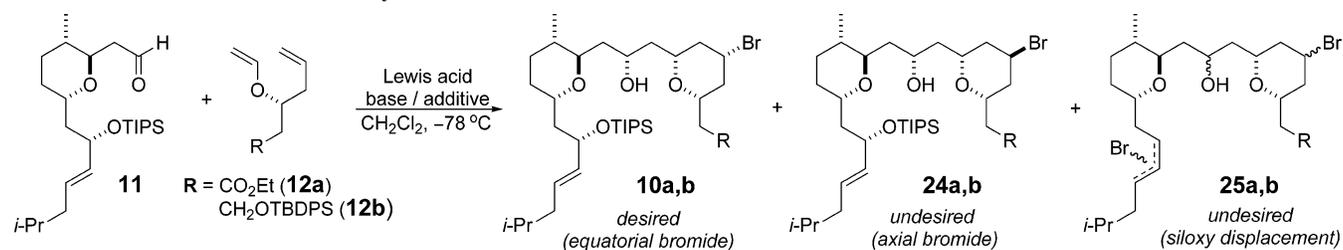
**The Mukaiyama Aldol–Prins Reaction with Acetals.** Before continuing on with the proposed synthesis, we decided to investigate the possibility of directly installing the C9 methyl ether through an acetal MAP reaction. Dimethyl acetal **27** was prepared by camphorsulfonic acid-catalyzed acetalization of aldehyde **11** (Table 3). The titanium tetrabromide/titanium tetraisopropoxide mixed Lewis acid system that was successful for the aldehyde MAP reaction was not optimal in the acetal MAP reaction, providing mainly starting materials (entries 1

(27) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945.

(28) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

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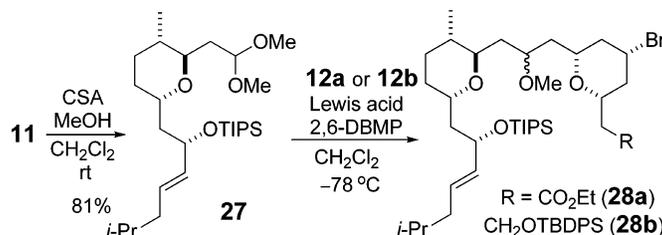
TABLE 2. MAP Reactions with Aldehydes



entry	enol ether	Lewis acid (equiv <sup>a</sup> )	base/additive (equiv)	yield <b>10+24</b> (%)	ratio <b>10:24</b> <sup>b</sup>	ratio of <b>10</b> alcohol	formation of <b>25</b>
1	<b>12a</b>	TiBr <sub>4</sub> (2.0)	2,6-DBMP <sup>c</sup> (1.5)	minor			major <sup>d</sup>
2		AlBr <sub>3</sub> (1.5)	Me <sub>3</sub> Al (0.3)	minor			major
3		TiBr <sub>4</sub> /Ti(O <sup>i</sup> Pr) <sub>4</sub> (1.0:1.0)	2,6-DBMP (1.5)	<10 <sup>e</sup>			0
4	<b>12b</b>	TiBr <sub>4</sub> /Ti(O <sup>i</sup> Pr) <sub>4</sub> (3.5:0.5)	2,6-DBMP (1.5)	57	1:2.0 <sup>f</sup>	ND <sup>g</sup>	0
5		TiBr <sub>4</sub> (2.0)	2,6-DBMP (1.5)	minor			major
6		AlBr <sub>3</sub> (1.5)	Me <sub>3</sub> Al (0.3)	minor			major
7		TiBr <sub>4</sub> /Ti(O <sup>i</sup> Pr) <sub>4</sub> (1.0:1.0)	2,6-DBMP (1.5)	0 <sup>e</sup>			0
8		TiBr <sub>4</sub> /Ti(O <sup>i</sup> Pr) <sub>4</sub> (1.8:0.2)	2,6-DBMP (1.5)	97	1.3:1	4.5:1	0

<sup>a</sup> All equivalents are relative to starting aldehyde. <sup>b</sup> As determined by crude <sup>1</sup>H NMR analysis. <sup>c</sup> 2,6-DBMP = 2,6-di-*tert*-butyl-4-methylpyridine. <sup>d</sup> The major product is the combined diastereomers and regioisomers of **25**. <sup>e</sup> Starting materials were recovered for these reactions. <sup>f</sup> Average of three runs; for these reactions, the bromide selectivity was inconsistent. <sup>g</sup> The alcohol ratio was not determined.

TABLE 3. MAP Reactions with Acetal Electrophiles



entry	enol ether	Lewis acid (equiv <sup>a</sup> )	yield <b>28a</b> or <b>28b</b> (%)	ratios <sup>b</sup> <b>28a</b> or <b>28b</b> (OMe epimers/eq-Br:ax-Br)	recovered acetal (%)
1	<b>12a</b>	TiBr <sub>4</sub> /Ti(O <sup>i</sup> Pr) <sub>4</sub> (3.5:0.5)	0		65
2		TiBr <sub>4</sub> (2.0)	69	2.5:1/3.9:1	15
3	<b>12b</b>	TiBr <sub>4</sub> /Ti(O <sup>i</sup> Pr) <sub>4</sub> (1.8:0.2)	61		39
4		TiBr <sub>4</sub> /Ti(O <sup>i</sup> Pr) <sub>4</sub> (3.5:0.5)	100	1.0:1/8.0:1	
5		TiBr <sub>4</sub> (4.0)	100	1.0:1/8.0:1	

<sup>a</sup> Equivalents are relative to the starting aldehyde. <sup>b</sup> As determined by crude <sup>1</sup>H NMR analysis.

and 3). Increasing the equivalents of this mixed Lewis acid (entry 4) or employing titanium tetrabromide alone (entries 2 and 5) afforded quantitative yields of bis-THP **28b** for the case of the TBDPS-substituted enol ether **12b** and a useful 69% yield for the ester-substituted enol ether **12a**. We presumed that lower yields with **12a** could be attributed to an electron-withdrawing effect as described earlier. It was surprising that titanium tetrabromide alone led to no observed siloxy displacement, which was prevalent in the aldehyde system with this Lewis acid. The diastereoselectivities from the acetal MAP reaction were also different. In the cases where enol ether **12b** was employed (entries 4 and 5), the initial aldol reaction into the acetal was completely unselective, but selectivity for the equatorial bromide improved significantly from ca. 1.3:1 to 8.0:1. A rationale for this interesting change in selectivity will be described in the Discussion section.

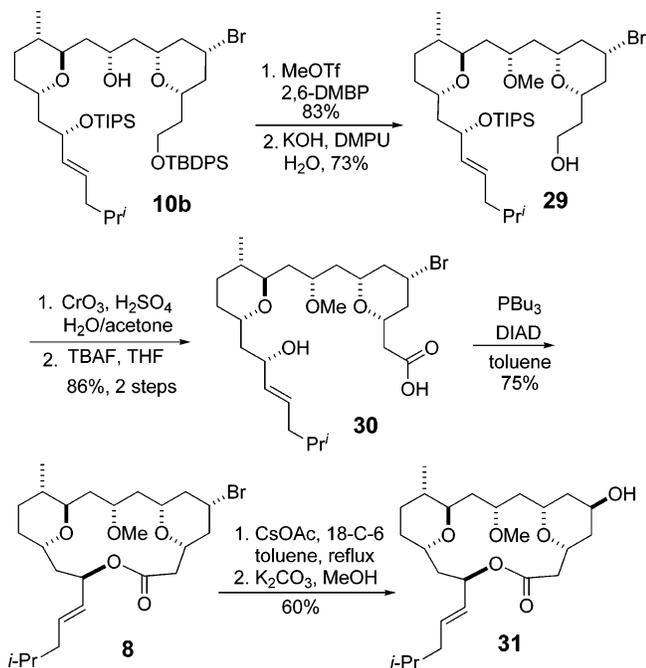
**Completion of the Leucascandrolide A Macrocycle.** Although the acetal MAP reaction provided excellent diastereoselectivity at the bromide center with enol ether **12b**, the 1:1 mixture at the methoxy center was inseparable and contributed to a lower overall yield of the desired diastereomer, as compared

to the aldehyde system. Because of these limitations, we chose to complete the leucascandrolide A macrocycle synthesis from intermediate **10b**, the major diastereomer obtained from the aldehyde MAP reaction (Scheme 4). Following methylation of the C9 alcohol, the TBDPS ether was deprotected under basic conditions to provide primary alcohol **29**. This alcohol could be transformed to the carboxylic acid in two steps by a Dess-Martin oxidation and subsequent Kraus oxidation,<sup>30,31</sup> or more directly by Jones oxidation to provide the acid in one step. The TIPS protecting group was removed with TBAF to provide seco acid **30** in 80% yield over two steps. A Mitsunobu reaction with tributylphosphine and diisopropyl azodicarboxylate (DIAD) afforded macrolactone **8** in 75% yield. The use of tributylphosphine was critical to avoid a macrocyclization with retention of configuration or DIAD-trapped products, which were com-

(30) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175–1176. (b) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890. (c) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

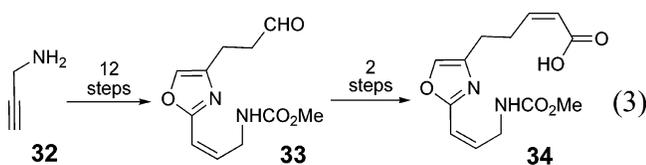
(31) In many syntheses of leucascandrolide A, a similar two-step oxidation is performed: see refs 4, 9, 10, and 11.

## SCHEME 4. Completion of a Formal Synthesis



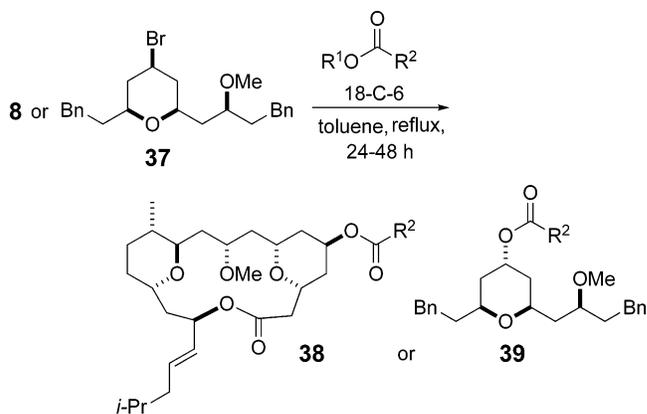
mon side reactions with triphenylphosphine. Displacement of the equatorial bromide generated in the MAP reaction with cesium acetate, followed by acetate methanolysis, provided macrocyclic alcohol **31** in 60% yield over the two steps. It is important to note that no elimination was observed during the bromide displacement, and the macrocyclic lactone was stable to the acetate cleavage conditions.

**Synthesis and Coupling of the Oxazole-Containing Side Chain.** Although the sequence described above constituted a formal synthesis of the natural product, we wanted to further highlight the utility of the equatorial bromide formed in the MAP reaction. A direct displacement of this bromide by the cesium carboxylate derivative of the side chain would complete the total synthesis in one step fewer than completion of the formal synthesis. The 12-step synthesis of side chain aldehyde **33** followed Leighton's reported procedure (eq 3).<sup>3</sup> The final two-step sequence, including a Still–Gennari olefination<sup>32</sup> and hydrolysis to form carboxylic acid **34**, was achieved through the procedure of Kozmin.<sup>5</sup>



The in situ formation of nucleophilic cesium carboxylates from cesium carbonate and their subsequent displacement reactions are well-precedented.<sup>33</sup> We anticipated that the addition of cesium carbonate to side chain acid **34**, 18-crown-6, and macrocyclic bromide **8** would generate leucascandrolide A in a single step. Unfortunately, elimination product **36** and an olefin

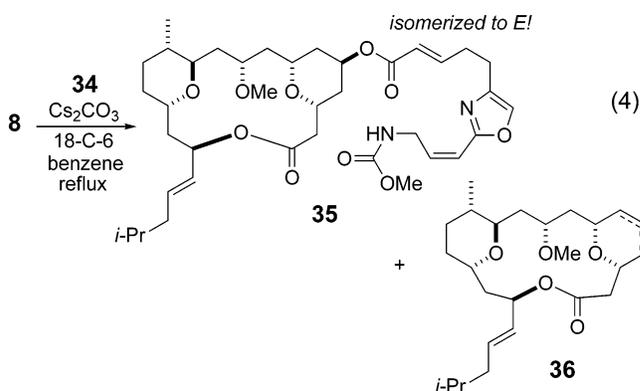
TABLE 4. Summary of Nucleophiles Investigated for Bromide Displacements



entry	<b>8</b> or <b>37</b>	R <sup>1</sup>	R <sup>2</sup>	pK <sub>a</sub> <sup>a</sup>	yield <b>38/39</b> (%)
1	<b>8</b>	Cs	CH <sub>3</sub> ( <b>40</b> )	4.74	85 <sup>b</sup>
2		H <sup>c</sup>	<b>34</b>	4.70 <sup>d</sup>	45 <sup>e</sup>
3		Cs	CH <sub>2</sub> SePh ( <b>41</b> )	3.75	78
4	<b>37</b>	Cs	CH <sub>2</sub> SePh ( <b>41</b> )	3.75	45 <sup>f</sup>
5		H <sup>c</sup>	CH <sub>2</sub> P(O)(OCH <sub>2</sub> CF <sub>3</sub> ) <sub>2</sub>	3.30 <sup>g</sup>	
6		Cs	CH <sub>2</sub> P(O)(OCH <sub>2</sub> CF <sub>3</sub> ) <sub>2</sub> ( <b>42</b> )	3.30 <sup>g</sup>	
7		H <sup>c</sup>	C≡CCH <sub>3</sub>	2.66	
8		Cs	C≡CCH <sub>3</sub> ( <b>43</b> )	2.66	

<sup>a</sup> For the cesium carboxylates, the numbers are for the corresponding acid. <sup>b</sup> See Scheme 4. <sup>c</sup> Cs<sub>2</sub>CO<sub>3</sub> was used as an additive. <sup>d</sup> Data are for a similar *Z*-olefinic acid. <sup>e</sup> See eq 4. <sup>f</sup> Remaining material was starting materials. <sup>g</sup> Data are for the corresponding ethyl phosphonate.

isomer of leucascandrolide A (**35**) were formed in a 1:1 mixture (eq 4). While **36** may have arisen from an excess of basic cesium carbonate in solution, it was presumed that the *Z* to *E* isomerization of **35** occurred by an addition/elimination of a cesium carboxylate nucleophile or a transient radical.

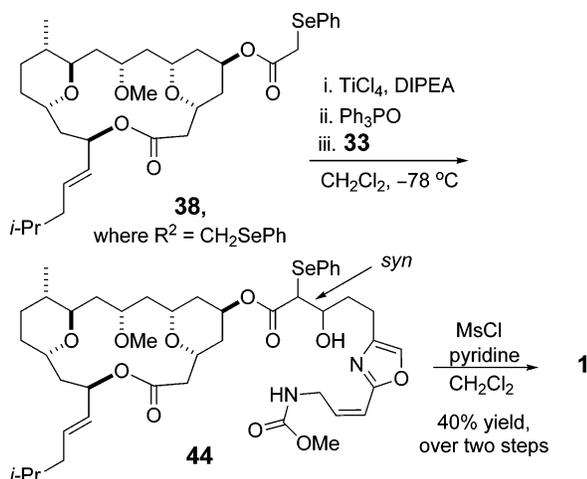


Model bromide **37** and macrocycle **8** were used to identify alternative nucleophiles that could be used in the displacement reaction and further derivatized in the real system to give the natural product (Table 4). Isolated  $\beta$ -phosphono-cesium carboxylate **42** or the corresponding carboxylic acid underwent decomposition in the harsh reaction conditions<sup>34</sup> (entries 5 and 6), and cesium 2-butyrate (**43**) or its corresponding acid

(32) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405–4408.

(33) (a) Kruijzinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, 103, 5183–5189. (b) Burch, J. D. Ph.D. Thesis, Harvard University, Cambridge, MA, 2005.

(34) Cesium carbonate is often used as a base in Horner–Emmons–Wadsworth reactions, and presumably decomposition occurs via deprotonation of an  $\alpha$ -proton: (a) Yamano, T.; Akiyama, T.; Ishida, E.; Abe, H.; Amemiya, M.; Inazu, T. *Chem. Lett.* **1989**, 335–337. (b) Bloch, R.; Seck, M. *Tetrahedron Lett.* **1987**, 28, 5819–5820.

**SCHEME 5. Completion of the Total Synthesis by Aldol Reaction and Dehydroselenation**


(entries 7 and 8) failed to displace the bromide. An examination of the approximate  $\text{p}K_{\text{a}}$  values of each of these acids provided insight into the displacement reaction. Cesium acetate (**40**) and an alkenyl cesium carboxylate with  $\text{p}K_{\text{a}}$  values of ca. 4.70 served as effective coupling partners (entries 1 and 2), but compounds with lower  $\text{p}K_{\text{a}}$  values were not effective.

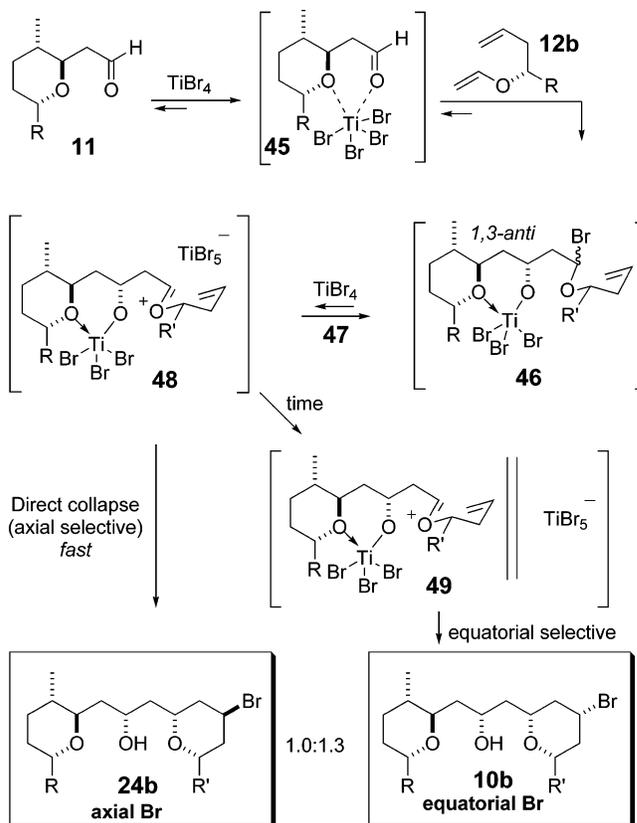
Cesium 2-(phenylselenanyl)acetate (**41**) was shown to be an effective coupling partner on both the model system and the macrocyclic bromide **8** (Table 4, entries 3 and 4). Utilizing methodology discovered by Toru,<sup>35</sup> the oxazole-containing side chain could then be attached through a *syn*-selective aldol reaction and stereospecific dehydroselenation to afford the Z-olefin and leucascandrolide A in an unoptimized 40% yield over the two steps (Scheme 5).<sup>36</sup> To confirm the structure of synthetic leucascandrolide A prepared by this method, the total synthesis was also completed by Leighton's two-step procedure, which included acylation of macrocyclic alcohol **31** and a subsequent Still–Gennari olefination reaction.<sup>3</sup>

**Discussion**

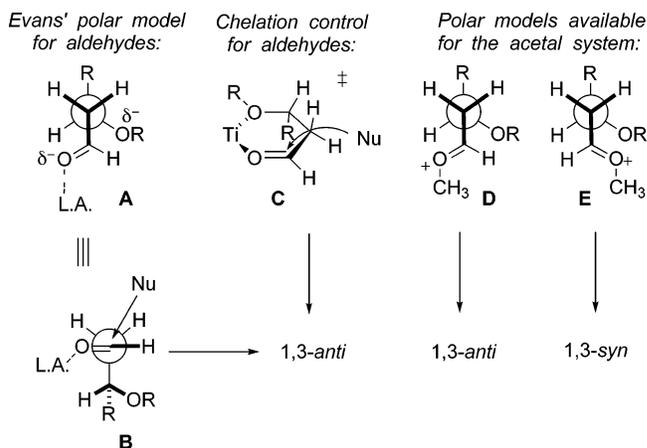
Recent studies with the segment coupling Prins reaction have provided insight into the stereoselectivity of the MAP process. Because of the disparity in diastereoselectivities derived from the aldehyde and acetal MAP reactions, they will be discussed separately. For  $\beta$ -alkoxy aldehydes, an initial coordination of titanium tetrabromide would provide intermediate **45**, which has been activated toward the nucleophilic attack of **12b** (Scheme 6). This coordination would be expected to favor 1,3-*anti* attack through six-membered transition state **C** (see Figure 3, left), and this model is consistent with the reaction outcome. Additionally,  $\beta$ -alkoxy aldehydes have been described by Evans to favor a lowest-energy polarized transition state **A**, which also results in 1,3-*anti* aldol products upon the addition of a nucleophile.<sup>28</sup> Because of the use of a titanium Lewis acid in our system, it is most likely that the addition is controlled by the classic chelation model.

(35) Nakamura, S.; Hayakawa, T.; Nishi, T.; Watanabe, Y.; Toru, T. *Tetrahedron* **2001**, 6703–6711.

(36) This reaction was not optimized due to the lack of the aldehyde coupling partner at the end of the total synthesis. The unreacted starting material was recovered from the reaction, which shows that optimization should be possible.

**SCHEME 6. Mechanistic Rationale: Aldehyde MAP Reactions<sup>a</sup>**


<sup>a</sup> Note:  $\text{TiBr}_4$  and not the mixed Lewis acid system which was actually used for the synthesis was illustrated for simplicity.



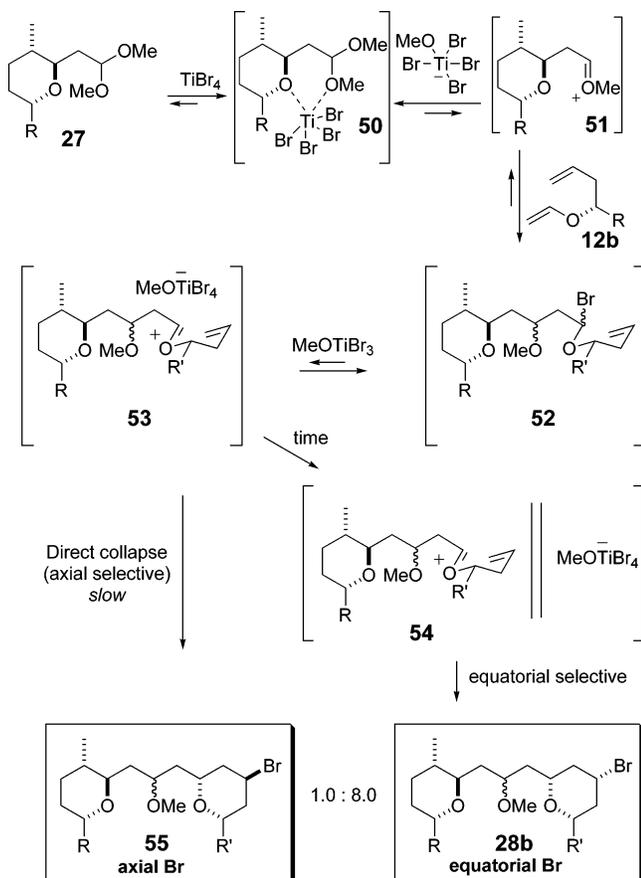
**FIGURE 3.** Rationale for the OH/OMe selectivity of MAP reactions.

The expected intermediate bromoether **46** would engage in the Prins cyclization upon activation by a Lewis acid.<sup>37</sup> Interaction of **46** and titanium tetrabromide would generate the contact ion pair **48**. Cyclization to the THP cation, as modeled by Alder,<sup>38</sup> and direct collapse of this ion pair would favor the axial 4-bromo-THP **24b** through a least-motion pathway. This

(37) Bromoether intermediates have been identified in low-temperature NMR studies on simple Prins cyclization systems and were found to be major components in solution (ref 27).

(38) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, 124, 4960–4961.

## SCHEME 7. Mechanistic Rationale: Acetal MAP Reactions



outcome is similar to what we have observed for the bromotrimethylsilane-induced Prins cyclization.<sup>39</sup> Alternatively, if the reaction of the ion pair were slow, the contact ion pair would form a solvent-separated ion pair **49**, and this intermediate would cyclize to form the equatorial 4-bromo-THP **10b** preferentially, based on the preferred orbital alignment present in the tetrahydropyran cation.<sup>38</sup> The key partitioning event takes place at the contact ion pair **48**. We postulate that the chelated titanium oxocarbenium ion **48** is more reactive than a typical oxocarbenium ion. High reactivity of the electrophile would favor a fast collapse and lead to axial product. Lower reactivity would allow the ions to separate and ultimately lead to the equatorial product. Neither pathway is expected to be completely selective. The underlying reasons for greater reactivity of the titanium-chelated oxocarbenium ion **48** are not obvious.

For the acetal case, a slightly modified mechanistic scheme was proposed (Scheme 7). Initial coordination of titanium tetrabromide would provide intermediate **50**, which decomposes to oxocarbenium ion **51** and the methoxy titanium tetrabromide “ate” complex shown. A chelation-controlled nucleophilic addition to **51** is no longer possible, and because a 1:1 mixture of methoxy diastereomers was observed for this addition, it can be assumed that neither of the polar transition states **D** or **E** (Figure 3) was preferred. Ward also reported lower stereoselectivity for the aldol addition of an allylsilane to a  $\beta$ -alkoxy acetal (ca. 1:1) as compared to the corresponding aldehyde (>9:1), but offered no explanation of these results.<sup>40</sup> The Mukaiyama aldol reaction with **12b** would generate bromoether intermediate

**52**. In this case, the active Lewis acid in the system is either titanium tetrabromide or titanium tribromomethoxide. Activation with these Lewis acids would lead to contact ion pair **53** (or the TiBr<sub>5</sub><sup>-</sup> analogue). As discussed above, direct collapse of this contact ion pair would favor the axial product **55**, and formation of a solvent-separated ion pair **54** would favor the equatorial product **28b**. In this case, the oxocarbenium ion **53** shows the expected Prins reactivity, and most of the material passes through the solvent-separated ion pair **54** en route to the equatorial 4-bromo-THP **28b**. We attribute the difference in selectivity between the aldehyde and acetal substrates to the higher reactivity of the aldehyde-derived contact ion pair **48** compared with **53**.

Recall that the unusual preference for an axial 4-bromo-Prins adduct does not correlate with the Mukaiyama aldol–Prins reaction or even the use of  $\alpha$ - or  $\beta$ -alkoxy aldehydes. The axial selectivity is found with  $\alpha$ - or  $\beta$ -alkoxy aldehydes that are expected to chelate effectively, such as benzyl ethers, and it is not observed with nonchelating alkoxy groups such as TBS ethers.<sup>12</sup> The model that we propose here is based on the unusual reactivity of the titanium-chelated oxocarbenium ion **48** and is consistent with the observed higher axial selectivity for fast-collapsing ion pairs.<sup>39,41</sup>

Scheme 7 also provides an explanation for the absence of solvolysis of the allyl siloxy group without titanium tetraiso-propoxide attenuation of titanium tetrabromide. During the formation of oxocarbenium ion **46**, 1 equiv of methoxide ion was dissociated from **46**, thus forming the attenuated Lewis acid MeOTiBr<sub>3</sub> in situ.

## Conclusion

A total synthesis of the structurally complex marine natural product leucascandrolide A has been completed. The synthesis required 17 steps for the longest linear sequence from known alcohol **15** with an overall yield of 4.3%. The MAP reaction with aldehyde **11** was demonstrated to be a highly efficient and diastereoselective process in forming the core of the molecule. The MAP reaction with acetals was also introduced in this synthesis as a method for installing methyl ethers and obtaining high diastereoselectivity for a tetrahydropyranyl equatorial bromide. Studies of this key step led us to formulate mechanistic rationales for both classes of MAP reactions, which led to a better understanding of the origins of diastereoselectivity. Furthermore, this synthesis is the first application of Toru’s two-step Z-selective olefination on a complex molecule and highlights it as a new method for the installation of the leucascandrolide A side chain unit.

## Experimental Section

General experimental details, experimental data for all intermediates, and spectra for key intermediates and leucascandrolide A can be found in the Supporting Information.

**Lactone 18.** To a solution of acrylate **17** (0.76 g, 2.2 mmol, 1.0 equiv) in anhydrous, degassed 1,2-dichloroethane (45 mL) was added Grubbs’ second generation ruthenium catalyst<sup>42</sup> (47.0 mg, 0.056 mmol, 0.03 equiv). The solution was heated at reflux for 2

(39) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904–9905.

(40) Ward, D. E.; Gai, Y.; Kaller, B. F. *J. Org. Chem.* **1995**, *60*, 7830–7836.

(41) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640–13648.

(42) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

h, then another equal portion of the catalyst (47.0 mg, 0.056 mmol, 0.03 equiv) was added. After heating at reflux for an additional 90 min, the dark brown solution was allowed to cool to 23 °C. The open reaction vessel was quickly transferred to a Parr bomb, which was then pressurized with hydrogen gas (100 psi), and stirred vigorously for 16 h. The reaction mixture was then concentrated in vacuo and purified by flash chromatography (10–40% diethyl ether/hexanes) to afford 0.64 g (91%) of **18** as a clear, colorless oil:  $[\alpha]_D^{25} +63.7$  ( $c = 1.00$ , chloroform); IR (neat) 2943, 2868, 1742, 1094  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.16 (td,  $J = 10.4, 2.4$  Hz, 1H), 3.94–3.84 (m, 2H), 2.61 (ddd,  $J = 17.7, 6.8, 4.8$  Hz, 1H), 2.47 (ddd,  $J = 17.7, 9.6, 6.0$  Hz, 1H), 1.95 (dddd,  $J = 14.5, 8.6, 6.3, 2.4$  Hz, 1H), 1.92 (ddt,  $J = 13.4, 6.9, 4.8$  Hz, 1H), 1.82–1.70 (m, 2H), 1.61–1.52 (m, 1H), 1.07–1.03 (m, 24H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.9, 82.9, 59.1, 37.1, 32.7, 29.7, 28.0, 18.2, 17.7, 12.1; HRMS (EI) calcd for  $\text{C}_{14}\text{H}_{27}\text{O}_3\text{Si}$   $[\text{M} - i\text{Pr}]^+$  271.1729, found 271.1733.

**Tetrahydropyran 19.** To a solution of acetoxy ether **13** (0.62 g, 1.79 mmol, 1.0 equiv) and silyl enol ether **14** (0.71 g, 3.58 mmol, 2.0 equiv) in anhydrous dichloromethane (18 mL) was added zinc bromide (40.0 mg, 0.179 mmol, 0.1 equiv). The slurry was stirred for 4 h then was concentrated in vacuo and immediately purified by flash chromatography (0–7% diethyl ether/hexanes) to give 0.70 g (92%) of **19** as a clear, colorless oil with a 2,6-*trans/cis* diastereomeric ratio of >95:5 (as determined by crude proton NMR spectroscopy):  $[\alpha]_D^{25} +35.5$  ( $c = 100$ , chloroform); IR (neat) 2956, 1673, 1629, 1463, 1092, 883  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.72 (dt,  $J = 15.8, 7.4$  Hz, 1H), 6.04 (td,  $J = 15.8, 1.4$  Hz, 1H), 4.39 (app q,  $J = 6.1$  Hz, 1H), 3.90 (ddd,  $J = 7.7, 6.4, 2.6$  Hz, 2H), 3.54 (ddd,  $J = 9.6, 6.4, 3.3$  Hz, 1H), 2.83 (dd,  $J = 15.0, 7.1$  Hz, 1H), 2.43 (dd,  $J = 15.0, 6.4$  Hz, 1H), 1.95–1.87 (m, 1H), 1.80 (td,  $J = 7.5, 3.3$  Hz, 1H), 1.77 (td,  $J = 6.8, 1.4$  Hz, 2H), 1.56–1.36 (m, 4H), 1.34–1.26 (m, 1H), 1.14–1.18 (m, 24H), 0.88 (d,  $J = 6.8$  Hz, 3H), 0.75 (d,  $J = 6.7$  Hz, 6H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  195.9, 145.3, 132.1, 74.1, 67.9, 60.8, 44.3, 41.7, 36.3, 33.6, 28.1, 28.0, 26.8, 22.4, 18.5, 18.4, 12.4; HRMS (EI) calcd for  $\text{C}_{22}\text{H}_{41}\text{O}_3\text{-Si}$   $[\text{M} - i\text{Pr}]^+$  381.2825, found 381.2834. Anal. Calcd for  $\text{C}_{25}\text{H}_{48}\text{O}_3\text{-Si}$ : C, 70.70; H, 11.39. Found: C, 70.90; H, 11.33.

**Aldehyde 11.** To a solution of the primary alcohol from **23** (50.0 mg, 0.117 mmol, 1.0 equiv) in anhydrous dichloromethane (3 mL) was added pyridine (40.0  $\mu\text{L}$ , 0.492 mmol, 4.2 equiv), followed by Dess-Martin periodinane (99.0 mg, 0.234 mmol, 2.0 equiv). This mixture was stirred for 2 h then diluted with diethyl ether (10 mL). A 1:1 mixture of saturated aqueous sodium bicarbonate and saturated aqueous sodium bisulfite (5 mL) was added, and the resultant biphasic mixture was stirred for 5 min. The layers were separated, and the aqueous layer was extracted with diethyl ether (3  $\times$  20 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (1  $\times$  20 mL) and brine (1  $\times$  20 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude oil was purified by flash chromatography on deactivated silica gel (1% triethylamine in the desired eluant) (5–60% diethyl ether/hexanes) to provide 45 mg (91%) of **11** as a clear, colorless oil:  $[\alpha]_D^{25} +35.3$  ( $c = 0.90$ , chloroform); IR (neat) 2931, 2718, 1731, 1094  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.79 (dd,  $J = 3.4, 2.0$  Hz, 1H), 5.53 (dt,  $J = 14.9, 7.1$  Hz, 1H), 5.38 (dd,  $J = 15.4, 7.6$  Hz, 1H), 4.25 (td,  $J = 8.1, 4.6$  Hz, 1H), 3.93 (dq,  $J = 9.3, 4.9$  Hz, 1H), 3.80 (ddd,  $J = 12.5, 8.6, 3.9$  Hz, 1H), 2.58 (ddd,  $J = 15.7, 3.8, 2.0$  Hz, 1H), 2.49 (ddd,  $J = 15.4, 8.8, 3.2$  Hz, 1H), 2.20 (ddd,  $J = 13.9, 9.5, 4.6$  Hz, 1H), 1.96–1.86 (m, 2H), 1.82–1.73 (m, 1H), 1.67–1.58 (m, 2H), 1.54–1.35 (m, 4H), 1.09–1.03 (m, 21H), 0.93–0.86 (m, 9H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  202.2, 134.2, 130.5, 72.0, 71.7, 69.3, 47.6, 41.8, 40.2, 35.1, 28.9, 28.6, 27.2, 22.7, 22.5, 18.3, 12.6; HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{48}\text{O}_3\text{SiNa}$   $[\text{M} + \text{Na}]^+$  447.3271, found 447.3279. Anal. Calcd for  $\text{C}_{25}\text{H}_{48}\text{O}_3\text{Si}$ : C, 70.70; H, 11.39. Found: C, 70.56; H, 11.45.

**(R)-3-(Vinylxy)hex-5-enyloxy-tert-butylidiphenylsilane (12b).** To a solution of secondary alcohol **16b** (2.00 g, 5.64 mmol, 1.0

equiv) in ethyl vinyl ether (30.0 mL) was added mercuric trifluoroacetate (241 mg, 0.564 mmol, 0.10 equiv). This mixture was allowed to stir in a capped vessel for 48 h. The mixture was then diluted with diethyl ether (75 mL), and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude oil was immediately purified by flash chromatography on deactivated silica gel (1% triethylamine in the desired eluant) (0–10% diethyl ether/hexanes) to provide 1.93 g (90%) of **12b** as a clear, colorless oil:  $[\alpha]_D^{25} -9.26$  ( $c = 2.00$ , dichloromethane); IR (neat) 3072, 2931, 2858, 1636, 1112  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76–7.68 (m, 4H), 7.50–7.41 (m, 6H), 6.37 (dd,  $J = 14.1, 6.6$  Hz, 1H), 5.84 (ddt,  $J = 16.9, 14.1, 7.0$  Hz, 1H), 5.14 (d,  $J = 4.1$  Hz, 1H), 5.11 (s, 1H), 4.36 (dd,  $J = 14.1, 1.4$  Hz, 1H), 4.22–4.13 (m, 1H), 4.03 (dd,  $J = 6.6, 1.4$  Hz, 1H), 3.83 (dt,  $J = 13.2, 6.7$  Hz, 1H), 3.75 (dt,  $J = 10.7, 5.4$  Hz, 1H), 2.42–2.35 (m, 2H), 1.88–1.79 (m, 2H), 1.10 (s, 9H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.6, 135.8, 134.2, 133.9, 129.8, 127.9, 117.7, 88.3, 76.2, 60.2, 38.8, 36.9, 27.1, 19.4; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{36}\text{O}_2\text{SiN}$   $[\text{M} + \text{NH}_4]^+$  398.2515, found 398.2498. Anal. Calcd for  $\text{C}_{24}\text{H}_{32}\text{O}_2\text{Si}$ : C, 75.74; H, 8.47. Found: C, 75.90; H, 8.51.

**MAP Products 10b and 24b.** Aldehyde **11** (62.2 mg, 0.146 mmol, 1.0 equiv), enol ether **12b** (55.7 mg, 0.146 mmol, 1.0 equiv), and 2,6-di-*tert*-butyl-4-methylpyridine (45.0 mg, 0.219 mmol, 1.5 equiv) were dissolved in anhydrous dichloromethane (6.0 mL). This solution was cooled to  $-78$  °C, and a 9:1 titanium tetrabromide/titanium tetraisopropoxide Lewis acid blend<sup>43</sup> as a solution in dichloromethane (0.78 mL, 0.298 mmol, 0.34 M, 2.0 equiv) was added dropwise. After 2 h, a 1:1 mixture of methanol and triethylamine (6 mL) was added dropwise, followed by the addition of saturated aqueous sodium bicarbonate (2 mL). The biphasic mixture was allowed to warm to 23 °C and was diluted with diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3  $\times$  10 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (1  $\times$  10 mL), water (1  $\times$  10 mL), and brine (1  $\times$  10 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude oil was purified by flash chromatography (0–100% diethyl ether/hexanes) to yield 68.0 mg (53%) of **10b** as a 4.5:1 mixture of diastereomers at the alcohol center and 57 mg (44%) of **24b** as a 7.8:1 mixture of diastereomers at the alcohol center. **10b**:  $[\alpha]_D^{25} +21.9$  ( $c = 1.15$ , dichloromethane); IR (thin film) 3515, 2952, 2930, 2865, 1111  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 6.4$  Hz, 4H), 7.46–7.36 (m, 6H), 5.56 (dt,  $J = 14.5, 7.0$  Hz, 1H), 5.41 (dd,  $J = 15.5, 7.3$  Hz, 1H), 4.29 (app q,  $J = 8.4$  Hz, 1H), 4.10 (tt,  $J = 10.1, 5.0$  Hz, 1H), 4.06–3.95 (m, 2H), 3.77 (dtd,  $J = 11.5, 5.4, 1.2$  Hz, 1H), 3.71 (dt,  $J = 10.6, 5.8$  Hz, 1H), 3.67 (d,  $J = 1.6$  Hz, 1H), 3.60–3.42 (m, 2H), 2.29–2.13 (m, 3H), 1.97–1.86 (m, 2H), 1.86–1.25 (m, 16H), 1.13–1.00 (m, 30H), 0.92–0.87 (m, 6H), 0.85 (d,  $J = 6.5$  Hz, 3H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.0, 135.8, 135.7, 135.5, 134.5, 133.9, 133.8, 130.1, 129.9, 127.9, 75.1, 75.0, 73.6, 71.7, 71.6, 69.3, 67.1, 60.2, 45.5, 43.5, 43.3, 41.8, 40.0, 39.9, 38.9, 34.5, 29.1, 28.6, 27.5, 27.1, 22.7, 22.5, 19.4, 18.5, 18.4, 12.6; HRMS (ESI) calcd for  $\text{C}_{49}\text{H}_{81}\text{BrO}_5\text{Si}_2\text{Na}$   $[\text{M} + \text{Na}]^+$  907.4703, found 907.4703. Anal. Calcd for  $\text{C}_{49}\text{H}_{89}\text{O}_5\text{Si}_2\text{Br}$ : C, 66.41; H, 9.21. Found: C, 66.60; H, 9.44.

**24b**:  $[\alpha]_D^{25} +20.9$  ( $c = 2.15$ , dichloromethane); IR (thin film) 3518, 2952, 2930, 2865, 1095  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79–7.63 (m, 4H), 7.48–7.37 (m, 6H), 5.57 (dt,  $J = 15.0, 7.1$  Hz, 1H), 5.42 (dd,  $J = 15.4, 7.4$  Hz, 1H), 4.71 (t,  $J = 2.8$  Hz, 1H), 4.32 (dd,  $J = 12.9, 7.7$  Hz, 1H), 4.22–4.06 (m, 3H), 4.02–3.93 (m, 1H), 3.82–3.71 (m, 2H), 3.54–3.48 (m, 1H), 2.18 (ddd,  $J = 13.8, 8.8, 5.1$  Hz, 1H), 2.05 (dd,  $J = 12.6, 1.7$  Hz, 1H), 2.00–1.83 (m, 5H), 1.81–1.27 (m, 14H), 1.19–1.00 (m, 30H), 0.95–0.87 (m,

(43) See the Supporting Information for more details on the preparation of this Lewis acid.

6H), 0.87 (d,  $J = 6.4$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.0, 135.8, 135.7, 135.5, 134.5, 134.0, 133.9, 130.1, 129.8, 127.9, 73.4, 72.6, 71.6, 70.0, 69.9, 69.2, 67.8, 60.4, 50.2, 50.1, 43.2, 41.8, 40.3, 39.3, 38.5, 34.7, 29.0, 28.6, 27.5, 27.1, 22.7, 22.5, 19.4, 18.5, 18.4, 12.6; HRMS (ESI) calcd for  $\text{C}_{49}\text{H}_{81}\text{BrO}_5\text{Si}_2\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  907.4703, found 907.4714.

**Macrocyclic Bromide 8.** To a solution of tributylphosphine (0.40 mL, 1.59 mmol, 5.0 equiv) in degassed, anhydrous toluene (55 mL) was added neat diisopropyl azodicarboxylate (0.26 mL, 1.33 mmol, 4.2 equiv). Seco acid **30** (170 mg, 0.318 mmol, 1.0 equiv) was then added as a solution in degassed, anhydrous toluene (11 mL). After 50 min, the mixture was concentrated in vacuo and the crude oil was purified by flash chromatography (0–50% diethyl ether/hexanes) to provide 119 mg (75%) of macrocyclic bromide **8** as a white solid:  $[\alpha]_D^{25} +49.45$  ( $c = 0.62$ , chloroform); IR (thin film) 2955, 2925, 2854, 1732, 1088  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.71 (td,  $J = 14.3$ , 7.1 Hz, 1H), 5.50–5.30 (m, 2H), 4.18 (tt,  $J = 11.9$ , 4.2 Hz, 1H), 3.88 (d,  $J = 11.8$  Hz, 1H), 3.74 (t,  $J = 11.0$  Hz, 1H), 3.50 (q,  $J = 10.0$  Hz, 2H), 3.35 (s, 3H), 3.23 (t,  $J = 10.7$  Hz, 1H), 2.57 (dd,  $J = 13.2$ , 3.7 Hz, 1H), 2.38 (t,  $J = 14.5$  Hz, 1H), 2.31 (t,  $J = 13.6$  Hz, 1H), 2.19 (d,  $J = 9.6$  Hz, 1H), 2.01 (t,  $J = 12.2$  Hz, 1H), 1.96–1.20 (m, 14H), 1.17 (d,  $J = 7.0$  Hz, 3H), 1.08–0.97 (m, 1H), 0.86 (d,  $J = 6.6$  Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  169.1, 132.8, 130.2, 75.3, 74.2, 73.8, 73.5, 71.2, 63.2, 57.5, 45.4, 43.1, 43.0, 42.9, 42.9, 41.8, 39.1, 35.7, 31.2, 29.9, 28.3, 27.3, 24.3, 22.5, 18.4; HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{41}\text{BrO}_5\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  523.2035, found 523.2026.

**Macrocyclic Alcohol 31.** To a solution of the macrocyclic bromide **8** (5.0 mg, 0.010 mmol, 1.0 equiv) in anhydrous toluene (0.35 mL) were added cesium acetate (13.4 mg, 0.070 mmol, 7.0 equiv) and 18-crown-6 (18.4 mg, 0.010 mmol, 1.0 equiv). This mixture was heated at 110 °C in a sealed tube for 20 h. After cooling to 23 °C, the mixture was diluted with dichloromethane (5 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude oil was filtered through a silica gel plug (0–60% ethyl acetate/hexanes) to provide an oil, upon concentration of the fractions. This oil was dissolved in methanol (0.5 mL), and potassium carbonate (1.3 mg, 0.010 mmol, 1 equiv) was added. After 45 min, the mixture was filtered through Celite, and the resulting filtrate was concentrated in vacuo. The crude mixture was purified by flash chromatography (20–100% ethyl acetate/hexanes) to provide 2.6 mg (60% over the two steps) of macrocyclic alcohol **31** as a white solid:  $[\alpha]_D^{25} +32.9$  ( $c = 0.13$ , ethanol); IR (thin film) 3444, 2957, 2925, 2855, 1738, 1262, 1061, 1032  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.71 (td,  $J = 14.4$ , 7.3 Hz, 1H), 5.44–5.34 (m, 2H), 4.31 (br s, 1H), 4.17 (t,  $J = 11.4$  Hz, 1H), 3.90 (d,  $J = 11.5$  Hz, 1H), 3.73 (dt,  $J = 9.3$ , 3.4 Hz, 1H), 3.60 (t,  $J = 10.6$  Hz, 1H), 3.55 (t,  $J = 10.8$  Hz, 1H), 3.36 (s, 3H), 2.54 (dd,  $J = 13.0$ , 3.9 Hz, 1H), 2.45 (t,  $J = 13.0$  Hz, 1H), 2.32 (t,  $J = 12.9$  Hz, 1H), 2.14–1.20 (m, 16H), 1.17 (d,  $J = 7.1$  Hz, 3H), 1.05–0.97 (m, 1H), 0.86 (dd,  $J = 6.6$ , 1.7 Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 132.5, 130.5, 73.9, 73.7, 70.9, 69.2, 69.1, 65.0, 63.2, 57.5, 43.6, 43.1, 41.8, 39.6, 38.8, 38.7, 35.9, 31.2, 29.9, 28.4, 27.3, 24.3, 22.5, 18.5;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_5\text{D}_5\text{N}$ )  $\delta$  6.39 (br s, 1H), 5.84–5.71 (m, 2H), 5.55 (dd,  $J = 15.2$ , 6.6 Hz, 1H), 4.64 (t,  $J = 11.6$  Hz, 1H), 4.42 (br s, 1H), 4.18 (t,  $J = 11.6$  Hz, 1H), 4.06 (d,  $J = 11.8$  Hz, 1H), 3.93 (t,  $J = 10.5$  Hz, 1H), 3.75 (t,  $J = 10.8$  Hz, 1H), 3.37 (s, 3H), 2.68 (dd,  $J = 12.9$ , 3.5 Hz, 1H), 2.54–2.45 (m, 2H), 2.11 (t,  $J = 12.9$  Hz, 1H), 1.99–1.80 (m, 4H), 1.80–1.40 (m, 3H), 1.40–1.15 (m, 7H), 1.15–0.97 (m, 2H), 1.09 (d,  $J = 7.0$  Hz, 3H), 0.79 (dd,  $J = 6.5$  Hz, 3H), 0.78 (dd,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_5\text{D}_5\text{N}$ )  $\delta$  170.3, 132.0,

131.5, 73.9, 73.8, 70.9, 69.9, 69.7, 63.8, 63.1, 56.7, 44.0, 43.4, 41.8, 39.9, 39.7, 39.5, 35.9, 31.4, 28.3, 27.4, 24.3, 22.3, 22.3, 18.4; HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{42}\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  461.2879, found 461.2859.

**Leucascandrolide A (1).** To a solution of  $\alpha$ -selenyl ester **38** (16.0 mg, 0.025 mmol, 1.0 equiv) in anhydrous dichloromethane (0.5 mL) at –78 °C was added titanium tetrachloride (55.0  $\mu\text{L}$ , 0.055 mmol, 1.0 M, 2.2 equiv) as a solution in anhydrous dichloromethane, dropwise. The addition of diisopropylethyl amine (9.6  $\mu\text{L}$ , 0.055 mmol, 2.2 equiv) followed, and the dark red solution was allowed to stir for 1 h. Triphenylphosphine oxide (15.3 mg, 0.055 mmol, 2.2 equiv), as a solution in 0.05 mL anhydrous dichloromethane, was then added. The resultant solution was stirred for 1 h, then a solution of aldehyde **33** (9.1 mg, 0.038 mmol, 1.5 equiv) in 0.05 mL of anhydrous dichloromethane was added. After stirring for an additional 1 h, saturated aqueous ammonium chloride (1 mL) was added and the mixture was stirred vigorously and allowed to warm to 23 °C. The mixture was then diluted with dichloromethane (5 mL) and water (5 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (1 × 5 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude oil was subjected to flash chromatography (10–100% ethyl acetate/hexanes), which provided 7.0 mg of the starting  $\alpha$ -selenyl ester **38** and 15.0 mg of a mixture of the desired aldol product, aldehyde **33**, and triphenylphosphine oxide. The latter mixture was redissolved in anhydrous dichloromethane (0.1 mL), and the resultant solution was cooled to 0 °C. A solution of methanesulfonyl chloride (12.2  $\mu\text{L}$ , 0.106 mmol, 6.2 equiv) and pyridine (13.7  $\mu\text{L}$ , 0.170 mmol, 10 equiv) in anhydrous dichloromethane (0.1 mL) was added, and the mixture was stirred for 3 h. Water (1 mL) was then added, and the biphasic mixture was allowed to warm to 23 °C. The mixture was then diluted with dichloromethane (5 mL) and water (5 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (1 × 5 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude oil was subjected to flash chromatography (5–60% ethyl acetate/hexanes), which provided 4.0 mg (40%, over the two steps) of leucascandrolide A as a clear, colorless oil:  $[\alpha]_D^{25} +39.5$  ( $c = 0.32$ , ethanol); IR (thin film) 3336, 2954, 2927, 2870, 1716, 1646, 1274, 1168, 1081  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (s, 1H), 6.34 (dt,  $J = 14.7$ , 7.7 Hz, 1H), 6.31 (d,  $J = 12.7$  Hz, 1H), 6.10 (dt,  $J = 12.7$ , 6.6 Hz, 1H), 5.91 (d,  $J = 11.5$  Hz, 1H), 5.75–5.67 (m, 1H), 5.57–5.47 (m, 1H), 5.40–5.33 (m, 2H), 5.27 (t,  $J = 2.6$  Hz, 1H), 4.36–4.26 (m, 2H), 4.02 (t,  $J = 11.3$  Hz, 1H), 3.90 (d,  $J = 11.9$  Hz, 1H), 3.69 (s, 3H), 3.62–3.51 (m, 3H), 3.36 (s, 3H), 3.11–3.00 (m, 2H), 2.74 (t,  $J = 7.2$  Hz, 2H), 2.60–2.50 (m, 1H), 2.47–2.27 (m, 2H), 2.00–1.82 (m, 4H), 1.80–1.48 (m, 7H), 1.36–1.20 (m, 4H), 1.17 (d,  $J = 7.1$  Hz, 3H), 1.07–0.99 (m, 1H), 0.86 (d,  $J = 6.6$  Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 165.5, 160.3, 157.4, 149.5, 141.3, 136.6, 134.1, 132.6, 130.3, 120.9, 116.9, 73.9, 73.5, 71.1, 70.2, 69.8, 67.5, 63.3, 57.5, 52.4, 43.5, 42.5, 41.8, 39.6, 39.4, 35.8, 35.7, 31.2, 29.9, 27.9, 27.4, 25.9, 24.5, 22.5, 18.5; HRMS (ESI) calcd for  $\text{C}_{38}\text{H}_{56}\text{O}_{10}\text{N}_2\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  723.3832, found 723.3845.

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**Supporting Information Available:** Experimental procedures and NMR spectra of the new compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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