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[4 + 2]-Annulations of Chiral Organosilanes: Application to the Total Synthesis of Leucascandrolide A

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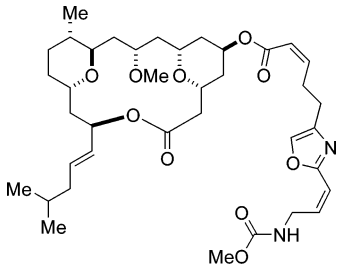


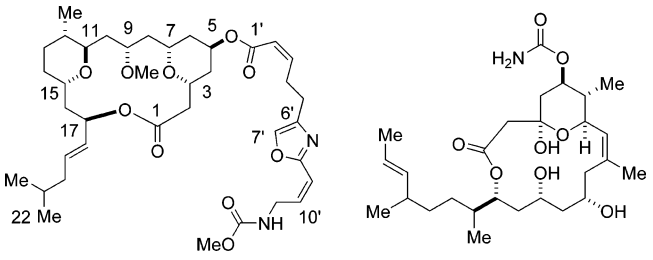
leucascandrolide A, **1**

Complete details of an asymmetric synthesis of leucascandrolide A (**1**) are described. The synthesis highlights the use of two diastereoselective [4 + 2]-annulations for the assembly of the functionalized bispyranyl macrolide **3**. An efficient assembly and union of the oxazole-containing side chain **4** with macrolide **3** was carried out using a Mitsunobu reaction. A convergent route to the oxazole side chain was developed using a Sonogashira cross-coupling between 2-trifloyloxazole **16** and alkyne **17**, which allowed for the installation of the C9′−C10′ (*Z*)-olefin.

Introduction

Leucascandrolide A (**1**) is a doubly O-bridged, 18-membered macrolide isolated from the calcareous sponge, *Leucascandra caveolata*, obtained from the northeastern coast of New Caledonia in the Coral Sea.[1] Further evaluation of the same sponge resulted in the isolation of the second member of leucascandrolide family, leucascandrolide B (**2**) (Figure 1), an extensive methyl-branched and polyoxygenated 16-membered macrolide.[2]

The relative stereochemistry of **1** was determined by extensive two-dimensional ^{1}H NMR analysis, while the absolute stereochemistry was assigned through correlation of the C5 stereocenter by employing Mosher's method at the C5 hydroxyl. It has been reported that leucascandrolide A exhibits high in vitro cytotoxicity against human KB and p388 tumor cell lines displaying low IC_{50}'s of 0.05 and 0.26 μg/mL, respectively. This agent also exhibits potent antifungal activity against *Candida albicans*, a pathogenic yeast that attacks AIDS patients and other immunocompromised individuals (Figure 1).



leucascandrolide A, **1** leucascandrolide B, **2**

FIGURE 1. The leucascandrolides.

Recent reports indicate that leucascandrolide A is no longer available from its original natural source, supporting the notion that **1** is not a metabolite of *Leucascandra caveolata*, but rather that of an opportunistic bacteria that colonized the sponge, as evidenced by the large amounts of dead tissue in the initial harvest of the marine sponge.[2] This fact, in addition to its structural complexity, has spurred many synthetic efforts including a report of the first total synthesis from the Leighton group.[3]

Herein, we detail our efforts that have culminated in an enantioselective total synthesis of (+)-leucascandrolide A (**1**).[4]

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

(2) D'Ambrosio, M.; Tato, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347.

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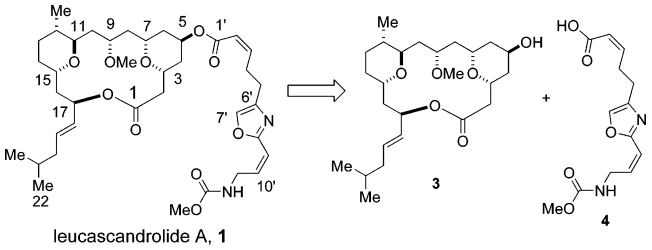
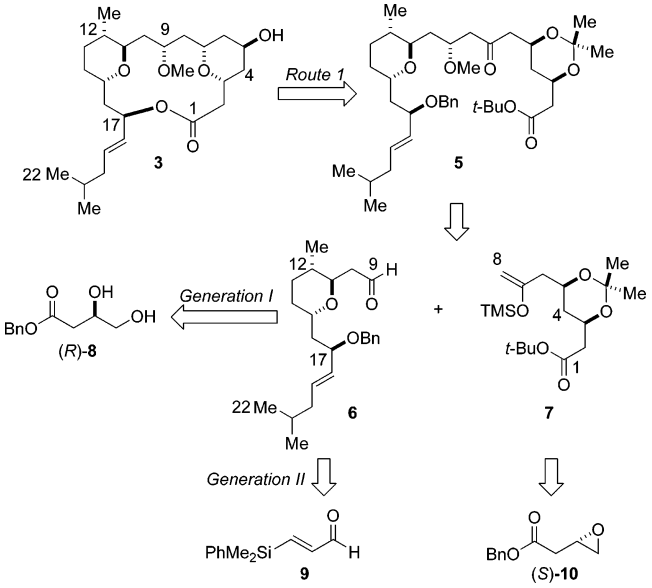
SCHEME 1. Retrosynthesis of Leucascandrolide A



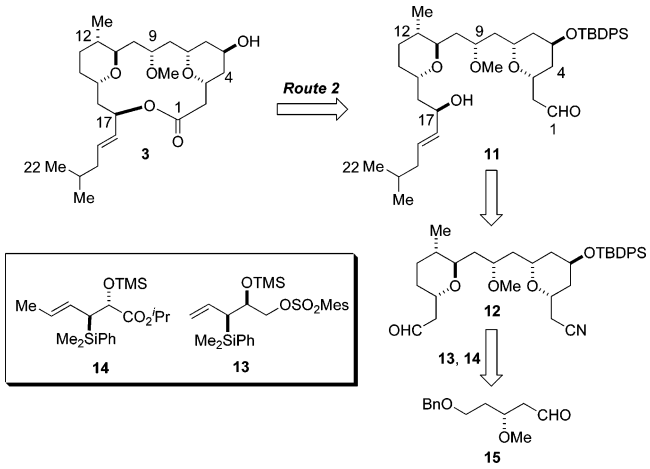
SCHEME 2. Retrosynthesis of the Leucascandrolide A Macrolide (Route 1)



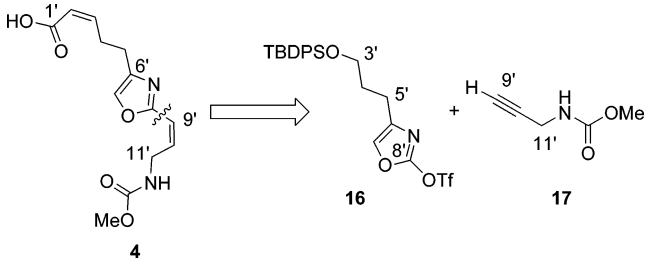
Retrosynthesis of Leucascandrolide A. Our retrosynthesis of **1** is depicted in Scheme 1 and begins with a disconnection of the C5 ester linkage, revealing macrolide **3** and oxazole-containing side chain **4**.

Retrosynthetic Analysis of the Leucascandrolide A Macrolide (3). The structurally challenging macrolide **3** attracted our interest in synthetic efforts toward **1**. In this fragment, two tetrahydropyrans are embedded in an 18-membered lactone, bearing eight stereogenic centers. Of the total number of routes designed to access the macrolide, two independent approaches were chosen to investigate the assembly of fragment **3**, both of which extensively integrated our pyran annulation methodology.

SCHEME 3. Retrosynthesis of the Leucascandrolide A Macrolide (Route 2)



SCHEME 4. Retrosynthesis of the C1′−C11′ Fragment of Leucascandrolide A



In our initial approach (Route 1), we envisioned that macrolide **3** could be derived from the C1−C22 fragment **5** (Scheme 2). Further analysis of **5** showed that it could be divided at the C8−C9 bond to give the Mukaiyama aldol-coupling partners: left tetrahydropyran **6** and silyl enol ether **7**. The latter material **7** could be derived from enantiopure terminal epoxide (*S*)-**10**. The C9−C22 left tetrahydropyran **6** can be synthesized either from diol (*R*)-**8** (first generation approach) or aldehyde **9** (second generation approach).

Concurrent with our study toward the total synthesis of **1**, an efficient formal [4 + 2]-annulation of chiral allylsilanes and aldehydes leading to the enantioselective formation of dihydropyrans was emerging from our laboratory.[5] Upon analysis of **3**, we envisioned that a spontaneous macrolactol formation from acyclic hydroxyaldehyde **11**, followed by a mild oxidation of the resulting macrolactol to its corresponding macrolactone, could be a feasible macrocyclization strategy (Route 2, Scheme 3). Retrosynthetically, the C17 allylic alcohol could be obtained from the addition of an alkenyl zinc species to aldehyde **12**. It was our thought that this segment **12** could be obtained in a stereocontrolled and efficient fashion employing two consecutive, formal [4 + 2]-annulations. The synthesis of this bis-tetrahydropyran intermediate could be an excellent testing ground of our formal [4 + 2]-annulation reactions. Accordingly, we could evaluate the feasibility and applicability of an annulation strategy using aldehyde **15**, chiral allylsilane **13**, and chiral crotylsilane **14** to generate the bispyran **12**.

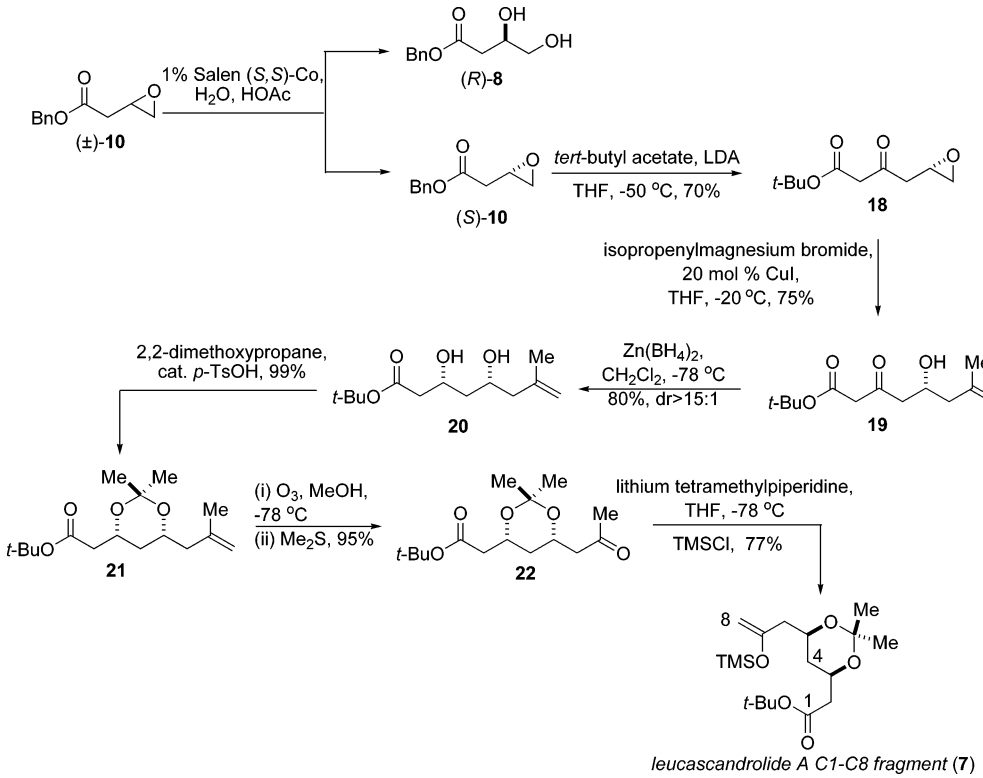
Retrosynthetic Analysis of the Leucascandrolide A Oxazole Side Chain (4). Aligned with our efforts toward the leucascandrolide A macrolide (**3**) was the synthesis of the

(3) For total syntheses of leucascandrolide A, see: (a) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894. (b) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670. (c) Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4098. (d) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343. (e) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274. (f) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833. (g) Wang, Y.; Jelena, J.; Kozmin, S. A. *Pure Appl. Chem.* **2005**, *77*, 1161. For syntheses of the leucascandrolide A macrolide, see: (h) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (i) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066. (j) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934. (k) Williams, D. R.; Patnaik, S.; Plummer, S. *Org. Lett.* **2003**, *5*, 5035. (l) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641. Other reports of leucascandrolide A fragments include: (m) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 579. (n) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (o) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812. (p) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2001**, *66*, 3242.

(4) Portions of these results have been published in the following communications: (a) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812. (b) Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 3995. (c) Su, Q.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223.

(5) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836.

SCHEME 5. Synthesis of the Leucascandrolide A Fragment 7



leucascandrolide A C1′−C11′ oxazole-containing side chain (**4**). From a retrosynthetic perspective, we anticipated that disconnection at the C8′−C9′ bond could reveal the two potential coupling partners: the 2-trifloyloxazole **16** and terminal alkyne **17** (Scheme 4). We planned to explore the viability of a Pd(0)-mediated cross-coupling strategy, specifically, a Sonogashira coupling, and partial hydrogenation of the alkyne−oxazole using Lindlar's catalyst to introduce the C9′−C10′ (*Z*)-olefin and finish the assembly of side chain **4** in a convergent manner.[6]

Results and Discussion

Initial Approach to the Leucascandrolide A Macrolide (3) (Route 1). Synthesis of silyl enol ether **7** began with the enantiomerically enriched epoxide (*S*)-**10** (99% ee), available from a hydrolytic kinetic resolution (HKR) of racemic terminal epoxide (±)-**10** (Scheme 5).[7] Treatment of (*S*)-**10** with the lithium enolate of *tert*-butyl acetate in THF at −50 °C gave the unstable *β*-ketoester **18** in 70% yield. Subsequent treatment of **18** with isopropenylmagnesium bromide in the presence of 20 mol % of CuI provided the *β*-hydroxy ketone **19** (75%). Treatment of **19** with freshly prepared $Zn(BH_4)_2$[8] in CH_2Cl_2 at −78 °C afforded a 1,3-*syn* reduction to the 1,3-diol **20** (80%, dr > 15:1). Protection of the diol as its acetonide (2,2-dimethoxypropane, *p*-TsOH, 99%) and cleavage of the terminal olefin (O_3, Me_2S, MeOH) gave the C1−C8 methyl ketone **22** in 95% yield. Finally, treatment of methyl ketone **22** with the bulky lithium anion of 2,2,6,6-tetramethylpiperidine gave the desired kinetic enolate, which was then trapped with TMSCl, completing the synthesis of the C1−C8 silyl enol ether coupling partner **7** (77%).

Two independent approaches have been developed to synthesize the left-hand tetrahydropyran subunit. The first route was initiated by differentiation of the two hydroxyls of HKR-derived diol (*R*)-**8** through a selective protection of the primary hydroxyl group as its *tert*-butyldiphenylsilyl ether (TBDPSCl, imidazole, 99%), followed by protection of the secondary hydroxyl group as its benzyl ether (NaH, BnBr, 95%) yielding ester **23** (Scheme 6). Ester **23** was then converted to its corresponding aldehyde **24**, which could be accomplished by treatment with DIBAL-H at −78 °C in CH_2Cl_2 for 15 min (80%). Aldehyde **24** served as the requisite electrophile for an *anti* 1,3-allylation by treatment with $TiCl_4$ and allyltrimethylsilane (90%, dr > 20:1), which cleanly installed leucascandrolide A's C15 stereochemistry. The stereochemical course of this reaction is documented and, in the present case, is consistent with a well precedented chelation-controlled *anti* 1,3-induction model.[9] The resulting allylic alcohol was protected as its *tert*-butyldimethylsilyl ether (TBSOTf, 2,6-lutidine, 95%) affording terminal olefin **25**. This material was converted to its corresponding primary iodide in a three-step process: ozonolysis of the olefin to the corresponding aldehyde (O_3, Me_2S, 99%), reduction of the generated aldehyde ($NaBH_4$) to the primary

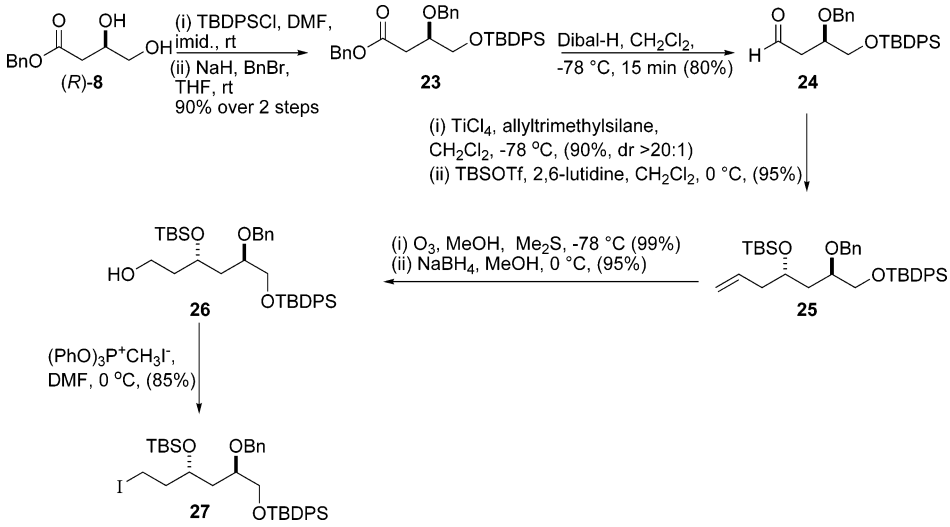
(6) (a) Campbell, I. B. In *Organocopper Reagents. A Pratical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; Chapter 10, pp 217−236. (b) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 521−548.

(7) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

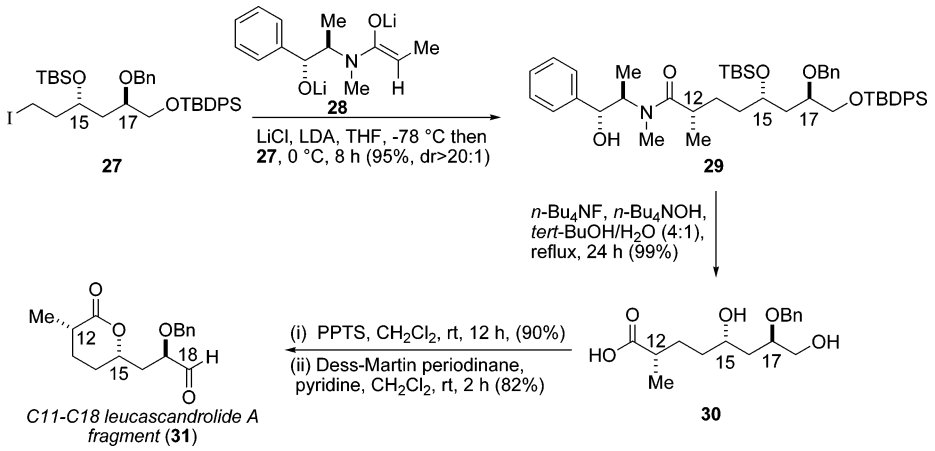
(8) For reviews on the preparation and synthetic applications of zinc borohydride, see: (a) Narasimhan, S.; Balakumar, R. *Aldrichimica Acta* **1998**, *31*, 19. (b) Hoyveda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (c) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921. (d) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 8, pp 5536−5539.

(9) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, 537. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang M. J. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

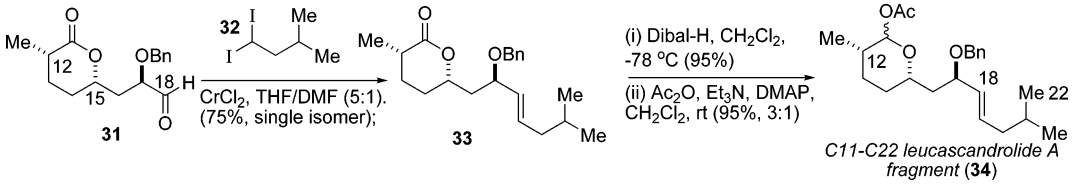
SCHEME 6. Synthesis of the Alkyl Iodide Fragment 27



SCHEME 7. Synthesis of the Leucascandrolide A Fragment 31



SCHEME 8. Synthesis of the Anomeric Acetate 34



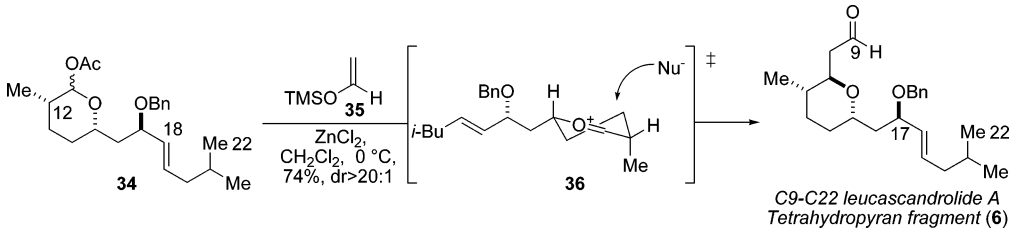
alcohol **26**, and then conversion of this material to alkyl iodide **27** by treatment with $(PhO)_3P^+CH_3I^-$ (85%). The alkyl iodide **27** would serve as the requisite electrophile for a diastereoselective alkylation to install the C12 stereocenter of the target molecule.

Treatment of alkyl iodide **27** with Myers' (*R*,*R*)-pseudoephedrine-derived amide enolate **28** cleanly installed the correct configuration at C12 giving amide **29** in excellent yield and diastereoselectivity (95%, dr > 20:1) (Scheme 7).[10] Cleavage of the chiral auxiliary and cyclization of the resulting carboxylic acid were best accomplished in a three-step process. This was initiated by treatment of amide **29** with a mixture of tetrabutylammonium fluoride and tetrabutylammonium hydroxide, which simultaneously deprotects the two silyl ethers while cleaving the (*R*,*R*)-pseudoephedrine auxiliary, yielding carboxylic acid **30** (99%). Subsequent cyclization of the crude carboxylic acid **30** was accomplished by treatment with a stoichiometric quantity of pyridinium *p*-toluenesulfonic acid at room temperature for 12 h, giving the required lactone (90%). The primary hydroxyl group at C18 was then oxidized to an aldehyde by treatment with Dess−Martin periodinane (82%), which yielded the key C11−C18 leucascandrolide A fragment **31**.

A modified Takai olefination between the C11−C18 aldehyde **31** and isovaleraldehyde-derived geminal diiodide **32** was utilized to generate the (*E*)-double bond isomer of lactone **33** (Scheme 8). This olefination was best performed using freshly flame-dried chromium(II) chloride in a mixed solvent system of tetrahydrofuran and *N*,*N*-dimethylformamide (v/v = 5:1), which gave the desired (*E*)-olefin **33** as a single isomer and in good yield (75%).[11] With the C19−C22 (*E*)-olefin alkyl chain installed, completion of tetrahydropyran **6** was the next objective. This was initiated by conversion of the lactone to the

(10) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

SCHEME 9. Synthesis of the C9−C22 Tetrahydropyran Fragment 6



anomeric acetate **34** through lactol formation using a DIBAL-H reduction followed by acetylation (Ac_2O, Et_3N) to afford the acylated hemiacetal **34** in 90% yield for the two steps.

The completion of tetrahydropyran **6** was accomplished by a $ZnCl_2$-mediated C-glycosidation of anomeric acetate **34** with the acetaldehyde-derived enol silane **35** (Scheme 9).[12] Treatment of acetate **34** with freshly fused $ZnCl_2$ generated oxonium ion **36** in situ, which was then trapped by the nucleophilic enol silane **35**. This reaction served to replace the anomeric acetate, completing the C9−C22 tetrahydropyran fragment **6** while efficiently installing leucascandrolide's C11 stereocenter (74%, dr > 20:1). The stereochemical outcome for this reaction is illustrated in Scheme 9, with carbon−carbon bond formation occurring preferentially in the pseudoaxial orientation. The pseudoaxial delivery yields the desired *anti* stereochemistry based on the stereoelectronic effect, specifically, that the approach of the nucleophile **35** toward the electrophile **36** occurs *anti*-periplanar to one of the lone pairs of electrons on the tetrahydropyran **6** via a low energy chair-like transition state. This reaction sequence completed the synthesis of the C9−C22 tetrahydropyran fragment **6** in 16 steps and 26% overall yield.

During the course of the synthesis of tetrahydropyran **6**, a viable and interesting alternative using a chiral crotylsilane approach to synthesize substituted dihydropyrans was discovered in our laboratories. It was found that treatment of *anti*-silane (*S*,*S*)-**37** with a substoichiometric amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of an aldehyde led to a stereoselective synthesis of dihydropyrans through a formal [4 + 2]-annulation mechanism.[5] This annulation is elegant in that it yields stereochemically well-defined dihydropyrans and creates two new stereocenters on the dihydropyran in a single step (Scheme 10). The resulting stereochemistry was reminiscent of the leucascandrolide A C9−C22 fragment **6**, and accordingly, it was postulated that chiral crotylsilane (*S*,*S*)-**37** could potentially serve as the starting material to constitute an alternative approach to fragment A.

To initiate the organosilane approach to the leucascandrolide C9−C22 tetrahydropyran fragment **6**, the [4 + 2]-annulation of silane (*S*,*S*)-**37** with appropriately functionalized aldehydes was evaluated. A crucial structural requirement of the aldehyde was that it needed to be able to serve as precursor for the C9 2°-hydroxyl-bearing stereocenter. In the initial screen, five protected 3-hydroxypropionaldehyde derivatives (**38a**−**e**) were evaluated in annulations with (*S*,*S*)-**37**; however, all gave the dihydropyrans (**39a**−**e**) in poor to modest yields (<71%) and diastereoselectivities (dr ≤ 5:1) (Table 1).

After careful examination, it was determined that the reaction of (*S*,*S*)-**37** with the α,β-unsaturated aldehyde, 3-(dimethylphenylsilyl)propenal (**40**), catalyzed by TMSOTf at −50 °C gave the requisite intermediate C9−C16 dihydropyran **41** in excellent yield (95%) and diastereoselectivity (dr > 20:1) (Scheme 11). The increased yield and enhanced level of diastereoselectivity obtained in this reaction may be attributed to a stabilization of the oxonium ion via a resonance delocalization of the positive charge. The utility of this annulation approach is illustrated by the efficient manner in which it installed the C11 and C12 stereocenters of leucascandrolide A in a *single step*, while the C15 stereocenter was already present in (*S*,*S*)-**37**.

With efficient access to dihydropyran **41**, construction of the aldehyde **6** was initiated (Scheme 12). Elaboration of **41** began with saturation of the olefins using standard hydrogenation conditions (H_2, Pd/C) to afford tetrahydropyran **42**. Next, it was necessary to oxidize the dimethylphenylsilyl substituent to give the necessary aldehyde synthon at C9. This conversion was best

SCHEME 10. Stereoselective Synthesis of Dihydropyrans

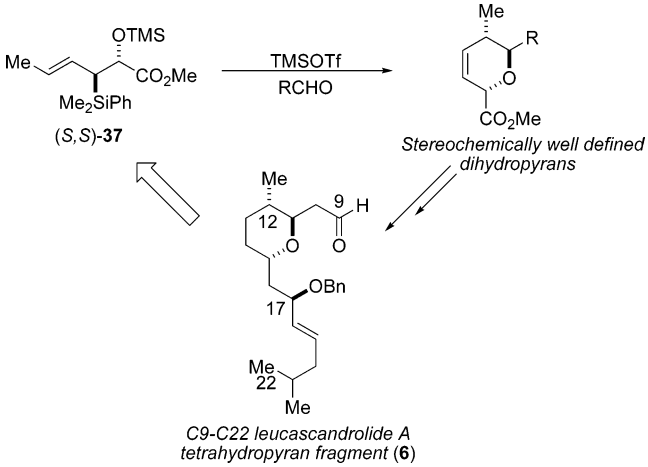
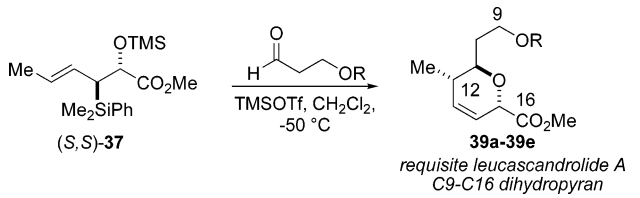


TABLE 1. Aldehyde Screen in the [4 + 2]-Annulation Toward the C9−C16 Dihydropyran



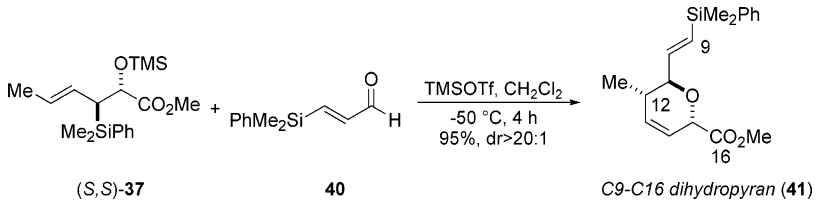
entry	aldehyde (R)	% yield[a]	diastereoselectivity[b]
1	**38a** (benzyl)	50	2:1
2	**38b** (*p*-methoxybenzyl)	40	2.5:1
3	**38c** (pivaloyl)	71	5:1
4	**38d** (benzoyl)	66	3:1
5	**38e** (trityl)	0	na

[a] Yields are based on pure materials isolated by chromatography on SiO_2. [b] The ratio of products was determined by ^1H NMR (400 MHz), operating at a S/N ratio of >200:1.

(11) (a) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951. For the preparation of geminal alkyl diiodies, see: (b) Pross, A.; Sternhill, S. *Aust. J. Chem.* **1970**, *23*, 989.

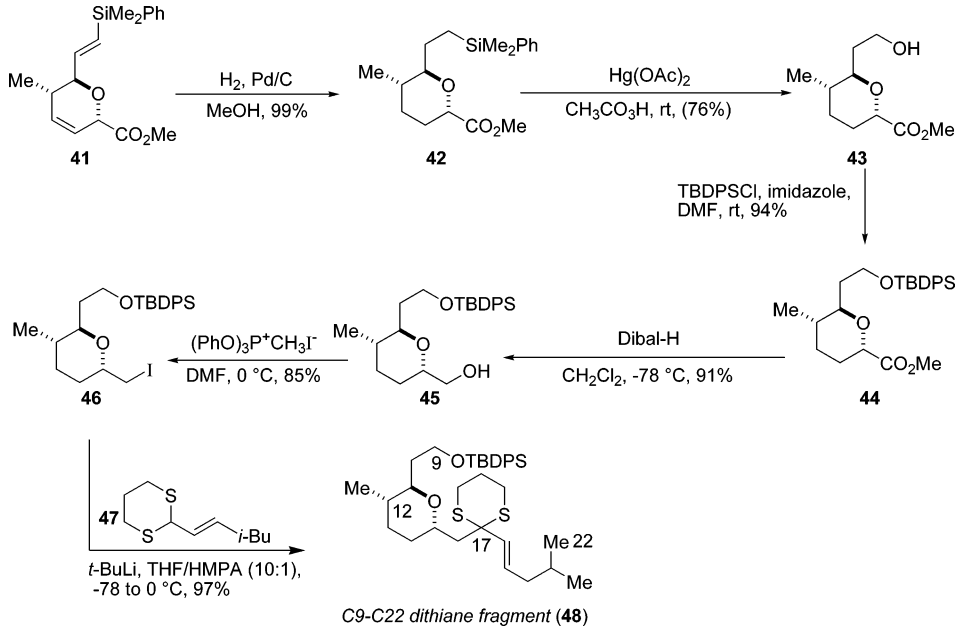
(12) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc*. **1982**, *104*, 4976. (b) Tino, J. A.; Lewis, M. D.; Kishi, Y. *Heterocycles* **1987**, *25*, 97.

SCHEME 11. Construction of the Leucascandrolide A C9−C16 Subunit 41



(*S,S*)-**37** **40** *C9-C16 dihydropyran* (**41**)

SCHEME 12. Synthesis of the C9−C22 Fragment 48



accomplished by a Fleming−Tamao oxidation[13] using $Hg(OAc)_2$ in peracetic acid to give primary alcohol **43** in 75% yield. Protection of the emerged C9 primary alcohol as its *tert*-butyldiphenylsilyl ether (TBDPSCl, imidazole) gave the primary silyl ether **44**. Reduction of the methyl ester (DIBAL-H) at C16 proceeded smoothly to give the primary alcohol **45**, which was then converted to the alkyl iodide **46** through treatment with $(PhO)_3P^+CH_3I^-$ in DMF (77% yield over two steps). At this stage, it was then necessary to install the C17−C22 side chain. Although several options were considered, it was ultimately accomplished via an alkylation of iodide **46** with the lithium anion of dithiane **47**[14] using a THF/HMPA (10:1) solvent system[15] to provide the fully elaborated C9−C22 carbon fragment **48** (97%).

At this stage, it was then necessary to unveil the α,β-unsaturated ketone through removal of the dithiane at C17. This proved more challenging than originally anticipated, and an extensive review of conditions that promote the removal of dithiane protecting groups was undertaken. Among the standard conditions surveyed was the use of *N*-halosuccinimide reagents,[16] mercury perchlorate,[17] and ceric ammonium nitrate.[18] All of these proved ineffective, giving low yields (below 40%) and significant amounts of decomposition. A notable exception was the application of Stork and Zhao's method in which bis-(trifluoroacetoxy)iodobenzene (BTI) in a $MeOH/H_2O$ solvent mixture was reported to remove a series of 1,3-dithianes.[19] Indeed, treatment of dithiane **48** with BTI in $MeOH/THF/H_2O$ (8:1:1) for 5 min afforded the desired α,β-unsaturated ketone **49** in a 70% yield. Varying amounts (∼15−20%) of multiple olefin isomers were obtained as side products. Increased reaction time (>10 min) resulted in larger amounts of decomposition to undesired materials.

Concerned by the prospect of significant material loss during scale-up procedures, we sought a milder and more predictable method for our dithiane removal. We postulated that Dess−Martin periodinane (DMP) would affect the desired transformation in a similar manner since it is well established that DMP tolerates a myriad of functional groups. Despite the widespread use of DMP in oxidative applications, there were no known reports of DMP-mediated thioacetal or thioketal removal. Gratifyingly, treatment of dithiane **48** with DMP in a $MeOH/THF/H_2O$ (8:1:1) solvent system for 12 h gave the desired α,β-unsaturated ketone **49** excellent yield (91%) (Scheme 13).[20]

The next task toward the assembly of the leucascandrolide A C9−C22 tetrahydropyran **6** was the installation of the C17

(13) (a) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317. (b) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, C37.

(14) Dithiane was prepared from the known α,β-unsaturated aldehyde: Vig, O. P.; Bari, S. S.; Puri, S. K.; Dua, D. M. *Ind. J. Chem.* **1981**, *20B*, 342.

(15) For leading references on dithiane alkylation, see: (a) Smith, A. B.; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925 and references therein. (b) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365−377. (c) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147−6212.

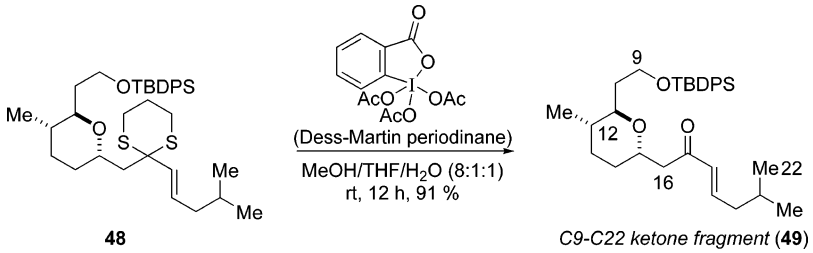
(16) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(17) Aso, M.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1989**, *54*, 5597.

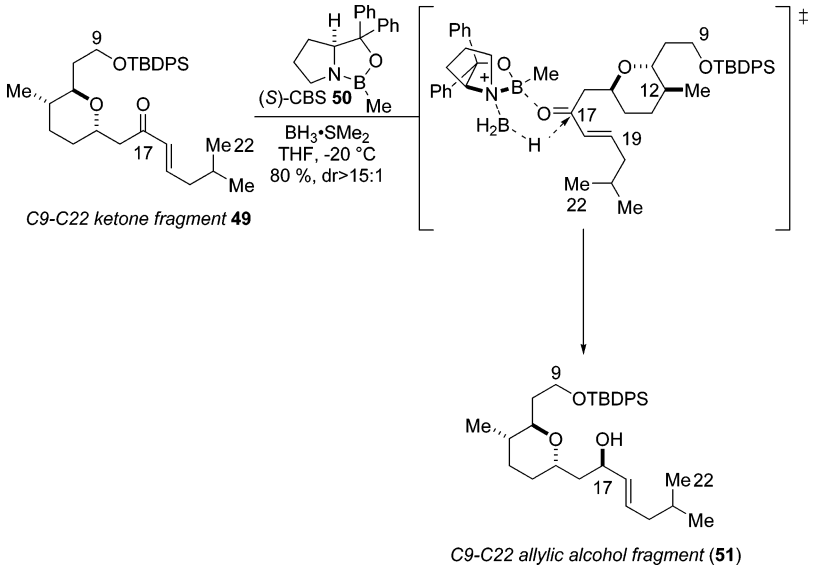
(18) Ho, T. L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.

(19) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

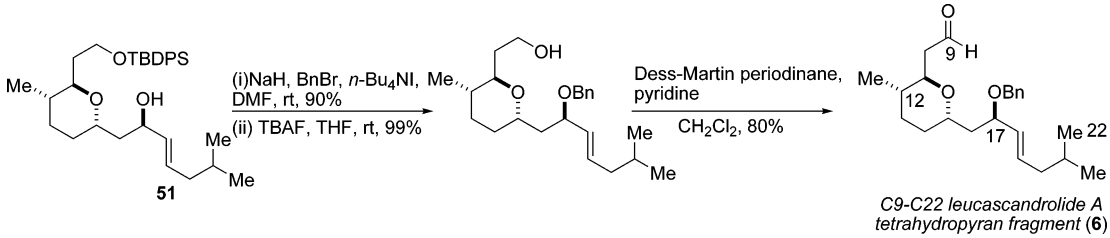
SCHEME 13. Dithiane Removal Mediated by Dess−Martin Periodinane



SCHEME 14. Synthesis of the Allylic Alcohol Fragment 51



SCHEME 15. Synthesis of the C9−C22 Aldehyde 6



stereocenter. After a careful examination of the system, it was found that the C17 stereocenter could be installed through a catalytic asymmetric reduction with Corey's chiral borane, (*S*)-CBS **50**, in the presence of BH_3•SMe_2 to cleanly give the desired (*R*)-alcohol **51** (80%, dr > 15:1).[21] The rationale for asymmetric reduction is provided by the model originally proposed by Corey, which differentiates the size of the substituents at the α and α′ positions of prochiral ketones. Analysis of Corey's model to the present case suggested that the C18−C22 α,β-unsaturated portion of ketone **49** is considered to be the large substituent, which adopts the least sterically demanding position, while the C9−C16 tetrahydropyran portion is considered to be the smaller substituent (Scheme 14). Indeed, this model holds true in our case, as the absolute stereochemistry of the reduction was assigned through the method of Mosher.[22]

To complete the C9−C22 tetrahydropyran fragment **6**, the emerged allylic alcohol at C17 was protected as its benzyl ether (BnBr, *n*-Bu_4NI, DMF, 90%). Installation of the C9 aldehyde was accomplished through deprotection of the primary silyl ether (TBAF, 99%) followed by a Dess−Martin oxidation of the resulting primary alcohol (80%). Thus, the synthesis of the C9−C22 tetrahydropyran **6** was completed in 12 steps with an overall yield of 32% (Scheme 15).

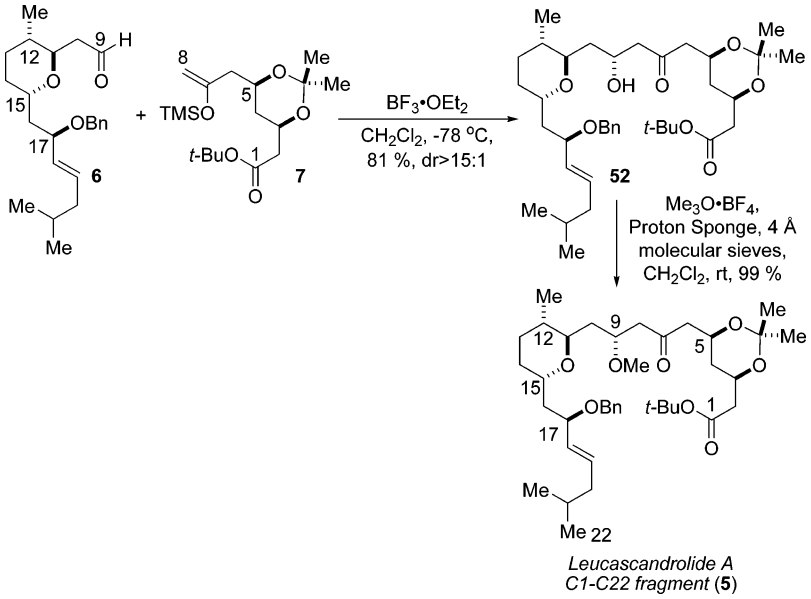
To undertake the assembly of the C1−C22 segment **5**, a fragment coupling using a Mukaiyama aldol between the C9−C22 aldehyde **6** and the C1−C8 silyl enol ether **7** was investigated. After a brief survey of the reaction, it was determined that the coupling was best accomplished by treatment of a mixture of **6** and **7** in CH_2Cl_2 with BF_3•OEt_2 at −78 °C for 4 h (Scheme 16). Gratifyingly, the coupling proceeded in good yield (81%) and diastereoselectivity (dr > 15:1) to provide

(20) For the initial communication of this reaction and a discussion of its scope, see: Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett*. **2003**, *5*, 575.

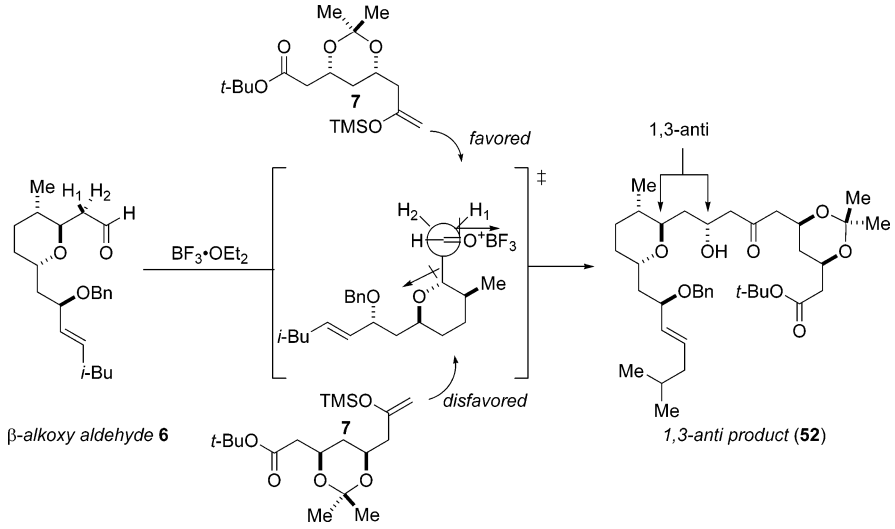
(21) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett*. **1990**, *31*, 611. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed*. **1998**, *37*, 1986.

(22) (a) Dale, J. A.; Mosher, H. S. L. *J. Am. Chem. Soc*. **1973**, *95*, 512. (b) Trost, B. M.; Belletire, J. L.; Godleski, J.; McDougal, D. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem*. **1986**, *51*, 2370.

SCHEME 16. Synthesis of C1−C22 Leucascandrolide Fragment 5



SCHEME 17. Proposed Model for 1,3-*anti* Induction



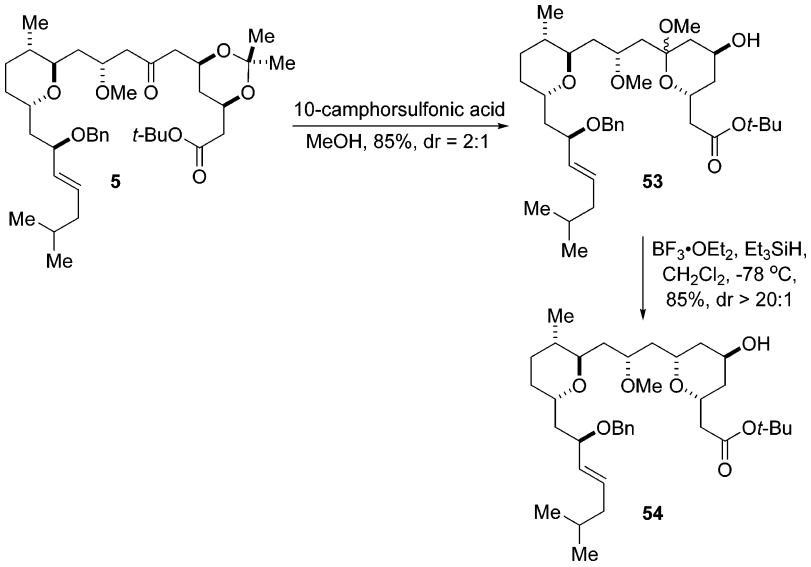
the desired 1,3-*anti* induction product alcohol **52**. Despite the monodentate nature of BF_3•OEt_2, there is ample precedent for 1,3-*anti* induction in similar systems.[23] The absolute stereochemistry at C9 was assigned using the method of Mosher.[22] Methylation of the emerged hydroxyl group at C9 was achieved by treatment of **52** with Meerwein's reagent in the presence of Proton Sponge (99%), thereby completing the C1−C22 fragment **5**.

It has been well documented that BF_3•OEt_2-catalyzed additions of enol silanes to β-alkoxy-substituted aldehydes proceed with a high level of diastereoselectivity favoring the *anti* isomer. A model proposed by Evans for 1,3-*anti* induction for BF_3•OEt_2-catalyzed enol silane additions to β-alkoxy-substituted aldehydes is shown in Scheme 17. In the illustrated transition state, the β-alkoxy tetrahydropyran orients itself *anti* to the carbonyl of the aldehyde, minimizing dipole interactions. Additionally, the system orients itself perpendicular to the carbonyl, giving the most stable staggered conformation based on sterics. The enol silane approach to the carbonyl is favored to proceed past the smaller hydrogens, giving the desired 1,3-*anti* induction. The conformer that would yield undesired 1,3-*syn* induction is destabilized via a steric interaction between the tetrahydropyran's bulky isobutyl side chain and the aldehyde carbonyl.

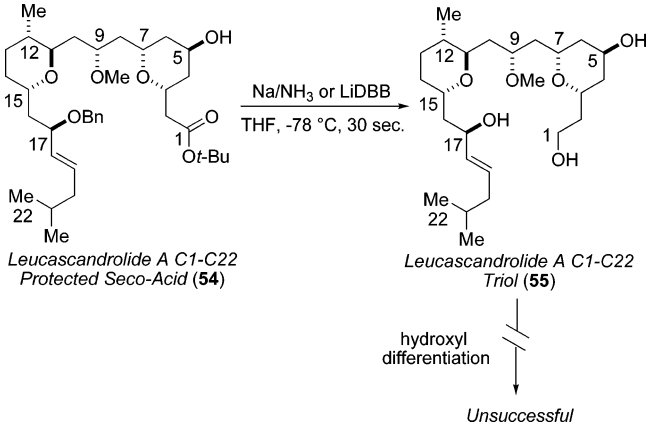
This synthesis of the leucascandrolide A C1−C22 fragment **5** completed the carbon framework of the macrocycle **3** and installed seven of the eight stereocenters of the natural product. The C1−C22 fragment **5** was now ready for the bis-tetrahydropyran to be assembled (Scheme 18). This sequence of transformations was initiated by the deprotection of the acetonide of **5** using a substoichiometric amount of 10-camphorsulfonic acid in anhydrous methanol. These conditions served to deprotect the acetonide, which spontaneously closed to form hemiacetal **53** as a 2:1 mixture of diastereomers (85%). Installation

(23) (a) Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261. (b) Evans, D. A.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8537. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (d) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

SCHEME 18. Synthesis of the Protected *seco*-Acid Fragment 54



SCHEME 19. Removal of the C17 Benzyl Ether Giving Undesired Triol



of the C7 stereochemistry was accomplished through a hydride reduction of hemiacetal **53** with $BF_3{\cdot}OEt_2$ and Et_3SiH through an intermediate oxonium ion.[12] The stereochemical outcome of the reduction is argued to be due to stereoelectronic control causing the hydride delivery to occur axially. This reaction cleanly gives the protected ester **54** of the leucascandrolide A macrolide (85%, dr > 20:1).

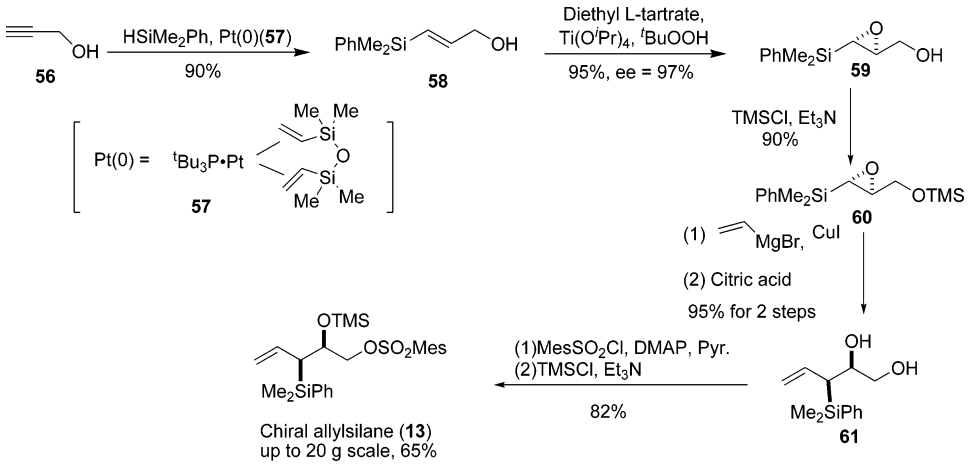
Completion of the assembly of the macrolide **3** was to be initiated by deprotection of the C17 benzyl ether, removal of the *tert*-butyl ester at C1, followed by macrolactonization. Due to the C18−C19 (*E*)-olefin in **54**, hydrogenolysis of the C17 benzyl ether was precluded. Initially, we examined dissolving metal reductions to remove the C17 benzyl ether. Unfortunately, treatment of benzyl ether **54** with either Na/NH_3[24] or lithium di-*tert*-butylbiphenyl (LiDBB)[25] in THF at −78 °C for 30 s resulted in clean benzyl ether deprotection and reduction of the *tert*-butyl ester at C1 to the primary alcohol, giving triol **55** exclusively (Scheme 19). Differentiation of the C1 primary alcohol and the C17 allylic alcohol proved unsuccessful, as attempts at monoprotection of different esters or silyl ethers gave mixtures of products. Unfortunately, the following common debenzylating reagents that were evaluated proved incompatible with the benzyl ether of **54** and resulted in extensive decomposition of the starting material along with loss of the protecting group: BCl_3,[26] $FeCl_3$,[27] DDQ,[28] and $SnCl_4$.[29]

Synthesis of the Leucascandrolide A Macrolide 3 (Route 2). During the course of our study of the synthesis of leucascandrolide A (**1**), we planned a revised route to synthesize the intriguing bis-tetrahydropyranyl ring system moiety using two consecutive pyran annulations (Scheme 3). We also believed the further development of this revised synthetic approach could lead to the synthesis of diastereomeric analogues of **1** for biological evaluation. This would be accomplished by employing a set of stereochemically diversified chiral silane reagents available in our laboratory. Syntheses of diastereomeric analogues of **1** are currently under investigation in our laboratory and will be reported at a later time.

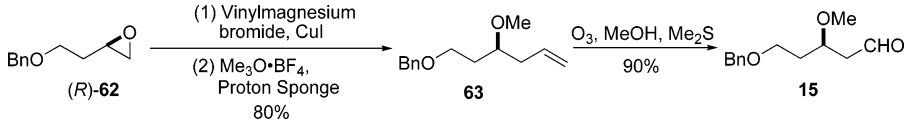
The synthesis started with hydrosilylation of commercially available propargylic alcohol **56** catalyzed by Pt(0) catalyst **57** in 90% yield (Scheme 20). Sharpless asymmetric epoxidation of the resulting allylic alcohol **58** provided the epoxy alcohol **59** in 95% yield and in excellent enantiomeric excess (ee = 97%).[30] Protection of the primary alcohol **59** as a TMS ether was necessary to achieve a high-yielding epoxide-opening reaction with vinylmagnesium bromide in the presence of CuI. This choice of protecting group shut down the potential Peterson olefination pathway, which is thought to proceed through a hypervalent silicate intermediate.[31] After exchanging the primary protecting group from a trimethylsilane to a mesitylenesulfonate (citric acid, MeOH, then $MesSO_2Cl$, DMAP, and pyridine), chiral allylsilane **13** was obtained in 65% overall yield. The sequence can be carried out on a 40 mmol scale, readily producing 20 g of the chiral allylsilane **13**. The success of this

(24) Philips, K. D.; Zemlicka, J.; Horowitz, J. P. *Carbohydr. Res.* **1973**, *30*, 281.
(25) Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791.
(26) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.
(27) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477.
(28) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 4560.
(29) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem*. **1989**, *54*, 1346.
(30) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(31) Peterson, D. J. *J. Org. Chem*. **1968**, *33*, 78.

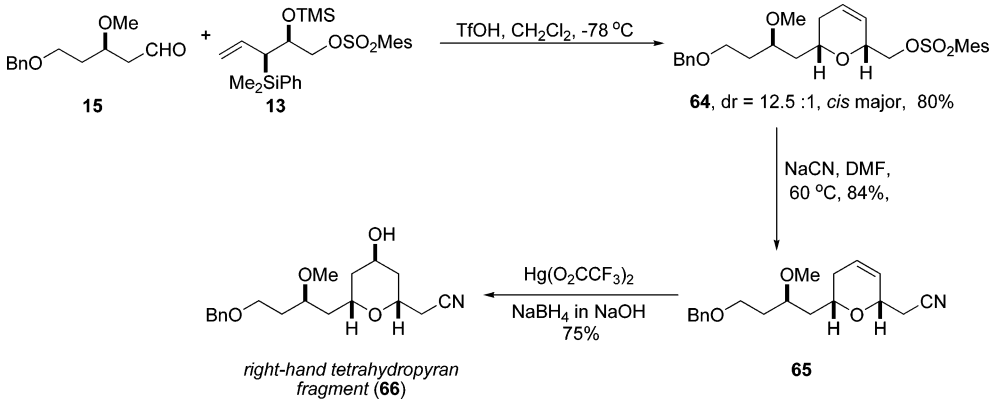
SCHEME 20. Synthesis of the Chiral *syn* Allylsilane 13



SCHEME 21. Synthesis of Aldehyde 15



SCHEME 22. Synthesis of the Right-Hand Tetrahydropyran Fragment 66



sequence for preparing chiral allylsilane reagents ensured our material supply for the synthesis of complex natural products.

The necessary [4 + 2]-annulation partner, aldehyde **15**, was readily prepared from the known chiral epoxide (*R*)-**62**, which was obtained from Jacobsen's HKR in excellent yield and enantiomeric excess (ee > 99%, Scheme 21).[7] A CuI-catalyzed opening of epoxide (*R*)-**62** was followed by methylation of the resulting secondary alcohol using Meerwein's reagent to produce methyl ether **63**. Ozonolytic cleavage of **63** provided the desired aldehyde **15** in good overall yield.

With both the chiral allylsilane and aldehyde available, we began our approach toward the synthesis of the leucascandrolide A macrolide (**3**). In that regard, we were pleased to find that annulation of aldehyde **15** with chiral allylsilane **13** proceeded smoothly in the presence of TfOH[32] to afford the desired 2,6-*cis*-dihydropyran **64** in 80% yield (dr = 12.5:1, Scheme 22). The presence of a sulfonate group in this product allowed for a necessary one-carbon homologation. An S_N2 displacement using NaCN installed a nitrile that was used as a masked carboxylate functionality and gave the one-carbon-homologated dihydropyran **65**. We next focused our attention on the installation of the C5 stereocenter. Stereocontrolled nucleophilic addition to a conformationally well-defined olefin (e.g., alkene on substituted cyclohexenes) with activation by an electrophile is documented in the elegant work of Brown. This work demonstrated that a highly diastereoselective functionalization of unsaturated six-membered rings could be achieved by an oxymercuration reaction.[33] Gratifyingly, the oxymercuration of the double bond of dihydropyran **65** using mercury(II) trifluoroacetate, followed by a subsequent reductive demercuration using $NaBH_4$, installed the required C5 axial hydroxyl group as a single regio- and diastereoisomer.

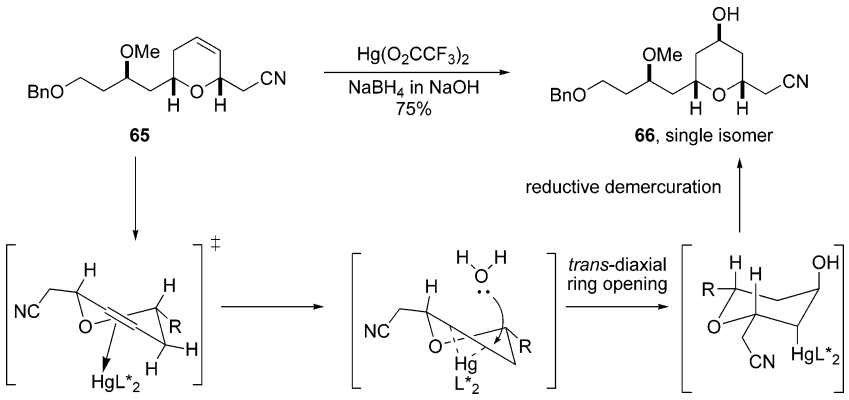
While many mechanistic scenarios can be envisioned, one possible explanation suggests the regio- and stereochemical course of the oxymercuration may be determined from steric and electronic considerations; *trans* diaxial trapping of the mercuronium ion leads to a chair-like TS, where an equatorial opening would lead to a *trans*-diequatorial product thought a higher energy boat-like TS (Scheme 23).[34] The mercuronium

(32) Huang, H.; Panek, J. S. *Org. Lett*. **2004**, *6*, 4383.

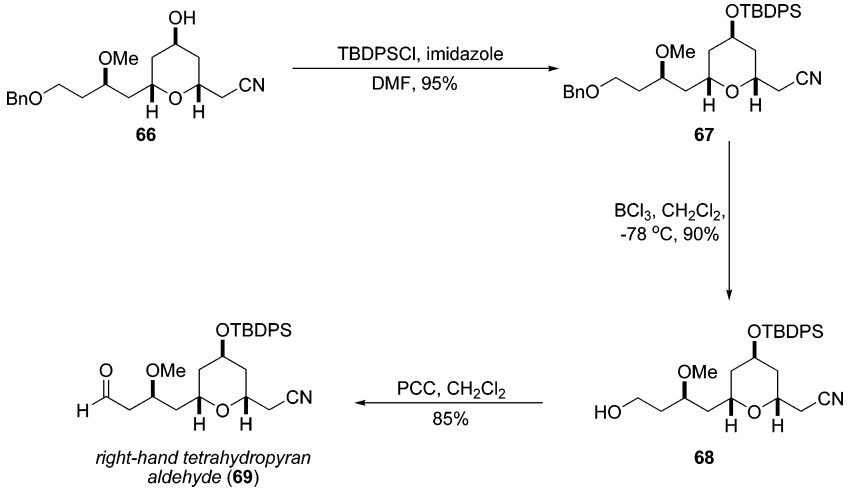
(33) Brown, H. C.; Geoghegan, P., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1522.

(34) (a) Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc*. **1971**, *93*, 6902. (b) Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 6909. (c) Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 7480. (d) Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 719.

SCHEME 23. Proposed Pathway for Oxymercuration of Dihydropyran 65



SCHEME 24. Synthesis of the Aldehyde Fragment 69



species underwent a regioselective attack by a nucleophile (H_2O) to produce a *trans*-diaxial intermediate (Fürst−Plattner rule).[35] Subsequent reductive demercuration afforded the hydroxyl pyran **66** in 75% yield.

The requisite aldehyde **69** to be used in the second [4 + 2]-annulation was obtained in a straightforward three-step reaction sequence. Protection of the C5 secondary alcohol **66** as a TBDPS ether was followed by subsequent debenzylation with BCl_3 that furnished the primary alcohol **68** (Scheme 24). A pyridinium chlorochromate (PCC) oxidation of the resulting alcohol provided aldehyde **69**.

After obtaining the β-methoxy aldehyde, our efforts were then directed to the second crucial [4 + 2]-annulation between aldehyde **69** and chiral crotylsilane **14**. Under the previously described annulation conditions (TMSOTf, DCM, −50 °C),[5,36] the reaction between aldehyde **69** and chiral crotylsilane **14a** proceeded smoothly, however, with a low selectivity (dr (2,6-*cis*/2,6-*trans*) = 1:2) of the newly formed left-hand dihydropyran (entry 1, Table 2). Considerable experimentation was needed to optimize the selectivity of this annulation, and the important results are summarized in Table 2.

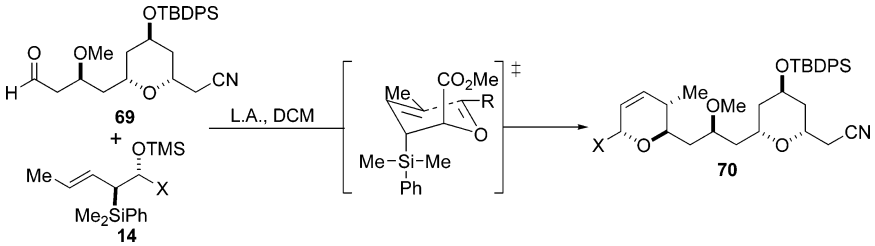
Annulation of silane **14b**, bearing an acetoxy group, with aldehyde **69** afforded the left-hand dihydropyran yet with lower selectivity (entry 2, Table 2). During experiments designed to optimize the selectivity of this annulation, a fact came to our attention that, for a monosubstituted cyclohexane ring, the *A* value of an ethyl ester is around 0.2 kcal/mol lower than that of a methyl ester ($A_{\text{methylester}}$ = 1.3 kcal/mol, $A_{\text{ethylester}}$ = 1.1 kcal/mol; *A* value is the free energy required for substituted groups to go from the equatorial position to the axial position and is used to demonstrate the extent of preference for the substituent to adopt the equatorial orientation).[37] In one of the possible transition states for this annulation, an axial orientation of the methyl ester would produce a *trans*-dihydropyran (inset, Table 2). Therefore, using this loose analogy, silane **14c** was synthesized and tested in the annulation reaction. Interestingly, a slight increase of selectivity was observed in this annulation (entry 3 vs entry 1, Table 2). Encouraged by this result, we synthesized the isopropyl derivative crotylsilane **14**, obtained by transesterification of corresponding methyl ester **14a** with isopropyl alcohol. To our delight, enhanced selectivity for the 2,6-*trans* isomer was observed (dr (2,6-*cis*/2,6-*trans*) = 1:5). Considering the instability of the *tert*-butyl group to the acidic reaction conditions, no further attempt to increase the steric bulkiness of the ester moiety of the silane reagent **14** was made. Another trial based on the consideration of *A* value was carried out, employing a cyanosilane (A_{CN} = 0.2 kcal/mmol) in this annulation. However, to our disappointment, the resulting cyanohydrin crotylsilane **14d** (X = CN, not shown) failed to participate in the annulation and was recovered intact after the

(35) (a) Fürst, A.; Plattner, A. *Helv. Chim. Acta* **1949**, *32*, 275. (b) Henbest, H. B.; Smith, M.; Thomas, A. *J. Am. Chem. Soc.* **1958**, *80*, 3253.

(36) (a) Huang, H.; Panek, J. S. *Org. Lett.* **2003**, *5*, 1991. (b) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, *SI*, 955.

(37) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; p 174.

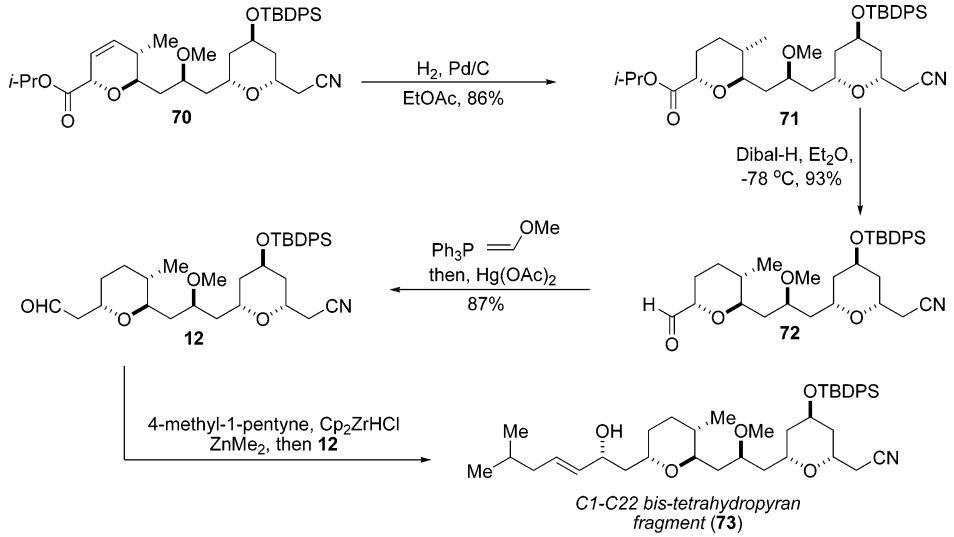
TABLE 2. Optimization of the Second [4 + 2]-Annulation[a]



entry	silane (X)	reaction temperature	Lewis acid	conversion (dr) 2,6-*trans*/2,6-*cis*)[a]
1	**14a** (CO_2Me)	−50 °C	TMSOTf	100% (2:1)
2	**14b** (CH_2OAc)	−50 °C	TMSOTf	100% (1:1)
3	**14c** (CO_2Et)	−50 °C	TMSOTf	100% (3:1)
4	**14** (CO_2iPr)	−50 °C	TMSOTf	100% (5:1)

[a] The % conversion and % dr were measured by ^1H NMR (400 MHz) analysis of the crude reaction mixture.

SCHEME 25. Synthesis of the C1−C22 Bis-tetrahydropyran Fragment 73



reaction. One possible explanation for the loss of the reactivity can be attributed to the strong electron-withdrawing ability of CN, therefore resulting in the attenuation of nucleophilicity of the neighboring silyl ether.

Having discovered the optimal conditions for the second annulation to produce **70** with useful selectivity (5:1) and yield (73%), we were ready to install the C17−C22 side chain while establishing the C17 stereocenter of the macrolactone (**3**). Reduction of dihydropyran **70** under a hydrogen atmosphere catalyzed by Pd/C produced the bis-tetrahydropyran **71** in 86% yield (Scheme 25). A fully chemoselective reduction of the tetrahydropyran isopropyl ester was carried out using DIBAL-H (2.1 equiv) in diethyl ether at −78 °C, thus providing aldehyde **72** in 93% yield. Homologation of aldehyde **72** via a phosphorus-based olefination with methoxymethylenetriphenylphosphine and subsequent mercury acetate-mediated hydrolysis of the resulting enol ether furnished aldehyde **12** in 87% yield over two steps.

At this stage, our approach called for the selective introduction of the C17 allylic alcohol, which we anticipated would take place with the use of a vinylmetal species. A one-pot preparation of the vinyl zinc reagent from an alkyne reported by Wipf was an attractive option.[38] Accordingly, hydrozirconation of 4-methyl-1-pentyne followed by transmetalation to the vinyl zinc species using dimethyl zinc afforded the desired vinyl zinc reagent. Addition of the alkenyl zinc to aldehyde **12** afforded allylic alcohol in a good combined yield (80%), albeit with disappointingly low selectivity ((*R*)-**17**:(*S*)-**17** = 2:1). To our satisfaction, the desired (*R*)-**17** alcohol **73** could be obtained in 53% yield as a single diastereomer after careful chromatographic separation of the two isomers.

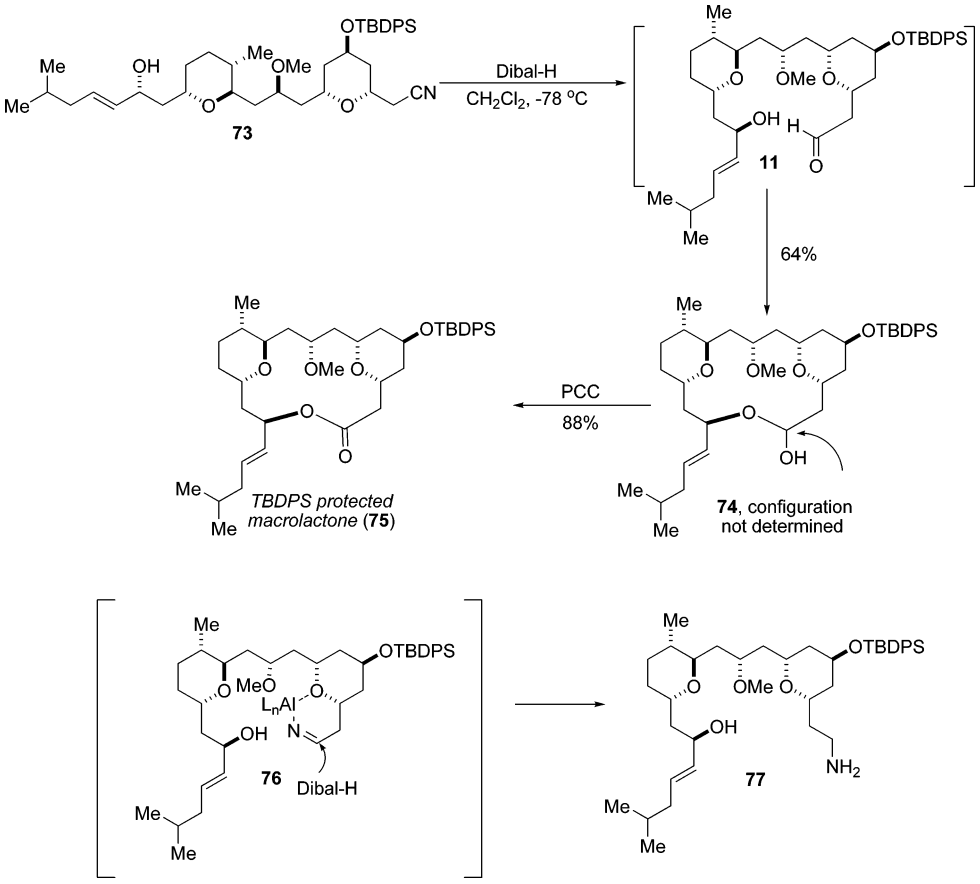
With the advanced hydroxyl nitrile **73** in hand, we were ready to examine the cyclization of this intermediate to form the macrolide. Inspired by the spontaneous lactol formation reported by Kozmin, we employed a similar set of conditions for our macrolactonization strategy.[3b] Accordingly, reduction of the nitrile group using a cold solution of DIBAL-H (−78 °C) in CH_2Cl_2 was followed by an acidic hydrolysis of the resulting imine to afford a transient hydroxyaldehyde **11** (Scheme 26). Gratifyingly, we found that this hydroxyaldehyde cyclized to form macrolactol **74**[39] at room temperature in 64% yield.

During the study of this macrolactol formation, an unexpected minor product **77** was observed. The primary amine **77** presumably results from over reduction of intermediate **76** and was isolated in variable quantities depending on the amount of DIBAL-H employed in the reaction. This observation implicates

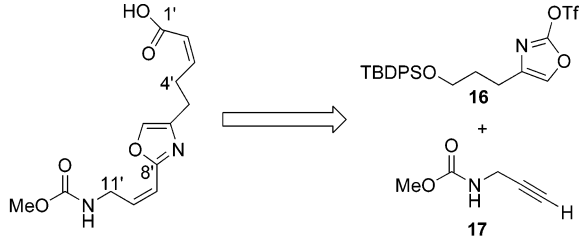
(38) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.

(39) Spontaneous lactolization produced **77** as a single diastereomer. However, the absolute stereochemistry was not determined.

SCHEME 26. Synthesis of the Leucascandrolide A TBDPS-Protected Lactone 75



SCHEME 27. Retrosynthetic Analysis of the C1′−C11′ Oxazole



C1′-C11′ leucascandrolide A side chain (**4**)

a possible involvement of activated intermediate **76** in the reduction process, which serves as circumstantial evidence for the preorganized conformation of the acyclic precursor **11**, which would properly align the π^* orbital of the aldehyde or imine for cyclization. Oxidation of **74** to the macrolactone **75** using PCC was followed by TBAF-promoted desilylation to furnish the completed leucascandrolide A macrolactone (**3**).

Synthesis of the Leucascandrolide A C1′−C11′ Oxazole Fragment (4) via a Sonogashira Coupling. Concurrent with our efforts toward the leucascandrolide A macrolide (**3**) was an efficient and high-yielding synthesis of the leucascandrolide A oxazole side chain (**4**). From a retrosynthetic perspective, disconnection at the C8′−C9′ bond revealed the two potential coupling partners: 2-trifloyloxazole **16** and terminal alkyne **17** (Scheme 27).

The synthesis began with the TBDPS protection of commercially available 4-penten-1-ol, giving silyl ether **78**, which was followed by dihydroxylation of the terminal olefin (OsO_4, TMANO) to afford racemic diol (±)-**79** (Scheme 28). Selective oxidation of the secondary alcohol using the conditions described by Ishii, 1.6 mol % of pyridinium peroxotungstophosphate (**80**) and H_2O_2, gave the hydroxy ketone **81** in 95% yield.[40] Cyclization of **81** to oxazolone **82** was accomplished using a three-step, one-pot protocol. Treatment of **81** with a solution of phosgene in toluene, followed by exposure to aqueous NH_4OH, and then brief acidification with concentrated H_2SO_4 (pH < 3.5) afforded oxazolone **82** in 85% yield. Treatment of **82** with 2,6-lutidine and trifluoromethanesulfonic anhydride (Tf_2O) completed the synthesis of the C3′−C8′ 2-trifloyloxazole **16**.

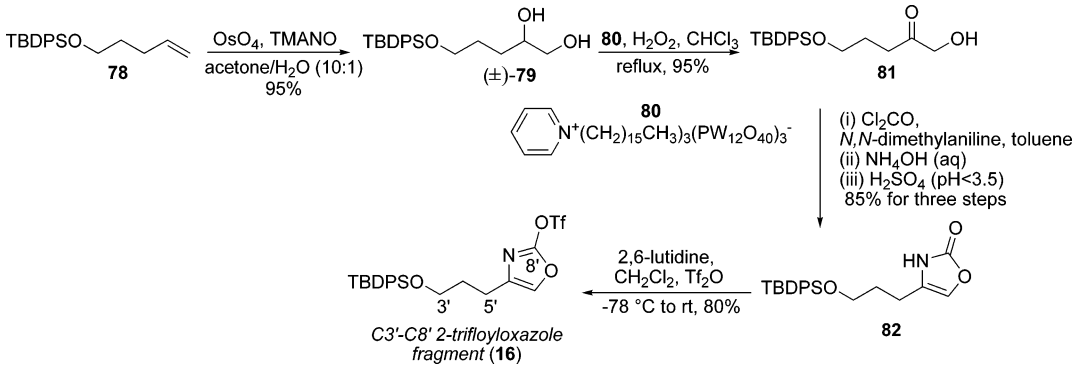
Alkyne **17** was synthesized through the addition of propargylamine (**83**) to methyl chloroformate (**84**), giving carbamate **17** in 75% yield (Scheme 29).

In an effort to expand the use of our earlier work concerning the development of Pd(0)-mediated cross-coupling of trifloyl-substituted heterocycles,[41] we sought an alternative coupling strategy that would allow for the construction of the key leucascandrolide A oxazole side chain intermediate **86**. Hoping that the 2-trifloyloxazole fragment **16** would not be limited to cross-couplings with organotin species, we explored the viability of a Sonogashira cross-coupling strategy. In this case, the alkynylmetal species **85** is copper-based and is generated in situ from a catalytic amount of Cu(I) (Scheme 30).

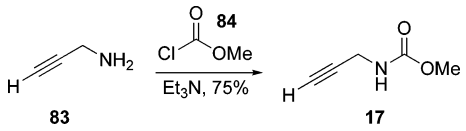
To determine the feasibility of the approach, we tested reaction conditions using the 2-trifloyloxazole **16** and alkyne **17**. With our initial Sonogashira coupling conditions (5% Pd(PPh_3)$_4$, 10% CuI, DMF, Et_3N, 65 °C, Table 3, entry 1), only

(40) Sakata, Y.; Ishii, Y. *J. Org. Chem.* **1991**, *56*, 6233.
(41) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469.

SCHEME 28. Synthesis of the 2-Trifloyloxazole Fragment 16



SCHEME 29. Synthesis of the Alkyne Fragment 17



SCHEME 30. Retrosynthesis of the C3′−C11′ Oxazole Fragment 86

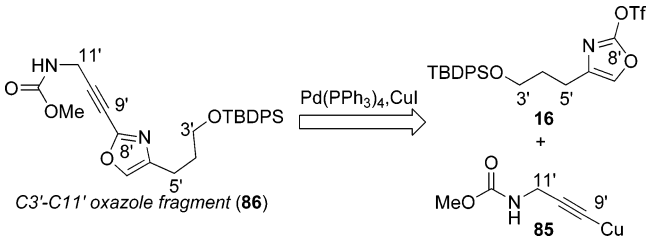
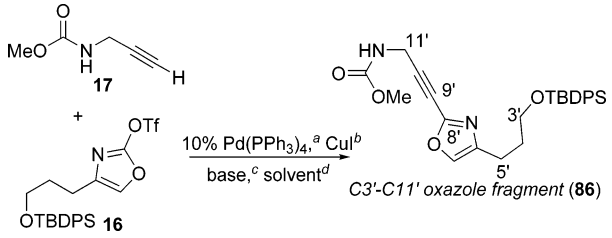


TABLE 3. Optimization of the Sonogashira Coupling of Fragments 16 and 17



entry	base	solvent	temp	time (h)	yield (%)[e]
1	Et_3N	DMF	65 °C	12	trace
2	2,6-lutidine	DMF	65 °C	12	55
3	2,6-lutidine	DMF	rt	12	trace
4	2,6-lutidine	dioxane	rt	4	84

[a] A brief Pd(0) source screen determined $Pd(PPh_3)_4$ was optimal. [b] A copper(I) source screen determined the following reactivity trend: CuI > CuBr > $(CH_3CN)_4CuPF_6$ > CuCl; 10 mol % of CuI was used. [c] Five equivalents of amine base were used. [d] Reactions run 0.3 M in solvent. [e] Isolated yield after SiO_2 chromatography.

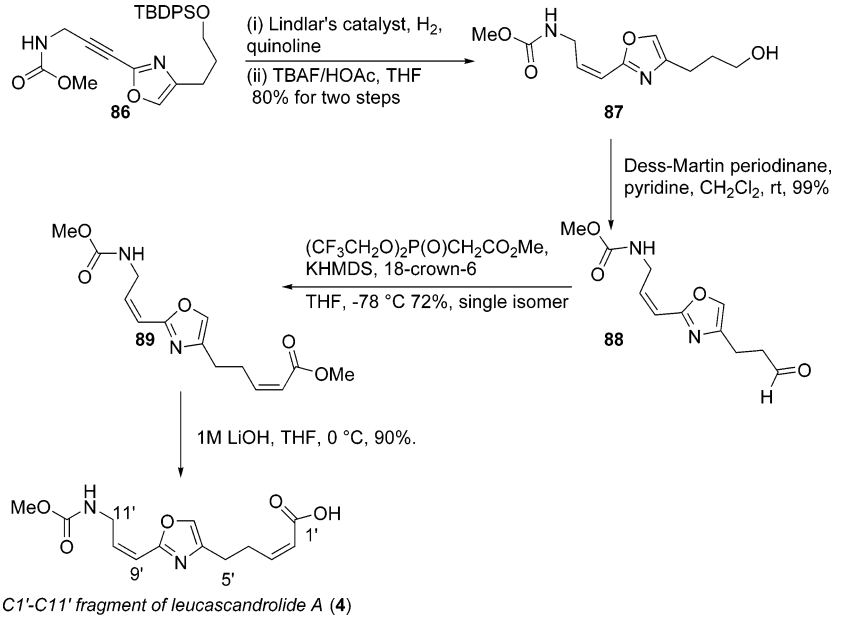
a trace amount of desired oxazole product **86** was obtained (<10% isolated yield), along with decomposition products of the 2-trifloyloxazole **16**. Due to the relative chemical instability of **16**, we sought milder conditions for the cross-coupling. In control experiments to examine the stability of 2-trifloyloxazole **16** in the reaction, it was observed that Et_3N caused extensive decomposition of **16** in approximately 25 min. Seeking a compatible amine, we examined a number of alternatives that could promote coupling without destroying the sensitive 2-trifloyloxazole **16**. Notably, treatment of **16** with 2,6-lutidine in DMF did not promote any unwanted decomposition even after 6 h. Indeed, substitution of Et_3N with 2,6-lutidine in DMF at 65 °C afforded the desired C3′−C11′ coupling fragment **86**, albeit in a modest 55% yield along with triflate decomposition products (Table 3, entry 2). In efforts to preserve the chemical integrity of **16** throughout the reaction, we attempted to lower the reaction temperature. Unfortunately, this approach did not yield significant amounts of the coupled fragment (<10% isolated yield). Empirically, it was determined that a solvent substitution of 1,4-dioxane for DMF greatly increased the efficiency of the Sonogashira coupling. Although the precise reasons for this remain unclear, the coupling now proceeded smoothly at ambient temperature with 2,6-lutidine in dioxane to provide the key C3′−C11′ coupling fragment **86** in 84% yield in only 4 h (Table 3, entry 4).

With the alkynyl oxazole **86** in hand, a straightforward sequence was used to complete the C1′−C11′ oxazole side chain of leucascandrolide A (**4**) (Scheme 31). Installation of the C9′−C10′ (*Z*)-olefin using a Lindlar reduction, followed by removal of the silyl protecting group with TBAF buffered with acetic acid gave the alcohol **87** in 80% yield for the two steps. Oxidation of this intermediate using Dess−Martin periodinane in the presence of pyridine cleanly afforded aldehyde **88** in 99% yield. A Still−Gennari olefination[42] installed the C2′−C3′ (*Z*)-olefin as a single isomer in 72% yield and completed the C1′−C11′ carbon chain, giving fragment **89**. Finally, hydrolysis of the C1′ methyl ester with aqueous 1 M LiOH completed the synthesis of the C1′−C11′ leucascandrolide A oxazole side chain (**4**).

Completion of the Total Synthesis of Leucascandrolide A (1). After completing the assembly of the side chain and with the macrolide in hand, we were positioned to complete the total synthesis of **1**. In this regard, it has been documented that the direct acylation of the axially oriented C5 hydroxyl group with the fully elaborated side chain **4** is difficult to achieve, due to the hindered nature of the alcohol and the (*Z*)-α,*β*-unsaturated carboxylic acid. Therefore, a Mitsunobu esterification method was employed to install the fully functionalized side chain onto the macrolide (Scheme 32). Accordingly, the C5 axial alcohol **3** was inverted to its equatorial isomer **91** using a two-step oxidation and reduction sequence. Dess−Martin periodinane oxidation of **3** furnished ketone **90** in a 95% yield. Reduction of ketone **90** with $NaBH_4$ produced the equatorial alcohol **91** (95%, dr = 14:1), consistent with an axially favored addition of the small hydride source to a conformationally biased cyclohexanone. Finally, union of the macrolactone **91** and the

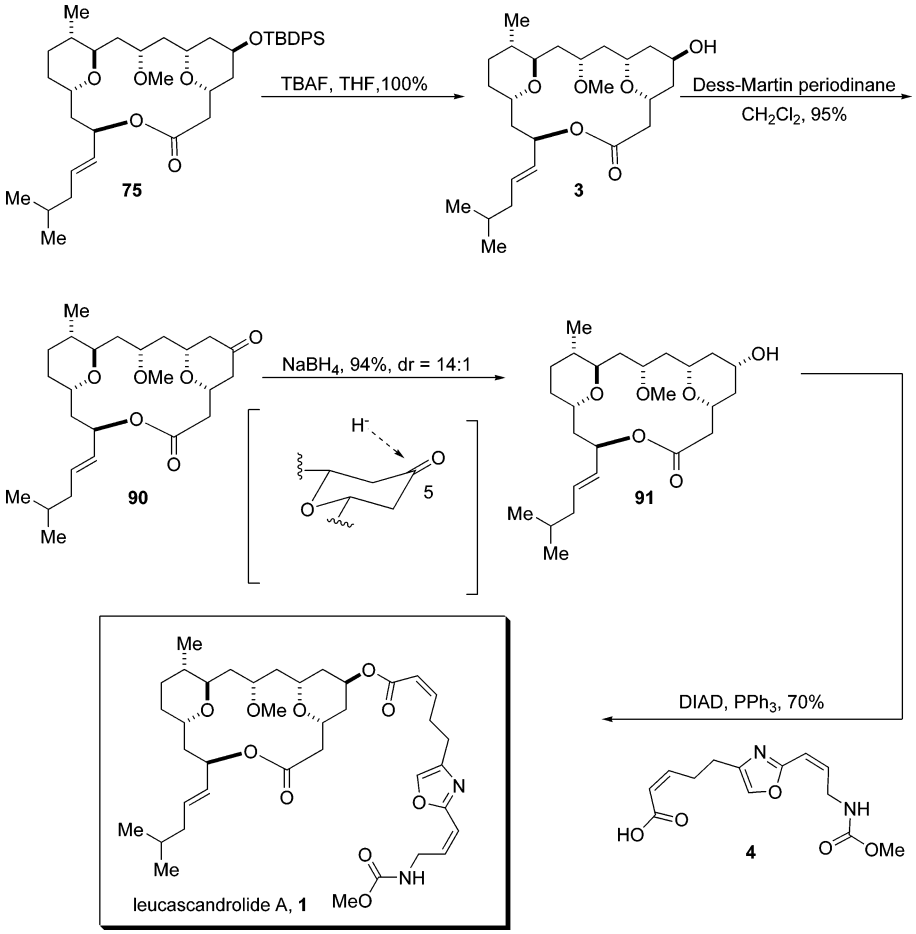
(42) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

SCHEME 31. Synthesis of the Leucascandrolide A Side Chain 4



C1′-C11′ fragment of leucascandrolide A (**4**)

SCHEME 32. Completion of Leucascandrolide A (1)



oxazole-containing side chain **4** under Mitsunobu conditions (DIAD, TPP) proceeded in 70% yield and completed our total synthesis of leucascandrolide A, **1**.[43]

Conclusions

In summary, a convergent total synthesis of the marine natural product, leucascandrolide A (**1**), was completed. The synthesis was accomplished in 17 steps over the longest linear sequence and in a 3.7% overall yield starting from readily available chiral

(43) Mitsunobu, O. *Synthesis* **1981**, 1.

silane reagent **13**. This synthesis was highlighted by the chiral silane-based methodology for the asymmetric synthesis of dihydropyrans and a Pd(0)-mediated Sonogashira cross-coupling to efficiently assemble the oxazole-containing side chain. This leucascandrolide A synthesis underscores the salient utility of chiral organosilane reagents in the stereocontrolled construction of oxygen heterocycles and their subsequent use in the enantioselective synthesis of complex natural products.

Experimental Section

General experimental details and spectra of key intermediates 64, 74, and 75 as well as leucascandrolide A (**1**) can be found in the Supporting Information.

(3*R*)-Benzyloxy-4-(*tert*-butyldiphenylsilanyloxy)butyric Acid Benzyl Ester (23). To a 250 mL round-bottom flask charged with a magnetic stir bar and 4.24 g (20.17 mmol) of (3*R*)-4-dihydroxybutyric acid benzyl ester was added 41 mL of anhydrous DMF. Imidazole (2.20 g/32.272 mmol) was added, the reaction was cooled to 0 °C, and *tert*-butyldiphenylsilyl chloride (5.74 mL/21.78 mmol) was added via syringe, and the reaction was allowed to stir for 2 h at 0 °C. The reaction was then diluted with ∼100 mL of H_2O and extracted 3 times with Et_2O. The combined organic extracts were then washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to give the crude reaction product which was purified by flash chromatography (SiO_2, 5% → 10% EtOAc/hexanes) giving 9.45 g (99%) of desired secondary alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.58 (2H, dd, J = 2.0, 4.8 Hz), 2.84 (1H, d, J = 4.8 Hz), 3.64 (2H, ddd, J = 4.4, 10.0, 15.2 Hz), 4.17 (1H, dddd, J = 3.6, 4.8, 10.0, 15.2 Hz), 5.11 (2H, s), 7.33−7.41 (11H, m), 7.62 (4H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 26.9, 38.2, 66.5, 66.7, 68.7, 127.8, 128.2, 128.6, 129.8, 133.1, 135.5, 135.7, 171.8; IR (neat) ν_{max} 3506, 3071, 2931, 2858, 1734, 1589, 1472, 1361, 1217, 1111, 998, 740; HRMS (CI, NH_3) m/z calcd for $C_{27}H_{32}O_4Si_1$ $[M + H]^+$ 449.2148, found 449.2131; $[\alpha]^{23}_D$ = +12.16° (c = 0.49, $CHCl_3$). To a 250 mL round-bottom flask charged with a magnetic stir bar and 9.45 g (21.06 mmol) of secondary alcohol was added 84 mL of anhydrous Et_2O. 2,2,2-Trichloroacetimidic acid benzyl ester (5.28 mL/28.44 mL) was added, and the reaction was cooled to 0 °C. Trifluoromethanesulfonic acid (60 μL/0.632 mmol) was added via syringe, and the reaction was allowed to warm slowly to room temperature with stirring over 12 h. The reaction was quenched by the addition of ∼100 mL of saturated aqueous solution of $NaHCO_3$. The layers were separated, and the aqueous layer was extracted 3 times with Et_2O. The combined organic extracts were then washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to give the crude reaction product which was purified by flash chromatography (SiO_2, 5% EtOAc/hexanes) giving 11.92 g (99%) of benzyl ether **23** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.62 (1H, dd, J = 8.0, 15.8 Hz), 2.74 (1H, dd, J = 4.8, 15.8 Hz), 3.64 (1H, dd, J = 5.4, 10.4 Hz), 3.74 (1H, dd, J = 5.4, 10.4 Hz), 4.03 (1H, dddd, J = 5.4, 10.4, 14.0, 15.8 Hz), 4.51 (2H, q_{AB}, J = 11.6 Hz), 5.09 (2H, q_{AB}, J = 12.8 Hz), 7.18−7.41 (16H, m), 7.59−7.63 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 26.9, 37.7, 65.4, 66.4, 72.5, 76.6, 127.5, 127.8, 128.2, 128.3, 128.5, 129.8, 133.3, 133.4, 135.6, 136.0, 138.5, 171.5; IR (neat) ν_{max} 3069, 2931, 2858, 1737, 1497, 1472, 1455, 1428, 1361, 1260, 1168, 1028, 739; HRMS (CI, NH_3) m/z calcd for $C_{34}H_{39}O_4Si_1$ $[M + H]^+$ 539.2617, found 539.2629; $[\alpha]^{23}_D$ = +11.92° (c = 0.97, $CHCl_3$).

(3*R*)-Benzyloxy-4-(*tert*-butyldiphenylsilanyloxy)butryaldehyde (24). To a 500 mL round-bottom flask charged with a magnetic stir bar and 11.09 g (20.58 mmol) of benzylester **23** was added 206 mL of anhydrous CH_2Cl_2. The reaction was cooled to −78 °C, and 51.46 mL of a 1 M solution of DIBAL-H in hexanes was added dropwise via syringe. The reaction was stirred for 15 min at −78 °C before being quenched with ∼20 mL of MeOH. The reaction was stirred to room temperature and diluted with ∼100 mL of H_2O. The layers were separated, and the aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic extracts were washed with ∼100 mL of 5% HCl, water, dried with $MgSO_4$, filtered, and concentrated giving the crude reaction product which was purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) giving 7.30 g (82%) of aldehyde **24** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.69 (2H, d, J = 6.0 Hz), 3.67 (1H, dd, J = 5.6, 10.4 Hz), 3.77 (1H, dd, J = 4.4, 10.4 Hz), 4.00−4.04 (1H, m), 4.53 (2H, q_{AB}, J = 12.0 Hz), 7.23−7.42 (11H, m), 7.60−7.63 (4H, m), 9.77 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.6, 26.8, 46.3, 65.2, 72.1, 74.9, 127.8, 128.0, 128.4, 129.6, 129.8, 133.1, 133.2, 134.8, 135.6, 138.1, 200.9; IR (neat) ν_{max} 3071, 2931, 2858, 1728, 1472, 1428, 1391, 1361, 1113, 1028, 740; HRMS (CI, NH_3) m/z calcd for $C_{27}H_{33}O_3Si_1$ $[M + H]^+$ 433.2199, found 433.2188; $[\alpha]^{23}_D$ = +20.27° (c = 1.12, $CHCl_3$).

(6*R*)-Benzyloxy-7-(*tert*-butyldiphenylsilanyloxy)hept-1-en-(4*S*)-*tert*-butyldimethylsilanol (25). To a 250 mL round-bottom flask charged with a magnetic stir bar and 5.63 g (13.01 mmol) of aldehyde **24** was added 44 mL of anhydrous CH_2Cl_2. The reaction was cooled to −78 °C, and 2.96 mL (15.62 mmol) of freshly distilled $TiCl_4$ was added dropwise via syringe. The reaction was allowed to stir for 5 min before 3.31 mL (20.82 mmol) of allyltrimethylsilane was added via syringe. The reaction was stirred for 20 min at −78 °C before the addition of ∼10 mL of EtOAc. The reaction was allowed to stir for 5 min followed by the addition of ∼50 mL of saturated aqueous $NaHCO_3$. The reaction mixture was extracted 3 times with CH_2Cl_2, the combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated. The crude reaction mixture was purified by flash chromatography (SiO_2, 5% → 15% EtOAc/hexanes) giving 4.94 g (80%, de > 20:1) of desired homoallylic alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.59−1.63 (1H, m), 1.64−1.78 (1H, m), 2.18 (2H, t, J = 7.2 Hz), 2.49 (1H, d, J = 3.6 Hz), 3.66−3.69 (1H, m), 3.70−3.79 (2H, m), 3.81−3.89 (1H, m), 4.58 (2H, q_{AB}, J = 11.6 Hz), 5.05 (1H, s), 5.08 (1H, d, J = 5.2 Hz), 5.73−5.84 (1H, m), 7.24−7.42 (11H, m), 7.64−7.67 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.9, 38.0, 42.3, 66.0, 67.7, 72.4, 117.5, 127.7, 127.9, 128.4, 129.8, 133.3, 133.4, 133.5, 134.9, 135.6, 138.5; IR (neat) ν_{max} 3457, 3071, 2930, 3858, 1653, 1641, 1589, 1472, 1391, 1028, 998, 824; HRMS (CI, NH_3) m/z calcd for $C_{30}H_{39}O_3Si_1$ $[M + H]^+$ 475.2668, found 475.2666; $[\alpha]^{23}_D$ = +23.41° (c = 0.68, $CHCl_3$). To a 250 mL round-bottom flask charged with a magnetic stir bar and 4.30 g (9.06 mmol) of the resulting homoallylic alcohol was added 45 mL of anhydrous CH_2Cl_2. To the mixture was added 2,6-lutidine (4.22 mL/36.2 mmol), and the reaction was cooled to 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (3.12 mL/13.59 mmol) was added via syringe, and the reaction was stirred for 2 h before being diluted with ∼100 mL of H_2O. The layers were separated, and the aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried with $MgSO_4$, and concentrated. The crude reaction mixture was purified by flash chromatography (SiO_2, 5% EtOAc/hexanes) giving 5.15 g (97%) of bis-silyl ether **25** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (3H, s), −0.01 (3H, s), 0.88 (9H, s), 1.05 (9H, s), 1.52−1.69 (2H, m), 2.17−2.28 (2H, m), 3.61−3.78 (3H, m), 3.95−4.01 (1H, m), 4.58 (2H, q_{AB}, J = 11.6 Hz), 4.99 (1H, d, J = 6.8 Hz), 5.02 (1H, s), 5.74−5.84 (1H, m), 7.22−7.43 (11H, m), 7.66 (4H, t, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −3.9, 18.1, 19.2, 25.8, 26.9, 39.8, 42.8, 66.8, 68.8, 71.8, 116.9, 127.3, 127.4, 127.5, 127.7, 128.2, 129.6, 133.7, 134.8, 135.6, 139.2; IR (neat) ν_{max} 3072, 2956, 1472, 1361, 1256, 998, 913, 739; HRMS (CI, NH_3) m/z calcd for $C_{36}H_{52}O_3Si_2$ $[M + H]^+$ 589.3533, found 589.3566; $[\alpha]^{23}_D$ = +26.62° (c = 0.71, $CHCl_3$).

(5*R*)-Benzyloxy-(3*S*)-(*tert*-butyldimethylsilanyloxy)-6-(*tert*-butyldiphenylsilanyloxy)hexan-1-ol (26). To a 500 mL round-bottom flask charged with a magnetic stir bar and 5.15 g (8.74 mmol) of terminal olefin **25** were added 175 mL of MeOH and 20 mL of CH_2Cl_2. Pyridine (2.83 mL/34.96 mmol) was added, and the reaction was cooled to −78 °C. Ozone was bubbled through the reaction for 45 min before dimethyl sulfide (6.42 mL/87.44 mmol) was added, and the reaction was allowed to warm slowly to room

temperature with stirring for 12 h. The solvent was removed under vacuum, giving the crude aldehyde which was immediately dissolved in 50 mL of MeOH. The reaction was cooled to 0 °C, and $NaBH_4$ (0.826 g/21.85 mmol) was added in one portion. The reaction was stirred for 20 min at 0 °C before being quenched by the addition of ~50 mL of a saturated aqueous solution of NH_4Cl. The layers were separated, and the aqueous layer was re-extracted 3 times with EtOAc. The combined organic extracts were washed with H_2O, dried with $MgSO_4$, and concentrated. The crude reaction product was purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) giving 3.80 g (75%) of primary alcohol **26** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 1.05 (9H, s), 1.59−1.64 (1H, m), 1.72−1.86 (3H, m), 2.03 (1H, br s), 3.58−3.72 (3H, m), 3.74−3.82 (2H, m), 4.06−4.10 (1H, m), 4.53 (2H, q_{AB}, J = 11.6 Hz), 7.24−7.42 (11H, m), 7.61−7.69 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, −4.3, 17.9, 19.2, 25.9, 26.9, 39.2, 39.8, 59.8, 66.3, 69.1, 71.7, 127.5, 127.6, 127.7, 128.3, 129.7, 133.4, 133.5, 135.6, 138.8; IR (neat) ν_{max} 3428, 3071, 2930, 2857, 1472, 1428, 1389, 1257, 1113, 836; HRMS (CI, NH_3) m/z calcd for $C_{35}H_{53}O_4Si_2$ $[M + H]^+$ 593.3482, found 593.3471; $[\alpha]^{23}_D$ = +15.52° (c = 0.71, $CHCl_3$).

(5*R*)-Benzyloxy-1-iodo-(3*S*)-(*tert*-butyldimethylsilanyloxy)-6-(*tert*-butyldiphenylsilanyloxy)hexane (27). To a 100 mL round-bottom flask charged with a magnetic stir bar and 4.16 g (7.02 mmol) of primary alcohol **26** was added 15 mL of anhydrous DMF. The reaction was cooled to 0 °C, $(PhO)_3P^+CH_3I^-$ (4.76 g/10.53 mmol) was added in one portion, and the reaction was stirred for 1 h at 0 °C before being diluted with ~50 mL of Et_2O. The reaction was poured onto water (~150 mL) and extracted 3 times with Et_2O. The combined organic extracts were then washed 4 times with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to give the crude reaction product which was purified by flash chromatography (SiO_2, 2.5% EtOAc/hexanes) giving 4.53 g (92%) of iodide **27** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 1.05 (9H, s), 1.57−1.63 (1H, m), 1.68−1.74 (1H, m), 1.94−2.06 (2H, m), 3.12−3.17 (2H, m), 3.59−3.63 (2H, m), 3.71−3.76 (1H, m), 3.87−3.91 (1H, m), 4.53 (2H, q_{AB}, J = 11.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.3, −4.1, 1.9, 18.0, 19.2, 25.9, 26.9, 39.7, 42.3, 66.2, 70.1, 127.4, 127.6, 127.7, 128.3, 129.7, 133.4, 133.5, 135.6, 138.8; IR (neat) ν_{max} 2955, 2929, 2857, 1472, 1428, 1361, 1257, 1217, 1006, 938; HRMS (CI, NH_3) m/z calcd for $C_{35}H_{51}I_1O_3Si_2$ $[M + H]^+$ 703.2459, found 703.2464; $[\alpha]^{23}_D$ = +12.38° (c = 0.42, $CHCl_3$).

(7*R*)-Benzyloxy-(5*S*)-(*tert*-butyldimethylsilanyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-2-methyloctanoic acid ((2*R*)-hydroxy-(1*R*)-methyl-2-phenylethyl)methyl amide (29). To a 250 mL round-bottom flask charged with a magnetic stir bar was added 3.4 g (24.64 mmol) of anhydrous LiCl. The flask was placed under vacuum, and the LiCl was flame-dried. The flask was allowed to cool under vacuum, removed, and immediately purged with argon. Diisopropylamine (3.71 mL/26.49 mmol) was added followed by 18 mL of anhydrous THF. The suspension was cooled to −78 °C, and 9.86 mL of a 2.5 M solution of *n*-BuLi in hexanes was added dropwise via syringe. The suspension was allowed to warm to room temperature for 5 min before being recooled to −78 °C. A 0 °C solution of 2.86 g (12.93 mmol) of (−)-pseudoephedrine amide **28** in 40 mL of anhydrous THF was then added dropwise via syringe. The reaction was stirred for 1 h at −78 °C, 15 min at 0 °C, and 5 min at room temperature before being recooled to 0 °C. A solution of 4.33 g (6.16 mmol) of alkyl iodide **27** in 10 mL of anhydrous THF was then added dropwise to the reaction. The reaction was then allowed to stir at 0 °C for 8 h before being quenched by the addition of ~100 mL of a saturated aqueous solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted 3 times with EtOAc. The combined organic extracts were then washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to give the crude reaction product which was purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) giving 4.68 g (95%, de > 20:1) of amide **29** as a 5:1 mixture of amide rotamers (minor rotamer peaks denoted by an asterisk) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.0 (6H, s), 0.86 (9H, s), 1.01−1.08 (15H, m), 1.25−1.41 (4H, m), 1.58−1.61 (3H, m), 2.49−2.51 (1H, m), 2.76 (2.4H, s), 2.83* (0.6H, s), 3.59−3.71 (3H, m), 3.82−3.90 (1H, m), 4.38−4.42 (1H, br s), 4.56 (1H, t, J = 7.2 Hz), 4.57 (2H, q_{AB}, J = 11.6 Hz), 7.19−7.42 (16H, m), 7.65 (4H, t, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, −3.9, 14.4, 17.1, 18.0, 19.2, 25.9, 26.8, 28.9, 32.8, 35.7, 36.7, 39.9, 66.7, 71.8, 77.1, 126.3, 126.9, 127.2, 127.3, 127.4, 127.6, 128.1, 128.3, 128.6, 129.6, 133.5, 135.6, 139.1, 142.5, 178.9; IR (neat) ν_{max} 3854, 3744, 3397, 2931, 2858, 1700, 1653, 1559, 1061, 836, 667; HRMS (CI, NH_3) m/z calcd for $C_{48}H_{70}N_1O_5Si_2$ $[M + H]^+$ 796.4792, found 796.4727; $[\alpha]^{23}_D$ = −6.86° (c = 0.69, $CHCl_3$).

(2*R*)-2-(Benzyloxy)-3-[(2*S*,5*S*)-5-methyl-6-oxotetrahydro-2*H*-pyran-2-yl]propanal (31). To a 250 mL round-bottom flask charged with a magnetic stir bar was added 4.68 g (5.88 mmol) of amide **29**. Anhydrous THF (30 mL) was added, and the reaction was cooled to 0 °C. Tetrabutylammonium fluoride (14.70 mL of a 1 M solution of in THF) was added via syringe, and the reaction was allowed to stir for 6 h before being concentrated in vacuo. The resulting oil was dissolved in 80 mL of a 3:1 *t*-BuOH/H_2O solvent system; 7.70 mL (29.4 mmol) of tetra-*n*-butylammonium hydroxide was added, and the resulting mixture was refluxed for 24 h. The reaction was then cooled to room temperature and acidified to pH ~4 by the addition of an aqueous 10% HCl solution. The reaction was then poured into a separatory funnel and extracted 4 times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated. The resulting residue was then dissolved in 75 mL of anhydrous CH_2Cl_2. Pyridinium *p*-toluenesulfonate (1.47 g/5.88 mmol) was added in one portion, and the reaction was allowed to stir for 24 h at ambient temperature. The reaction was quenched by the addition of ~50 mL of H_2O. The layers were separated, and the aqueous layer was extracted 3 times with EtOAc. The combined organic extracts were then washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to give the crude reaction product which was purified by flash chromatography (SiO_2, 20% → 75% EtOAc/hexanes) giving 1.47 g (90%) acie **30** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d, J = 6.4 Hz), 1.21−1.26 (1H, m), 1.28−1.71 (2H, m), 1.81−1.90 (2H, m), 1.99−2.04 (1H, m), 2.41 (1H, tq, J = 7.6, 10.8 Hz), 3.46−3.51 (1H, m), 3.81−3.89 (2H, m), 4.36 (1H, dd, J = 2.4, 10.4 Hz), 4.58 (2H, q_{AB}, J = 11.6 Hz), 7.24−7.39 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 25.6, 27.2, 32.9, 37.9, 64.0, 72.5, 74.4, 75.6, 127.9, 128.0, 128.5, 138.2, 175.9; IR (neat) ν_{max} 3466, 2935, 2876, 1734, 1617, 1496, 1455, 1380, 1191, 1028, 667; HRMS (CI, NH_3) m/z calcd for $C_{16}H_{23}O_4$ $[M + H]^+$ 796.4792, found 796.4727; $[\alpha]^{23}_D$ = +96.61° (c = 0.59, $CHCl_3$). To a 100 mL round-bottom flask charged with a magnetic stir bar and (6*S*)-((2*R*)-benzyloxy-3-hydroxypropyl)-(3*S*)-methyltetrahydropyran-2-one (0.64 g, 2.31 mmol) was added 23 mL of anhydrous CH_2Cl_2. Dess−Martin periodinane (1.96 g/4.62 mmol) was added followed by distilled pyridine (1.12 mL/13.86 mmol). The reaction was allowed to stir for 45 min at ambient temperature before being diluted with ~25 mL of a saturated aqueous solution of $NaHCO_3$. The layers were separated, and the aqueous phase was extracted 3 times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to give the crude reaction product which was purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) giving 0.520 g (82%) of aldehyde **31** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, d, J = 6.8 Hz), 1.44−1.73 (3H, m), 1.83−1.89 (1H, m), 1.91−2.09 (2H, m), 2.42−2.49 (1H, m), 4.20 (1H, dddd, J = 0.8, 2.8, 4, 10.8 Hz), 4.43 (1H, dddd, J = 2.8, 5.6, 10.8, 10.8 Hz), 4.52 (1H, d, J = 11.2 Hz), 4.74 (1H, d, J = 11.2 Hz), 7.27−7.36 (5H, m), 9.65 (1H, d, J = 0.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 25.5, 27.0, 33.1, 35.7, 73.2, 73.5, 77.2, 79.8, 128.3, 128.6, 137.1, 175.5, 202.0; IR (neat) ν_{max} 3020, 2937, 2877, 1497, 1455, 1382, 1190, 934; HRMS (CI, NH_3) m/z calcd for $C_{16}H_{21}O_4$ $[M + H]^+$ 277.1439, found 277.1442; $[\alpha]^{23}_D$ = +103.83° (c = 0.47, $CHCl_3$).

1,1-Diiodo-3-methyl butane (32). To a 100 mL round-bottom flask charged with a magnetic stir bar and 6.00 mL (56.0 mmol) isovaleraldehyde was added 10 mL of hydrazine hydrate. The reaction was warmed to 50 °C in an oil bath with stirring for 3 h before being diluted with ∼50 mL of H_2O. The layers were separated, and the aqueous layer was extracted 3 times with $CHCl_3$. The combined organic extracts were washed with H_2O, dried with $MgSO_4$, filtered, and concentrated giving the intermediate hydrazone which was used immediately without further purification. The hydrazone was dissolved in 50 mL of Et_2O and 38 mL of triethylamine in a 250 mL round-bottom flask equipped with a magnetic stir bar. A solution of 20 g of I_2 in 50 mL of Et_2O was added dropwise via a Pasteur pipet to the reaction until the cessation of N_2 was observed and the iodine color persisted. The reaction was then diluted with ∼50 mL of a 5% aqueous $Na_2S_2O_3$ solution and allowed to stir for 10 min. The layers were separated, and the organic extracts were washed with 100 mL of 10% aqueous HCl, 100 mL of a saturated solution of $NaHCO_3$, brine, dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, hexanes) giving 9.50 g (54%) of diiodide **32** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, d, J = 6.8 Hz), 1.69 (1H, tq, J = 6.8, 7.6 Hz), 2.24 (2H, dd, J = 6.4, 7.6 Hz), 5.04 (1H, t, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −27.2, 20.8, 30.8, 57.3; IR (neat) ν_{max} 3448, 3072, 2932, 2858, 1731, 1464, 1282, 1113, 821, 702; HRMS (CI, NH_3) *m*/*z* calcd for $C_5H_{10}I_2$ $[M + H]^+$ 324.8950, found 324.8961.

(6*S*)-((2*R*)-Benzyloxy-6-methylhept-3-enyl)-(3*S*)-methyltetrahydropyran-2-one (33). To a 100 mL round-bottom flask charged with a magnetic stir bar was added 1.84 g (15.04 mmol) of anhydrous $CrCl_2$. The flask was placed under vacuum, and the $CrCl_2$ was flame-dried. The flask was allowed to cool under vacuum, removed, and immediately purged with argon. The $CrCl_2$ was suspended in 38 mL of anhydrous THF and 1.16 mL of anhydrous DMF. A premixed solution of 1.20 g (3.77 mmol) of 1,1-diiodo-3-methyl butane **32** and aldehyde **31** in 6 mL of anhydrous THF was then added to the suspension with stirring. The reaction was allowed to stir for 1 h at ambient temperature before being diluted with ∼25 mL of H_2O. The layers were separated, and the aqueous layer was extracted 3 times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to give the crude reaction product which was purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) giving 0.466 g (75%) of the desired *trans* olefin **33** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84−0.90 (6H, m), 1.18 (3H, d, J = 6.8 Hz), 1.41−1.63 (3H, m), 1.74 (2H, t, J = 7.2 Hz), 1.81−1.90 (1H, m), 1.94 (2H, t, J = 5.6 Hz), 2.00−2.04 (1H, m), 2.52 (1H, ddt, J = 7.6, 10.8, 14.4 Hz), 4.07 (1H, q, J = 7.6 Hz), 4.42 (2H, q_{AB}, J = 11.6 Hz), 4.51−4.60 (1H, m), 5.31 (1H, dd, J = 8.8, 14.8 Hz), 5.67 (1H, dt, J = 7.2, 14.8 Hz), 7.23 = 7.38 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 22.2, 25.7, 27.1, 28.2, 33.1, 41.6, 42.2, 70.2, 74.4, 75.9, 76.6, 127.5, 127.9, 128.3, 131.1, 133.4, 138.7, 176.2; IR (neat) ν_{max} 2956, 2870, 1740, 1496, 1456, 1381, 1183, 1142, 1074, 1028, 754; HRMS (CI, NH_3) *m*/*z* calcd for $C_{21}H_{30}O_3$ $[M + H]^+$ 331.2273, found 331.2295; $[\alpha]^{23}_D$ = +116.32° (*c* = 0.44, $CHCl_3$).

Acetic acid (6*S*)-((2*R*)-Benzyloxy-6-methylhept-3-enyl)-(3*S*)-methyltetrahydropyran-2-yl Ester (34). To a 100 mL round-bottom flask charged with a magnetic stir bar and lactone **33** (0.987 g/3.00 mmol) was added 15 mL of anhydrous CH_2Cl_2. The reaction was cooled to −78 °C, and DIBAL-H (6.00 mL of a 1 M solution of in hexanes) was added dropwise via syringe. The reaction was stirred for 30 min at this temperature before being quenched with ∼10 mL of MeOH. The reaction was poured onto water, and the layers were separated. The aqueous layer was extracted 3 times with CH_2Cl_2, and the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated to yield the intermediate lactol which was immediately dissolved in 15 mL of anhydrous CH_2Cl_2. Triethylamine (1.04 mL/7.50 mmol), (dimethylamino)pyridine (∼10 mg), and acetic anhydride (0.567 mL/6.00 mmol) were then added sequentially, and the reaction was allowed to stir for 2 h at ambient temperature. The reaction was then quenched by the addition of ∼25 mL of H_2O. The layers were separated, and the aqueous layer was extracted 3 times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to give the crude reaction product which was purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) giving 0.864 g (77%) of acetate **34** as a colorless oil. The product was isolated as a 3:1 mixture of anomers that were used immediately. Characterization for the major anomer is as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−0.90 (6H, m), 1.02 (3H, d, J = 7.2 Hz), 1.35−1.42 (3H, m), 1.52−1.81 (5H, m), 1.84−1.93 (2H, m), 1.94 (3H, s), 3.96 (1H, dt, J = 4.0, 8.8 Hz), 4.10 (1H, dddd, J = 3.2, 6.4, 12.0, 14.4 Hz), 4.40 (2H, q_{AB}, J = 11.6 Hz), 5.30 (1H, dd, J = 8.8. 14.8 Hz), 5.62 (1H, dt, J = 7.0, 14.8 Hz), 5.78 (1H, br s), 7.22−7.35 (5H, m); IR (neat) ν_{max} 2954, 2868, 1751, 1653, 1497, 1454, 1437, 1385, 1371, 967, 698; HRMS (CI, NH_3) *m*/*z* calcd for $C_{23}H_{34}O_4$ $[M + H]^+$ 375.2535, found 375.2531; $[\alpha]^{23}_D$ = +38.87° (*c* = 0.62, $CHCl_3$).

[(6*S*)-((2*R*)-Benzyloxy-6-methylhept-3-enyl)-(3*S*)-methyltetrahydropyran-(2*S*)-yl]acetaldehyde (6). To a 50 mL round-bottom flask charged with a magnetic stir bar and acetate **34** (0.870 g/2.35 mmol) were added 5 mL of anhydrous CH_2Cl_2 and 5 mL of anhydrous Et_2O. Freshly prepared trimethylvinyloxysilane **35** (1.35 g/11.61 mmol) was added via syringe, and the reaction was cooled to 0 °C. A solution of freshly flame-dried $ZnCl_2$ (1.58 g/11.63 mmol) in 5 mL of CH_2Cl_2 was added dropwise via syringe. The reaction was stirred at 0 °C for 1 h before being diluted with a saturated solution of $NaHCO_3$ (∼15 mL). The phases were separated, and the aqueous phase was extracted 3 times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, 5% → 15% EtOAc/hexanes) giving 715 mg (86%) of aldehyde **6** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88−0.91 (9H, m), 1.26−1.44 (3H, m), 1.45−1.63 (2H, m), 1.65−1.81 (1H, m), 1.91−1.97 (4H, m), 2.50 (2H, dd, J = 2.80, 6.4 Hz), 3.72−3.83 (2H, m), 4.12 (1H, m, J = 2.6, 4.4, 9.2, 10.8 Hz), 4.41 (2H, q_{AB}, J = 11.6 Hz), 5.34 (1H, dd, J = 8.4, 15.2 Hz), 5.63 (1H, dt, J = 7.6, 15.2 Hz), 7.23−7.31 (5H, m), 9.67 (1H, t, J = 2.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 22.3, 22.4, 26.8, 28.2, 28.4, 34.5, 38.0, 41.6, 47.0, 68.5, 70.1, 71.8, 76.9, 127.3, 127.9, 128.2, 131.9, 132.7, 138.9, 201.9; IR (neat) ν_{max} 2955, 1727, 1457, 1383, 1070, 973, 735, 697; HRMS (CI, NH_3) *m*/*z* calcd for $C_{23}H_{35}O_3$ $[M + H]^+$ 359.2586, found 359.2577; $[\alpha]^{23}_D$ = +33.03° (*c* = 0.66, $CHCl_3$).

2(*E*)-3-(Dimethylphenylsilyl)propenal (40). To a 500 mL three neck bottom flask charged with a magnetic stir bar and fitted with a reflux condenser were added propargyl alcohol (3.00 g/53.5 mmol) and 100 mL of anhydrous THF. Dimethylphenylsilane (8.61 mL/56.19 mmol) was added followed by the addition of 15 mg of platinum hydrosilylation catalyst and 5 mg of sodium metal. The reaction was heated to reflux for 24 h before being cooled to room temperature. The THF was removed in vacuo, and the resulting crude reaction product was purified by flash chromatography (SiO_2, 10% → 25% EtOAc/hexanes) giving 9.37 g (90%) of the desired allylic alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (6H, s), 1.39 (1H, dd, J = 6.0, 7.2 Hz), 4.19 (2H, ddd, J = 1.6, 6.0, 7.2 Hz), 6.04 (1H, ddd, J = 1.6, 3.6, 18.8 Hz), 6.23 (1H, ddd, J = 4.4, 8.4, 18.8 Hz), 7.33−7.39 (3H, m), 7.49−7.52 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.8, 65.4, 127.2, 127.3, 127.9, 129.1, 133.9, 146.7; IR (neat) ν_{max} 3450, 3199, 1662, 1504, 1103, 891; HRMS (CI, NH_3) *m*/*z* calcd for $C_{11}H_{17}O_1Si_1$ $[M + H]^+$ 193.1048, found 193.1048. A 500 mL round-bottom flask charged with a magnetic stir bar were added 22 g of Celite and CH_2Cl_2 (170 mL). Pyridinium chlorochromate (22.0 g/98.8 mmol) was added to the slurry slowly over 10 min. To this mixture was added dropwise a solution of allylic alcohol (9.30 g/49.4 mmol) in 25 mL of CH_2Cl_2, and the reaction was allowed to stir at ambient temperature for 45 min before being filtered through a pad of SiO_2 and concentrated. The resulting residue was purified by flash chromatography (SiO_2, 10% → 25% EtOAc/hexanes) giving 7.00

g (75%) of aldehyde **40** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45 (6H, s), 6.52 (1H, dd, J = 7.2, 18.4 Hz), 7.32 (1H, d, J = 18.4 Hz), 7.37−7.39 (m, 3H), 7.49−7.53 (m, 2H), 9.51 (1H, d, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.6, 128.2, 129.8, 133.8, 135.8, 145.1, 156.5, 194.7; IR (neat) ν_{max} 3157, 3051, 1755, 1609, 1511, 1199, 855, 711; HRMS (CI, NH_3) *m/z* calcd for $C_{11}H_{14}O_1Si_1$ $[M + H]^+$ 191.0892, found 191.0881.

(6*S*)-[2-(Dimethylphenylsilyl)vinyl]-(5*S*)-methyl-5,6-dihydro-2*H*-pyran-(2*S*)-carboxylic Acid Methyl Ester (41). To a 1 L round-bottom flask charged with a magnetic stir bar were added organosilane (*S,S*)-**37** (9.30 g/26.52 mmol) and aldehyde **40** (6.06 g/31.82 mmol). CH_2Cl_2 (530 mL) was added, and the reaction mixture was cooled to −50 °C. Freshly distilled TMSOTf (2.94 g/13.26 mmol) was added dropwise to the reaction. The reaction was allowed to stir at −50 °C for 4 h before being quenched by the addition of saturated aqueous $NaHCO_3$ (∼200 mL) and allowed to stir while warming to room temperature. The reaction mixture was poured into a separatory funnel and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, 3% EtOAc/hexanes) giving 7.97 g (95%) of **41** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (3H, s), 0.36 (3H, s), 0.91(3H, d, J = 7.2 Hz), 2.09−2.19 (1H, m), 3.73 (3H, s), 3.89 (1H, dd, J = 5.6, 8.8 Hz), 4.78 (1H, br d, J = 2.8 Hz), 5.76−5.86 (2H, m), 6.10−6.18 (2H, m), 7.30−7.33 (3H, m), 7.49−7.52 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.8, −2.9, 16.6, 32.9, 51.9, 72.2, 79.8, 122.3, 127.8, 129.0, 131.6, 133.2, 133.9, 138.4, 145.4, 171.6; IR (neat) ν_{max} 3069, 3040, 2957, 1755, 1622, 1427, 1148, 733; HRMS (CI, NH_3) *m/z* calcd for $C_{18}H_{24}O_3Si_1$ $[M + H]^+$ 316.4669, found 316.1520; $[\alpha]^{23}_D$ = −41.21° (*c* = 0.82, $CHCl_3$).

(6-{5-[6-(2-Benzyloxy-6-methylhept-3-enyl)-3-methyltetrahydropyran-2-yl]-4-hydroxy-2-oxopentyl}-2,2-dimethyl-[1,3]dioxan-4-yl)acetic acid *tert*-Butyl Ester (52). To a 25 mL round-bottom flask charged with a magnetic stir bar were added aldehyde **6** (220 mg/0.614 mmol) and silyl enol ether **7** (220 mg/0.614 mmol). CH_2Cl_2 (5 mL) of was added, and the reaction was cooled to −78 °C. Freshly distilled $BF_3{\cdot}OEt_2$ (117 μL/0.921 mmol) was then added dropwise to the cooled reaction mixture. The reaction was allowed to stir at this temperature for 90 min before being quenched by the addition of saturated aqueous $NaHCO_3$ (∼10 mL). The reaction mixture was poured into a separatory funnel and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, 15% EtOAc/hexanes) to give 321 mg (81%) of secondary alcohol **52** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.91 (9H, m), 1.24 (1H, q, J = 6.8 Hz), 1.30 (3H, s), 1.41 (9H, s), 1.42 (3H, s) 1.46−1.47 (2H, m), 1.55−1.67 (7H, m), 1.71−1.79 (1H, m), 1.94 (2H, t, J = 6.4 Hz), 1.95−1.99 (1H, m), 2.15−2.39 (3H, m), 2.47 (1H, dd, J = 4.0, 16.8 Hz), 2.54−2.64 (2H, m), 3.46 (1H, d, J = 3.2 Hz), 3.49 (1H, dt, J = 5.6, 8.4 Hz), 3.91 (1H, dt, J = 3.2, 9.6 Hz), 4.11−4.18 (1H, m), 4.21−4.29 (3H, m), 4.45 (2H, q_{AB}, J = 7.6 Hz), 5.35 (1H, dd, J = 8.4, 15.2 Hz), 5.63 (1H, dt, J = 7.2, 15.2 Hz), 7.21−7.29 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 19.6, 22.3, 22.4, 27.2, 28.1, 28.2, 28.7, 29.9, 34.4, 36.2, 37.8, 38.9, 41.6, 42.7, 49.7, 51.0, 64.5, 65.5, 66.1, 68.5, 70.1, 72.6, 80.6, 98.9, 127.2, 127.6, 128.3, 131.9, 132.8, 139.0, 170.0, 209.0; IR (neat) ν_{max} 3472, 2953, 1730, 1456, 1381, 1368, 1201, 1154, 1070, 977, 846, 697; HRMS (CI, NH_3) *m/z* calcd for $C_{38}H_{61}O_8$ $[M + H]^+$ 645.4366, found 645.4397; $[\alpha]^{23}_D$ = +21.86° (*c* = 0.22, $CHCl_3$).

(6-{5-[6-(2-Benzyloxy-6-methylhept-3-enyl)-3-methyltetrahydropyran-2-yl]-4-methoxy-2-oxopentyl}-2,2-dimethyl-[1,3]dioxan-4-yl)acetic acid *tert*-Butyl Ester (5). To a 50 mL round-bottom flask charged with a magnetic stir bar was added alcohol **53** (270 mg/0.42 mmol). The alcohol was dissolved in 17 mL of CH_2Cl_2 followed by the addition of Proton Sponge (538 mg/2.51 mmol), 800 mg of dry 4 Å molecular sieves, and $Me_3O{\cdot}BF_4$ (311 mg/2.1 mmol). The reaction was stirred for 1 h before being diluted with EtOAc (∼20 mL) and passed through a glass-fritted funnel. The EtOAc was washed once with H_2O, 2 × 80 mL with 1 M aqueous $CuSO_4$, dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) to give 273 mg (99%) of methyl ether **5** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.92 (9H, m), 1.09 (1H, q, J = 11.6 Hz), 1.30 (3H, s), 1.42 (9H, s), 1.43 (3H, s), 1.46−1.56 (4H, m), 1.57−1.74 (6H, m), 1.86−1.90 (1H, m), 1.94 (2H, t, J = 7.2 Hz), 2.24 (1H, dd, J = 5.6, 15.2 Hz), 2.32−2.38 (2H, m), 2.46−2.65 (3H, m), 3.25 (3H, s), 3.39 (1H, dt, J = 4.0, 7.6 Hz), 3.79−3.82 (1H, m), 3.89 (1H, dt, J = 3.2, 9.6 Hz), 4.04−4.11 (1H, m), 4.20−4.33 (2H, m), 4.46 (2H, q_{AB}, J = 11.6 Hz), 5.34 (1H, dd, J = 8.4, 15.2 Hz), 5.62 (1H, dt, J = 7.2, 15.2 Hz), 7.21−7.31 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 19.6, 22.2, 22.3, 26.9, 28.0, 28.2, 28.4, 29.9, 34.6, 36.2, 38.6, 41.6, 42.7, 48.7, 50.1, 57.1, 65.4, 66.0, 67.9, 70.0, 72.1, 73.7, 77.2, 80.5, 98.8, 127.2, 127.6, 128.3, 132.1, 132.5, 139.0, 170.0, 206.9; IR (neat) ν_{max} 3112, 2997, 1729, 1466, 1307, 1201, 1175, 942, 882, 751; HRMS (CI, NH_3) *m/z* calcd for $C_{39}H_{63}O_8$ $[M + H]^+$ 659.4523, found 659.4521; $[\alpha]^{23}_D$ = +19.07° (*c* = 0.60, $CHCl_3$).

((6*S*)-{3-[6-((2*R*)-Benzyloxy-6-methylhept-3-enyl)-(3*S*)-methyltetrahydropyran-(2*S*)-yl]-(2*R*)-methoxypropyl}-(4*S*)-hydroxy-6-methoxytetrahydropyran-(2*R*)-yl)acetic acid *tert*-Butyl Ester (53). A 50 mL round-bottom flask was charged with a magnetic stir bar and 86 mg (0.132 mmol) of acetonide **5**. Methanol (22 mL) was added followed by 10-camphorsulfonic acid (30.8 mg/0.132 mmol). The reaction was allowed to stir for 24 h at ambient temperature. The reaction was quenched by the addition of ∼10 mL of a saturated aqueous solution of $NaHCO_3$. The reaction was poured into a separatory funnel and extracted 3 times with EtOAc. The combined organic phase was washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) giving 57 mg (68%, dr ∼ 2:1) of acetal **53** as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76−0.93 (9H, m), 1.03−1.09 (2H, m), 1.28−1.41 (5H, m), 1.42 (9H, s), 1.58−1.75 (6H, m), 1.86 (1H, dd, J = 5.6, 14.4 Hz), 1.94 (2H, t, J = 6.8 Hz), 1.98−2.16 (2H, m), 2.18 (1H, dd, J = 3.2, 12.8 Hz), 2.30 (1H, dd, J = 4.8, 15.0 Hz), 2.41 (1H, dd, J = 8.4, 15.0 Hz), 3.16 (3H, s), 3.28 (1H, s), 3.29 (2H, s), 3.29−3.39 (1H, m), 3.48−3.53 (1H, m), 3.61−3.66 (1H, m), 3.83−3.97 (2H, m), 4.05−4.08 (1H, m), 4.45 (2H, q_{AB}, J = 11.6 Hz), 5.34 (1H, dd, J = 8.0, 15.4 Hz), 5.60 (1H, dt, J = 6.8, 15.4 Hz), 7.23−7.31 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 22.3, 27.0, 28.1, 28.2, 28.5, 29.7, 34.8, 36.6, 38.3, 39.1, 39.9, 40.4, 41.6, 42.4, 47.5, 55.4, 56.8, 66.0, 68.3, 70.1, 72.1, 73.2, 77.2, 80.5, 100.6, 127.3, 127.7, 128.3, 132.1, 132.4, 138.9, 170.5; IR ($CHCl_3$ thin film) ν_{max} 3459, 3020, 3055, 3020, 2956, 2928, 2400, 1735, 1717, 1534, 1366, 1216, 1148, 928, 754; HRMS (EI) *m/z* calcd for $C_{37}H_{60}O_8$ $[M+]^+$ 632.4288, found 632.4331; $[\alpha]^{23}_D$ = +11.55° (*c* = 0.09, $CHCl_3$).

((6*S*)-{3-[(6*S*)-((2*R*)-Benzyloxy-6-methylhept-3-enyl)-(3*S*)-methyltetrahydropyran-(2*S*)-yl]-(2*S*)-methoxypropyl}-(4*R*)-hydroxytetrahydropyran-(2*R*)-yl)acetic acid *tert*-Butyl Ester (54). To a 25 mL conical flask charged with a magnetic stir bar was added acetal **53** (58.5 mg/0.092 mmol). Anhydrous CH_2Cl_2 (2 mL) and freshly distilled triethylsilane (0.293 mL/1.84 mmol) were added. The reaction was then cooled to −78 °C, and freshly distilled $BF_3{\cdot}OEt_2$ (0.12 mL/0.93 mmol) was then added dropwise via syringe. The reaction was warmed to −50 °C and allowed to stir for an additional 4 h before being quenched by the addition of ∼5 mL of a saturated aqueous solution of $NaHCO_3$. The reaction was poured into a separatory funnel and extracted 4 times with CH_2Cl_2. The combined organic phase was washed with H_2O, dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) giving 41 mg (73%, dr > 9:1) of bis-tetrahydropyran **54** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.90 (9H, m), 1.10−1.21 (2H, m), 1.24−1.37 (1H, m), 1.41 (9H, s), 1.42−1.53 (4H, m), 1.56−1.79 (9H, m), 1.89−1.91 (1H, m), 1.94 (2H, t, J = 7.6 Hz), 2.24 (1H, dd, J = 6.4, 14.8 Hz), 2.41 (1H, dd, J = 6.8, 14.8 Hz), 3.20 (3H, s), 3.36−3.42 (3H, m), 3.62−3.71 (1H, m), 3.89 (1H, dt, J =

3.2, 8.6 Hz), 4.08−4.13 (1H, m), 4.45 (2H, q_{AB}, J = 11.2 Hz), 5.35 (1H, dd, J = 8.6, 15.0 Hz), 5.60 (1H, dt, J = 7.6, 15.0 Hz), 7.24−7.31 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 22.3, 23.5, 27.1, 28.2, 28.3, 29.7, 31.1, 31.9, 34.9, 38.4, 38.8, 40.5, 41.7, 43.0, 56.1, 68.1, 70.2, 71.9, 74.2, 74.5, 74.8, 76.0, 80.2, 127.3, 127.7, 128.3, 132.2, 132.3, 139.0, 170.6; IR ($CHCl_3$ thin film) ν_{max} 3601, 3391, 3105, 1706, 1655, 1580, 1200, 989, 791; HRMS (EI) *m*/*z* calcd for $C_{37}H_{60}O_8$ $[M+]^+$ 632.4288, found 632.4331; $[\alpha]^{23}_D$ = +22.22° (*c* = 0.22, $CHCl_3$).

(2*S*,3*S*)-2,4,6-Trimethylbenzenesulfonic acid 3-(dimethylphenylsilanyl)-2-trimethylsilanyloxypent-4-enyl Ester (13). Mesitylenesulfonyl chloride (14.52 g, 66 mmol) was added to a solution of diol **61** (13.1 g, 55.5 mmol), pyridine (8.8 g, 111 mmol), and DMAP (677 mg, 0.55 mmol) in DCM (150 mL). The mixture was stirred for 72 h at room temperature. Removal of the solvents under reduced pressure and purification by flash column chromatography (silica gel, 8% EtOAc in hexane) afforded the corresponding sulfonate as a pale yellow oil (20.6 g, 89%). A solution of the resulting sulfonate (1.67 g, 4 mmol) in THF (20 mL) was treated with pyridine (1.26 g, 16 mmol) and TMSCl (1.29 g, 12 mmol). The reaction mixture was stirred for 12 h before water (20 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification by flash column chromatography (silica gel, 2% EtOAc in hexane) afforded the silyl ether **13** as a pale yellow oil (1.8 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, m), 7.32−7.25 (3H, m), 6.93 (2H, s), 5.58 (1H, m), 4.88 (1H, dd, J = 10, 1.6 Hz), 4.74 (1H, d, J = 16.8 Hz), 3.97 (1H, m), 3.70 (1H, dd, J = 4, 10 Hz), 3.62 (1H, dd, J = 6.4, 10 Hz), 2.54 (6H, s), 2.30 (3H, s), 1.97 (1H, dd, J = 14.4, 5.2 Hz), 0.25 (6H, s), 0.00 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 139.7, 137.7, 135.9, 134.0, 131.6, 130.4, 128.9, 127.5, 114.8, 72.6, 71.8, 40.0, 22.3, 20.7, 0.03, −3.1, −3.5; IR (neat) ν_{max} 2956, 1604, 1358, 1251, 977; $[\alpha]^{23}_D$ = −4.6° (*c* = 0.65, CH_2Cl_2); CIHRMS $[M]^+$ calcd for $C_{25}H_{38}O_4SSi_2$ 490.2029, found 490.2007.

(5*S*)-(3-Methoxyhex-5-enyloxymethyl)benzene (63). In a 1000 mL round-bottom flask, trimethyloxonium tetrafluoroborate (7.8 g) was added to a solution of alcohol[44] (4 g, 19.4 mmol), molecular sieves (13.6 g), and Proton Sponge (13.6 g) in DCM (400 mL). The resulting mixture was stirred for 2 h before additional portions of Proton Sponge (9 g) and trimethyloxonium tetrafluoroborate (5 g) were added. The suspension was stirred overnight before being filtered through a pad of Celite. The yellow filtrate was washed with an HCl solution (1 N), and the organic layer was dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash chromatography (silica gel, 5% EtOAc in hexane) afforded the methyl ether **63** (3.8 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (5H, m), 5.79 (1H, m), 5.06 (1H, m), 5.03 (1H, m), 4.48 (2H, abq, J = 11.6 Hz), 3.54 (2H, m), 3.38 (1H, m), 3.32 (3H, s), 2.26 (2H, dd, J = 6, 7.2 Hz), 1.77 (2H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 138.5, 134.6, 128.3, 127.6, 127.5, 117.1, 77.5, 73.0, 66.9, 56.8, 37.9, 33.9; IR (neat) ν_{max} 2925, 1604, 1094; $[\alpha]^{23}_D$ = +28.1° (*c* = 3.3, CH_2Cl_2); CIHRMS M^+ calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1425.

(3*R*)-5-Benzyloxy-3-methoxypentanal (15). Ozone gas was bubbled through a solution of **63** (3.5 g, 15.9 mmol) in DCM (317 mL) at −78 °C until the solution turned blue. PPh_3 (12.5 g) was then added. The mixture was slowly warmed to room temperature and stirred overnight. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 25% EtOAc in hexane) afforded the aldehyde **15** (3.88 g, ca. 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 3 Hz), 7.35−7.25 (5H, m), 4.47 (2H, s), 3.89 (1H, m), 3.55 (2H, m), 3.33 (3H, s), 2.59 (2H, m), 1.90 (1H, m), 1.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 138.3, 128.4, 127.7, 73.7, 73.0, 66.2, 56.9, 48.1, 34.0; IR (neat) ν_{max} 2930, 1723, 1095; $[\alpha]^{23}_D$ = +13.5° (*c* = 0.93, CH_2Cl_2); CIHRMS M^+ calcd for $C_{13}H_{18}O_3$ 223.1289, found 223.1314.

(44) For the physical data of the alcohol, see: Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892.

(2*R*,6*R*)-2,4,6-Trimethylbenzenesulfonic acid 6-[(4*R*)-(4-benzyloxy-2-methoxybutyl)]-5,6-dihydro-2*H*-pyran-2-ylmethyl Ester (64). A solution of aldehyde **15** (930 mg, 4.2 mmol) and silane **13** (3.56 g, 7.3 mmol) in DCM at −78 °C (65 mL) was treated with TfOH (833 mg, 5.55 mmol). The mixture was stirred for 12 h at this temperature before a saturated aqueous solution of $NaHCO_3$ (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 60 mL), and combined organic layers were dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 20% EtOAc in hexane) afforded the pyran **64** as a pale yellow oil (1.67 g, 82%, dr = 12:1 (*cis*:*trans*)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (5H, m), 6.92 (2H, s), 5.87 (1H, m), 5.53 (1H, dd, br, J = 2, 10 Hz), 4.47 (2H, s), 4.29 (1H, m), 3.96 (1H, dd, J = 4, 10 Hz), 3.87 (1H, dd, J = 6, 10 Hz), 3.62 (1H, m), 3.52 (2H, m), 3.45 (1H, m), 3.25 (3H, s), 2.61 (6H, s), 2.27 (3H, s), 1.90 (2H, m), 1.77 (3H, m), 1.49 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 140.0, 138.5, 131.7, 131.6, 128.4, 127.8, 127.7, 127.6, 124.9, 74.9, 72.9, 72.3, 70.7, 70.5, 66.7, 56.3, 39.3, 33.7, 30.8, 22.4, 20.8; IR (neat) ν_{max} 2939, 1604, 1355 1097; $[\alpha]^{23}_D$ = +20.5° (*c* = 0.55, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{27}H_{36}O_6S$ 488.2266, found 489.2333.

(2*S*,6*S*)-{6-[(2*R*)-(4-Benzyloxy-2-methoxybutyl)]-5,6-dihydro-2*H*-pyran-2-yl}acetonitrile (65). A solution of sulfonate **64** (1.62 g, 3.3 mmol) in DMF (11 mL) was treated with NaCN (650 mg, 13.3 mmol). The mixture was stirred for 60 h at 60 °C before water (50 mL) was added. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (4 × 20 mL) and dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 15−20% EtOAc in hexane) afforded the pyran **65** as a pale yellow oil (0.9 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (5H, m), 5.97 (1H, m), 5.62 (1H, m), 4.48 (2H, s), 4.35 (1H, m), 3.72 (1H, m), 3.59−3.48 (3H, m), 3.29 (3H, s), 2.51 (2H, m), 2.00 (2H, m), 1.85 (3H, m), 1.60 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.2, 127.8, 127.5, 127.4, 126.4, 117.0, 74.7, 72.7, 70.8, 69.9, 66.6, 56.2, 39.1, 33.7, 30.5, 24.1; IR (neat) ν_{max} 2926, 2862, 2250, 1454, 1093; $[\alpha]^{23}_D$ = +23.4° (*c* = 0.44, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{19}H_{25}NO_3$ 316.1868, found 316.1924.

(2*S*,4*S*,6*S*)-{6-[(2*R*)-(4-Benzyloxy-2-methoxybutyl)]-4-hydroxytetrahydropyran-2-yl}acetonitrile (66). A solution of olefin **65** (650 mg, 2.06 mmol) in THF (16 mL) and water (12 mL) was treated with mercury trifluoroacetate (4.38 g, 10.3 mmol). The mixture was stirred for 18 h before NaOH solution (3 N, 13.6 mL) and $NaBH_4$ (392 mg in NaOH solution (3.7 mL, 3 N)) were added. The mixture was stirred for 10 min and extracted with EtOAc (2 × 40 mL), and the combined organic layers were dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 50−60% EtOAc in hexane) afforded the pyran **66** as a pale yellow oil (522 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (5H, m), 4.48 (2H, abq, J = 12.8 Hz), 4.27 (1H, m), 4.03 (1H, m), 3.95 (1H, m), 3.58−3.46 (3H, m), 3.29 (3H, s), 2.45 (2H, m), 1.87−1.72 (3H, m), 1.64−1.55 (2H, m), 1.53−1.38 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.3, 127.7, 127.5, 117.3, 75.0, 72.8, 68.8, 67.0, 66.8, 63.6, 56.2, 39.3, 37.9, 37.1, 33.6, 24.3; IR (neat) ν_{max} 3438, 2922, 2251, 1074; $[\alpha]^{23}_D$ = +16.7° (*c* = 0.55, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{19}H_{27}NO_4$ 334.1974, found 334.1990.

(2*S*,4*S*,6*S*)-{6-[(2*R*)-(4-Benzyloxy-2-methoxybutyl)]-4-(*tert*-butyldiphenylsilanyloxy)tetrahydropyran-2-yl}acetonitrile (67). A solution of alcohol **66** (630 mg, 1.89 mmol) in DMF (3.8 mL) was treated with imidazole (386 mg, 5.67 mmol) and TBDPSCl (780 mg, 2.85 mmol). The resulting mixture was stirred for 72 h before water (50 mL) was added. The mixture was then extracted with EtOAc (2 × 40 mL), and the combined organic layers were washed with brine (3 × 20 mL) and dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, DCM then 20% EtOAc

in hexane) afforded the pyran **67** as a pale yellow oil (1.03 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (4H, m), 7.44−7.25 (11H, m), 4.49 (2H, m), 4.22 (1H, m), 4.14 (2H, m), 3.55 (2H, m), 3.45 (1H, m), 3.27 (3H, s), 2.42 (2H, m), 1.82 (2H, m), 1.76 (1H, m), 1.60 (2H, m), 1.44 (1H, m), 1.35 (1H, m), 1.23 (1H, m), 1.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 135.7, 135.7, 133.8, 133.77, 129.9, 128.4, 127.8, 127.7, 127.69, 127.5, 117.3, 74.9, 72.9, 69.3, 67.5, 66.8, 65.5, 56.5, 39.7, 38.2, 37.8, 34.0, 26.8, 24.5, 19.1; IR (neat) ν_{max} 2929, 2251, 1107; $[\alpha]^{23}_D = +0.65°$ ($c = 0.77$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{35}H_{45}NO_4Si$ 572.3151, found 572.3189.

(2*S*,4*S*,6*R*)-{4-(*tert*-Butyldiphenylsilanyloxy)-6-[(2*R*)-(4-hydroxy-2-methoxybutyl)]tetrahydropyran-2-yl}acetonitrile (68). A solution of benzyl ether **67** (1130 mg, 1.97 mmol) in DCM (44 mL) at −78 °C was treated with BCl_3 (13.3 mL, 1.0 M in hexane). The mixture was stirred for 20 h at this temperature before MeOH (10 mL) and a saturated aqueous $NaHCO_3$ solution (100 mL) were added. The mixture was stirred for 20 min and then extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (3 × 20 mL) and dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 45% EtOAc in hexane) afforded the pyran **68** as a pale yellow oil (957 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (4H, m), 7.44−7.34 (6H, m), 4.23 (1H, m), 4.16 (1H, m), 4.07 (1H, m), 3.77 (2H, m), 3.59 (1H, m), 3.32 (3H, s), 2.59 (1H, br), 2.43 (2H, m), 1.86 (2H, m), 1.74 (1H, m), 1.61 (1H, m), 1.50 (1H, m), 1.44 (1H, m), 1.35 (1H, m), 1.27 (1H, m), 1.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 135.7, 133.8, 133.7, 130.0, 127.8, 127.8, 117.5, 77.8, 69.2, 67.7, 65.5, 60.9, 56.4, 38.8, 38.4, 37.8, 35.5, 26.9, 24.6, 19.1; IR (neat) ν_{max} 3439, 2930, 2252, 1105; $[\alpha]^{23}_D = +6.91°$ ($c = 0.55$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{28}H_{39}NO_4Si$ 482.2682, found 482.2696.

[4-(*tert*-Butyldiphenylsilanyloxy)-6-(2-methoxy-4-oxobutyl)-tetrahydropyran-2-yl]acetonitrile (69). A solution of alcohol **68** (475 mg, 0.99 mmol) and molecular sieves (2.4 g) in DCM (37 mL) was treated with PCC (804 mg, 2.9 mmol). The mixture was stirred for 2 h and then filtered through a short pad of silica to afford the pyran **69** as a pale yellow oil (402 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, dd, $J = 2.0$, 2.4 Hz), 7.60 (4H, m), 7.44−7.34 (6H, m), 4.23 (1H, m), 4.16 (1H, m), 4.11 (1H, m), 3.88 (1H, m), 3.31 (3H, s), 2.67 (1H, d, $J = 2$ Hz), 2.66 (1H, d, $J = 2.4$ Hz), 2.43 (2H, m), 1.83 (1H, m), 1.60 (1H, m), 1.53 (1H, m), 1.49 (1H, m), 1.38−1.22 (2H, m), 1.07 (9H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 201.4, 135.5, 133.6, 135.5, 129.7, 129.6, 117.2, 73.0, 68.6, 67.5, 65.4, 56.4, 47.8, 39.0, 38.2, 37.7, 26.9, 24.5, 19.1; IR (neat) ν_{max} 2930, 2251, 1724, 1427, 1105; $[\alpha]^{23}_D = -1.05°$ ($c = 0.47$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{28}H_{37}NO_4Si$ 480.2525, found 480.2587.

(2*R*,3*S*,4*E*)-3-(Dimethylphenylsilanyl)-2-hydroxyhex-4-enoic Acid Isopropyl Ester (14). A solution of the methyl ester[45] (582 mg, 2.09 mmol) in ^{i}PrOH (15 mL) was treated with Otera's catalyst (119 mg).[46] The mixture was refluxed for 120 h in a sealed tube (ca. 110 °C). The resulting mixture was concentrated and purified by silica column chromatography (2% EtOAc in hexane) to afford the crotylsilane as a pale yellow oil (530 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, m), 7.34 (3H, m), 5.38 (1H, m), 5.25 (1H, m), 4.99 (1H, hept, $J = 6.4$ Hz), 4.14 (1H, m), 2.84 (1H, br d, $J = 4.8$ Hz), 2.06 (1H, dd, $J = 2.8$, 10.4 Hz), 1.59 (3H, dd, $J = 2$, 6.8 Hz), 1.19 (3H, d, $J = 6.4$ Hz), 1.15 (3H, d, $J = 6.4$ Hz), 0.37 (3H, s), 0.31 (3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.8, 137.7, 134.2, 128.9, 127.6, 126.8, 124.9, 71.3, 69.2, 38.2, 21.9, 21.8, 18.1, −3.8, −4.0; IR (neat) ν_{max} 3513, 2980, 1723, 1247, 1106; $[\alpha]^{23}_D = +35.1°$ ($c = 0.49$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{17}H_{26}O_3Si$ 307.1685, found 307.1719.

(2*S*,5*S*,6*R*,3*Z*)-6-{3-(2*R*,4*S*,6*S*)[4-(*tert*-Butyldiphenylsilanyloxy)-6-cyanomethyltetrahydropyran-2-yl]-(2*S*)-2-methoxypropyl}-5-methyl-5,6-dihydro-2*H*-pyran-2-carboxylic Acid Isopropyl Ester (70). A solution of aldehyde **69** (400 mg, 0.83 mmol) and crotylsilane **14** (463 mg, 1.51 mmol) in DCM (16.7 mL) at −50 °C was treated with TMSOTf (240 mg, 1.08 mmol). The resulting mixture was stirred for 12 h at this temperature before a saturated aqueous solution of $NaHCO_3$ (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. Removal of the solvents under reduced pressure yielded a crude mixture (dr = 5:1 (*trans*:*cis*), determined by ^{1}H NMR analysis of the crude reaction mixture). Purification of the residue by flash column chromatography (silica gel, 15−20% EtOAc in hexane) afforded the *trans*-pyran **70** as a pale yellow oil (385 mg, 73%, a single *trans*-diastereoisomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (4H, m), 7.44−7.34 (6H, m), 5.82 (1H, m), 5.72 (1H, m), 5.06 (1H, hept, $J = 6.4$ Hz), 4.63 (1H, m), 4.22 (1H, m), 4.21−4.14 (2H, m), 3.75 (1H, m), 3.65 (1H, m, $J = 9.2$ Hz), 3.4 (3H, s), 2.43 (2H, m), 2.03 (1H, m), 1.90−1.75 (3H, m), 1.66−1.49 (3H, m), 1.36−1.29 (1H, m), 1.25 (3H, d, $J = 6$ Hz), 1.22 (3H, d, $J = 6$ Hz), 1.21 (1H, m), 1.06 (9H, s), 0.94 (3H, d, $J = 7.2$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.3, 135.6, 135.6, 133.8, 133.7, 133.4, 129.7, 129.7, 127.7, 127.6, 122.5, 117.3, 74.5, 74.1, 72.1, 69.4, 68.1, 67.5, 65.7, 56.7, 40.0, 39.5, 38.5, 37.9, 33.8, 26.9, 24.6, 21.8, 19.2, 17.2; IR (neat) ν_{max} 2930, 2251, 1746, 1106; $[\alpha]^{23}_D = -24°$ ($c = 0.67$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{37}H_{51}NO_6Si$ 633.3486, found 633.3457.

(2*S*,6*R*)-6-{3-(2*R*,4*S*,6*S*)-[4-(*tert*-Butyldiphenylsilanyloxy)-6-cyanomethyltetrahydropyran-2-yl]-2-(2*S*)-methoxypropyl}-5-(5*S*)-methyltetrahydropyran-2-carboxylic Acid Isopropyl Ester (71). A solution of olefin **70** (385 mg, 0.61 mmol) in EtOAc (23 mL) was treated with Pd/C (77 mg) and then placed under a H_2 atmosphere and stirred for 18 h. The heterogeneous solution was filtered through a pad of Celite. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 20% EtOAc in hexane) afforded the *trans*-pyran **71** as a pale yellow oil (342 mg, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (4H, m), 7.44−7.34 (6H, m), 5.09 (1H, hept, $J = 6.4$ Hz), 4.36 (1H, m), 4.22 (1H, m), 4.21−4.12 (2H, m), 3.66−3.59 (2H, m), 3.39 (3H, s), 2.43 (2H, m), 2.06 (1H, m), 1.87−1.72 (3H, m), 1.65−1.50 (5H, m), 1.44−1.15 (4H, m), 1.25 (3H, d, $J = 6.8$ Hz), 1.24 (3H, d, $J = 6$ Hz), 1.06 (9H, s), 0.84 (3H, d, $J = 6.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.8, 135.6, 135.6, 133.8, 133.7, 129.7, 129.7, 127.7, 127.6, 117.2, 75.7, 74.5, 72.5, 69.4, 67.9, 67.5, 65.7, 56.9, 40.4, 39.6, 38.5, 37.8, 35.1, 28.7, 27.0, 26.9, 24.6, 21.9, 21.8, 19.2, 18.2; IR (neat) ν_{max} 2929, 2251, 1738, 1106; $[\alpha]^{23}_D = +14.4°$ ($c = 0.52$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{37}H_{53}NO_6Si$ 636.3676, found 636.3668.

(2*S*,4*S*,6*R*)-{4-(*tert*-Butyldiphenylsilanyloxy)-(2*S*)-6-[(2*R*,3*S*,6*S*)-3-(6-formyl-3-methyltetrahydropyran-2-yl)-2-methoxypropyl]tetrahydropyran-2-yl}acetonitrile (72). A solution of ester **70** (110 mg, 0.17 mmol) in Et_2O (4.3 mL) at −78 °C was treated with DIBAL-H (0.363 mL, 1.0 M in hexane). The mixture was stirred for 1 h before MeOH (1 mL) was added at −78 °C followed by the addition of a saturated aqueous solution of Rochelle's salts (10 mL). The mixture was stirred for 1.5 h and slowly warmed to room temperature. The reaction mixture was acidified (5% aqueous HCl, 3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 40% EtOAc in hexane) afforded the aldehyde **72** as a pale yellow oil (92 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (1H, d, $J = 2$ Hz), 7.62 (4H, m), 7.44−7.33 (6H, m), 4.23 (1H, m), 4.21−4.08 (3H, m), 3.71 (1H, m), 3.41 (1H, m), 3.35 (3H, s), 2.44 (2H, m), 2.09 (1H, m), 1.87−1.69 (3H, m), 1.66−1.45 (5H, m), 1.42−1.22 (4H, m), 1.07 (9H, s), 0.82 (3H, d, $J = 6.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 205.8, 135.6, 133.7, 133.7, 129.8, 129.7, 127.7, 127.6, 117.2, 78.8, 77.1, 73.9, 69.2, 67.5, 65.7, 56.7, 39.8, 38.7, 38.6, 37.8, 34.7, 28.9, 26.9, 24.6, 23.9, 19.2, 17.9; IR

(45) Panek, J. S.; Yang, M.; Solomon, J. S. *J. Org. Chem.* **1993**, *58*, 1003.

(46) For preparation of Otera's catalyst, see: Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.

(neat) ν_{max} 2929, 2251 1732, 1105; $[\alpha]^{23}_D = +35.3°$ ($c = 0.30$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{34}H_{47}NO_5Si$ 578.3257, found 578.3353.

(2*S*,4*S*,6*R*)-(4-(*tert*-Butyldiphenylsilanyloxy)-(2*S*)-6-{2-methoxy-(2*R*,3*S*,6*S*)-3-[3-methyl-6-(2-oxoethyl)tetrahydropyran-2-yl]-propyl}tetrahydropyran-2-yl)acetonitrile (12). Preparation of Wittig reagent (0.25 M in THF): A suspension of (methoxymethyl)-triphenylphosphonium chloride (800 mg) in THF (6.32 mL) at −78 °C was treated with LiHMDS (2.12 mL, 1.0 M in THF). The reaction mixture was then warmed to room temperature. A deep red solution formed. A solution of aldehyde **72** (92 mg, 0.16 mmol) in THF (2 mL) at −78 °C was treated with the solution (1.5 mL) prepared above. The mixture was stirred for 4.5 h and slowly warmed to room temperature before water (10 mL) was added. The reaction mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvents afforded the enol ether as a dark brown oil. A solution of the crude enol ether in THF (4.8 mL) and water (2.4 mL) was treated with mercury acetate (432 mg). The reaction mixture was stirred for 15 min before KI solution (8% in water, 25 mL) was added. The resulting mixture was stirred for another 20 min and was extracted with DCM (3 × 10 mL). The combined organic layers were dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 30−50% EtOAc in hexane) afforded the aldehyde **12** as a pale yellow oil (82 mg, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, m), 7.62 (4H, m), 7.44−7.33 (6H, m), 4.38 (1H, m), 4.22 (1H, m), 4.18 (1H, m), 4.09 (1H, m), 3.55 (1H, m), 3.45 (1H, m), 3.26 (3H, s), 2.85 (1H, ddd, $J = 2.4, 8.4, 16$ Hz), 2.44 (2H, m), 2.42 (1H, ddd, ovrlp, $J = 1.2, 4.8$ Hz), 1.75−1.23 (13H, m), 1.06 (9H, s), 0.97 (3H, d, $J = 6.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 201.6, 135.6, 133.7, 129.8, 127.7, 127.6, 117.3, 74.1, 73.2, 69.2, 67.5, 66.5, 65.7, 56.6, 46.7, 39.7, 38.6, 38.0, 37.9, 33.5, 27.6, 26.9, 26.2, 24.6, 19.2, 18.2; IR (neat) ν_{max} 2929, 2251 1725, 1105; $[\alpha]^{23}_D = +20.4°$ ($c = 0.30$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{34}H_{47}NO_5Si$ 591.3380, found 591.3379.

(2*S*,4*S*,6*R*)-(4-(*tert*-Butyldiphenylsilanyloxy)-(2*S*)-6-{(2*R*,3*S*,6*S*)-3-[6-(2*S*,3*E*)-(2-hydroxy-6-methylhept-3-enyl)-3-methyltetrahydropyran-2-yl]-2-methoxypropyl}tetrahydropyran-2-yl)-acetonitrile (73). A suspension of bis(cyclopentadienyl)zirconium chloride hydride (250 mg, 0.97 mmol) in DCM (4.4 mL) at room temperature was treated with 4-methyl-1-pentyne (114.3 μL, 0.97 mmol). The mixture was stirred for 15 min until a clear yellow solution was formed. The resulting solution was cooled to −60 °C and was treated with $ZnMe_2$ (0.486 mL, 2.0 M in toluene). The reaction mixture was stirred for 20 min at this temperature and was warmed to 0 °C and stirred for another 5 min. A solution of aldehyde **12** (115 mg, 0.19 mmol) in DCM (5 mL) was cooled to 0 °C before being transferred to the vinyl zinc solution prepared as described above. The mixture was stirred at 0 °C for 3.5 h before a saturated aqueous solution of NH_4Cl (10 mL) was added. The reaction mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed by brine (20 mL) and dried over $MgSO_4$. Removal of solvent and filtration through a short pad of silica (80% EtOAc in hexane) afforded the alcohol as a mixture of diastereomers (105 mg, 80%, dr = 2:1). The resulting mixture was subjected to a careful purification by flash column chromatography (10/12.5/15% EtOAc in DCM) to afford desired alcohol **73** (72 mg, 55% as a single diastereomer) as a clear thick oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.59 (4H, m), 7.44−7.33 (6H, m), 5.64 (1H, m), 5.48 (1H, dd, $J = 6, 11.2$ Hz), 4.33 (1H, m), 4.22 (1H, m), 4.18 (1H, m), 4.06 (2H, m), 3.60 (2H, m), 3.31 (3H, s), 2.42 (2H, m), 2.09 (1H, m), 1.97−1.22 (18H, m), 1.06 (9H, s), 0.97 (3H, d, $J = 6.4$ Hz), 0.86 (3H, d, $J = 6.8$ Hz), 0.85 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 135.7, 134.3, 133.9, 133.8, 129.9, 129.4, 127.8, 127.8, 117.4, 74.4, 72.9, 69.2, 68.7, 67.6, 67.4, 65.7, 56.5, 41.6, 40.0, 39.4, 38.6, 37.9, 37.6, 33.5, 28.2, 27.8, 26.9, 26.3, 24.6, 22.2, 22.2, 19.1, 18.4; IR (neat) ν_{max} 3456, 2928, 1427, 1105; $[\alpha]^{23}_D = +16.5°$ ($c = 0.32$, CH_2Cl_2); CIHRMS $[M]^+$ calcd for $C_{41}H_{61}NO_5Si$ 675.4319, found 675.4334.

(1*R*,3*S*,5*R*,7*R*,9*R*,12*R*,14*S*,17*S*,18*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-3-methoxy-18-methyl-13-(1*E*)-(4-methylpent-1-enyl)-12,19,20-trioxatricyclo[13.3.1.15,9]icosan-11-one (75). A solution of nitrile **73** (55 mg, 0.0815 mmol) in DCM (2.0 mL) at −78 °C was slowly treated with DIBAL-H (0.212 mL, 1.0 M in hexane). The mixture was stirred for 2 h at this temperature before HCl (1.0 N, 3 mL) was added at −78 °C, and the resulting mixture was stirred for 20 min and slowly warmed to room temperature. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, EtOAc) afforded the crude aldehyde. The mixture was kept at room temperature for 18 h. Purification by flash column chromatography (silica gel, 20% EtOAc in hexane) afforded the lactol as a thick oil (29 mg, 55%), and the polar residue was kept at room temperature for another 5 days before another portion of lactol **74** (5 mg, 9%) was isolated. A solution of lactol **74** (25 mg) and molecular sieves (300 mg) in DCM (3 mL) was treated with PCC (50 mg), and the mixture was stirred at room temperature for 22 h. Purification by flash column chromatography (silica gel, 20% EtOAc in hexane) afforded the lactone **75** as a thick oil (22 mg, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (4H, m), 7.44−7.33 (6H, m), 5.70 (1H, m), 5.41−5.28 (2H, m), 4.28−4.25 (2H, m), 3.93−3.87 (2H, m), 3.64 (1H, m, $J = 10.8$ Hz), 3.51 (1H, m, $J = 10.8$ Hz), 3.32 (3H, s), 2.50−2.42 (2H, m), 2.23 (1H, m, $J = 12.4$ Hz), 1.94−1.00 (17H, m), 1.16 (3H, d, $J = 7.2$ Hz), 1.09 (9H, s), 0.83 (6H, d, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 135.7, 135.7, 134.1, 134.1, 132.2, 130.2, 129.9, 129.9, 127.8, 73.6, 73.5, 70.7, 69.5, 69.4, 66.2, 63.2, 57.2, 43.2, 43.0, 41.6, 38.9, 38.6, 38.5, 35.5, 30.8, 29.6, 28.0, 27.1, 26.9, 24.0, 22.2, 19.3, 18.2; IR (neat) ν_{max} 2928, 1741, 1111; $[\alpha]^{23}_D = +41.3°$ ($c = 0.375$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{41}H_{60}O_6Si$ 677.4193, found 677.4428.

((*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-3-(2*R*,4*S*,6*S*)-6-(2-aminoethyl)-4-(*tert*-butyldiphenylsilyloxy)tetrahydro-2*H*-pyran-2-yl)-2-methoxypropyl)-5-methyltetrahydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-ol (77): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, br), 7.61−7.58 (4H, m), 7.43−7.33 (6H, m), 5.61 (1H, m), 5.48 (1H, dd, $J = 6, 11.2$ Hz), 4.24 (1H, m), 4.12 (2H, m), 4.00 (2H, m), 3.52 (1H, m), 3.37 (1H, m), 3.32 (3H, s), 3.28 (1H, m, ovlp), 3.1 (1H, m), 2.11 (1H, m), 1.87 (5H, m), 1.73−1.23 (8H, m), 1.12 (1H, m), 1.06 (14H, s), 0.88 (3H, d, $J = 6$ Hz), 0.84 (3H, d, $J = 6.8$ Hz), 0.83 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.1, 134.0, 133.8, 129.8, 129.7, 127.7, 127.7, 74.3, 73.2, 71.4, 69.7, 68.3, 68.1, 65.5, 56.2, 41.6, 39.3, 39.0, 38.7, 38.3, 37.5, 35.4, 32.2, 28.8, 28.2, 27.4, 27.0, 22.4, 22.3, 19.3, 18.2; IR (neat) ν_{max} 3396, 2929, 1462, 1111; $[\alpha]^{23}_D = +22.8°$ ($c = 1.0$, CH_2Cl_2); CIHRMS $[M + 1]^+$ calcd for $C_{41}H_{65}NO_5Si$ 680.4666, found 680.4660.

Trifluoromethanesulfonic Acid 4-[3-(*tert*-butyldiphenylsilanyloxy)propyl]oxazol-2-yl Ester (16). A 100 mL round-bottom flask was charged with oxazolone **82** (0.250 g/0.655 mmol) and a stir bar. CH_2Cl_2 (3.5 mL) was added, and the reaction was cooled to −78 °C. 2,6-Lutidine (0.140 g/1.31 mmol) was then added via syringe followed by the addition of Tf_2O (0.277 g/0.983 mmol). The reaction was then allowed to warm to room temperature with stirring for 30 min before being diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on SiO_2 (10% Et_2O/pentane) to give 0.280 g of **16** (80%) as a colorless oil. Triflate **16** is chemically unstable and used immediately after preparation: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.60 (m, 4H), 7.41−7.34 (m, 6H), 7.12 (s, 1H), 3.67 (t, 2H, $J = 6.0$ Hz), 2.61 (t, 2H, $J = 7.6$ Hz), 1.85 (tt, 2H, $J = 6.0, 7.6$ Hz), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 142.1, 135.5, 133.9, 133.7, 129.8, 129.6, 127.7, 127.6, 118.5 (q, CF_3, $J = 319.7$ Hz), 62.54; IR (neat) ν_{max}

2932, 2361, 1735, 1426, 1248, 1030, 702; HRMS (CI, CH_4) *m*/*z* calcd for $C_{23}H_{26}NO_5SSi$ $[M]^+$ 513.1253, found 513.1282.

(3-{4-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]oxazol-2-yl}-prop-2-ynyl)carbamic Acid Methyl Ester (86). A 50 mL round-bottom flask was charged with freshly prepared triflate **16** (0.130 g/0.253 mmol) and a stir bar. 1,4-Dioxane (1.2 mL) and 2,6-lutidine (0.136 g/1.23 mmol) were added with stirring. Alkyne **17** (0.045 g/0.405 mmol), $Pd(PPh_3)_4$ (30 mg/0.025 mmol), and CuI (3 mg/0.013 mmol) were added, and the reaction was stirred at room temperature for 4−5 h. The reaction was then diluted with EtOAc (∼10 mL) and filtered through a thin pad of SiO_2 and concentrated in vacuo. The residue was purified on SiO_2 (30% EtOAc/hexanes) to give 0.101 g of **86** (84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.62 (m, 4H), 7.41−7.32 (m, 6H), 7.21 (s, 1H), 4.90 (br s, 1H), 4.22−4.19 (m, 2H), 3.69 (br s, 3H), 3.66 (t, 2H, J = 6.4 Hz), 2.61 (t, 2H, J = 7.6 Hz), 1.87 (tt, 2H, J = 6.4, 7.6 Hz), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 145.5, 141.7, 135.5, 135.1, 133.7, 129.5, 127.6, 87.9, 71.3, 62.7, 52.5, 31.2, 30.8, 26.8, 22.4, 19.1; IR (neat) ν_{max} 3542, 3072, 2956, 2931, 2859, 2252, 1724, 1515, 1253, 1110, 734; HRMS (CI, CH_4) *m*/*z* calcd for $C_{28}H_{33}N_2O_4Si$ $[M + H]^+$ 477.2209, found 477.2208.

(1*R*,3*S*,5*R*,7*R*,9*R*,12*R*,14*S*,17*S*,18*S*)-7-Hydroxy-3-methoxy-18-methyl-13-(1*E*)-(4-methylpent-1-enyl)-12,19,20-trioxatricyclo-[13.3.1.15,9]icosan-11-one (3). A solution of silyl ether **75** (35 mg, 0.052 mmol) in THF (3.5 mL) at −20 °C was treated with TBAF (0.26 mL, 1.0 M in THF). The mixture was warmed to room temperature and stirred for 2 h. The same operation was repeated 3 times. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl (10 mL) and was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 80% EtOAc in hexane) afforded the alcohol **3** as a thick oil (22.5 mg, ca. 100%): ^{1}H NMR (400 MHz, C_5D_5N) δ 5.85−5.76 (2H, m), 5.58 (2H, dd, J = 6.4, 15.2 Hz), 4.68 (2H, m), 4.46 (1H, m), 4.22 (1H, m, J = 11.2 Hz), 4.09 (1H, m, J = 11.2 Hz), 3.96 (1H, m), 3.78 (1H, m), 3.41 (3H, s), 2.73 (1H, dd, J = 13.2, 4 Hz), 2.57−2.49 (2H, m), 2.15 (1H, dd, J = 12.8, 10.4 Hz), 1.97−1.85 (5H, m), 1.77 (1H, m), 1.69 (2H, m), 1.55 (2H, m), 1.43−1.20 (2H, m), 1.14−1.04 (2H, m), 1.10 (3H, d, J = 6.4 Hz), 0.82 (3H, d, J = 6.8 Hz), 0.81 (3H, d, J = 6.4 Hz); ^{13}C NMR (75 MHz, C_5D_5N) δ 170.8, 132.4, 131.9, 74.3, 74.2, 71.3, 70.2, 70.0, 64.1, 63.5, 57.0, 44.2, 43.7, 42.0, 40.2, 39.9, 39.8, 36.1, 31.7, 28.6, 27.6, 24.5, 22.6, 22.5, 18.7; IR (neat) ν_{max} 3435, 2927, 1739, 1652, 1464, 1385, 1274, 1110; $[\alpha]^{23}_D$ = +27° (c = 0.1, EtOH); CIHRMS $[M + 1]^+$ calcd for $C_{25}H_{42}O_6$ 439.3015, found 439.3087.

(1*R*,3*S*,5*R*,9*R*,12*R*,14*S*,17*S*,18*S*)-3-Methoxy-18-methyl-13-(1*E*)-(4-methylpent-1-enyl)-12,19,20-trioxatricyclo[13.3.1.15,9]icosan-7,11-dione (90). A solution of alcohol **3** (19 mg, 0.043 mmol) in DCM (1.2 mL) was treated with DMP (55.2 mg, 0.13 mmol) and pyridine (10.5 μL). The mixture was stirred for 2 h before diluting with saturated aqueous solutions of $NaHCO_3$ and NaS_2O_3 (10 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 20% EtOAc in DCM) afforded the ketone **90** as a thick oil (18 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (1H, m), 5.33 (2H, m), 4.00 (1H, m), 3.87 (1H, m), 3.48 (3H, m), 3.35 (3H, s), 2.62 (1H, dd, J = 3.6, 13.2 Hz), 2.44 (2H, m), 2.36−2.22 (4H, m), 2.08 (1H, m), 1.86 (3H, m), 1.73−1.22 (6H, m), 1.28 (2H, m), 1.13 (3H, d, J = 7.2 Hz), 1.03 (1H, m), 0.84 (3H, s), 0.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 168.7, 132.9, 129.9, 74.4, 73.5, 73.4, 71.2, 63.1, 57.3, 47.8, 47.3, 43.3, 42.7, 41.5, 39.5, 35.5, 30.8, 28.0, 27.0, 24.0, 22.1, 18.1; $[\alpha]^{23}_D$ = +54° (c = 0.05, EtOH); IR (neat) ν_{max} 2927, 1740, 1464, 1385, 1270, 1155; CIHRMS $[M + 1]^+$ calcd for $C_{25}H_{40}O_6$ 437.2858, found 437.2863.

(1*R*,3*S*,5*R*,7*S*,9*R*,12*R*,14*S*,17*S*,18*S*)-7-Hydroxy-3-methoxy-18-methyl-13-(1*E*)-(4-methylpent-1-enyl)-12,19,20-trioxatricyclo-[13.3.1.15,9]icosan-11-one (91). A solution of ketone **90** prepared as described above (15 mg, 0.034 mmol) in MeOH (0.7 mL) at 0 °C was treated with $NaBH_4$ (2.6 mg, 0.068 mmol). The mixture was stirred for 0.5 h before adding AcOH (19 μL). The resulting mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 80% EtOAc in hexanes) to afford the alcohol **91** as a thick oil (14 mg, 93% as a 15:1 mixture of diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (1H, m), 5.33 (2H, m), 3.86 (2H, m), 3.68 (1H, m), 3.49 (2H, m), 3.33 (3H, s), 3.19 (1H, t, J = 11.2 Hz), 2.54 (1H, dd, J = 3.6, 13.2 Hz), 2.35 (2H, m), 2.00 (2H, m), 1.86 (4H, m), 1.69−1.39 (6H, m), 1.31−1.18 (4H, m), 1.14 (3H, d, J = 5.4 Hz), 0.98 (1H, m), 0.82 (3H, d, J = 6.4 Hz), 0.82 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 132.4, 130.1, 73.6, 73.5, 73.0, 72.2, 70.8, 67.9, 63.0, 57.2, 43.0, 42.8, 41.5, 41.0, 40.7, 39.1, 35.4, 30.9, 28.0, 27.0, 24.0, 22.1, 18.1; $[\alpha]^{23}_D$ = +55° (c = 0.05, EtOH); IR (neat) ν_{max} 3435, 2927, 1739, 1652, 1464, 1385, 1274, 1110; CIHRMS $[M + 1]^+$ calcd for $C_{25}H_{42}O_6$ 439.3015, found 439.3013.

Leucascandrolide A (1). A solution of alcohol **91** (15 mg, 0.034 mmol), acid **4** (34.4 mg, 0.122 mmol), and triphenyl phosphine (35.53 mg, 0.135 mmol) in benzene (1.87 mL) and THF (0.5 mL) at 0 °C was treated with DIAD (26.67 μL). The mixture was stirred for 14 h and warmed to room temperature. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 20−40% EtOAc in DCM) to afford the leucascandrolide A (**1**) as thick glass (18.5 mg, 77%). The chromatographic and spectroscopic data of synthetic **1** are fully consistent with those of an authentic sample:[47] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, s), 6.31 (1H, m), 6.26 (1H, m), 6.07 (1H, m), 5.87 (1H, d, J = 11.6 Hz), 5.68 (1H, m), 5.52 (1H, br), 5.32 (2H, m), 5.23 (1H, t, J = 2.8 Hz), 4.29 (2H, t, J = 5.6 Hz), 3.99 (1H, m), 3.87 (1H, m), 3.66 (3H, s), 3.53 (3H, m), 3.32 (3H, s), 3.02 (2H, m), 2.70 (2H, t, J = 7.2 Hz), 2.51 (1H, dd, J = 4, 13.2 Hz), 2.32 (2H, m), 1.95−1.80 (5H, m), 1.72−1.17 (11H, m), 1.14 (3H, d, J = 7.2 Hz), 0.97 (1H, m), 0.82 (6H, d, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 165.4, 160.1, 157.2, 149.4, 141.1, 136.4, 134.0, 132.5, 131.1, 120.7, 116.6, 73.6, 73.3, 70.8, 70.0, 69.6, 67.3, 63.0, 57.2, 52.1, 43.2, 42.7, 41.5, 39.3, 99.1, 35.5, 35.4, 30.9, 28.0, 27.5, 27.0, 25.6, 24.2, 22.1, 18.1; $[\alpha]^{23}_D$ = +41° (c = 0.065, EtOH); IR (neat) ν_{max} 2953, 1717, 1276; CIHRMS $[M + 1]^+$ calcd for $C_{38}H_{56}N_2O_{10}$ 700.3935, found 700.3912.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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