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An Enantioselective Convergent Route to Pamamycin 621A

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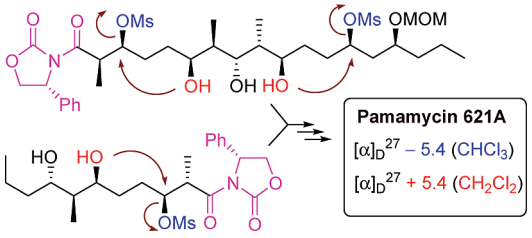

An effective approach to the total synthesis of natural antibiotic pamamycin 621A is described, in which the stereogenic centers at the C-13 and C-15 were taken from a chiral building block derived from the inexpensive D-glucolactone while all others (except the C-10) were installed via chiral auxiliary-induced asymmetric Evans/Crimmins aldol reactions. In the synthesis of the smaller/lower fragment, an antiselective Evans aldol condensation was found to occur only if a stoichiometric (rather than catalytic as reported in the literature) amount of magnesium chloride was present. A previously unknown effect of the steric bulkiness of the pyridine base employed on the stereochemical outcome of the formation of the THF ring in the presence of a chiral auxiliary was also observed. The THF rings in the larger/upper fragment were similarly synthesized with a high level of stereoselectivity from a linear precursor carrying a chiral auxiliary via intramolecular O-alkylations, most notably even under acidic conditions. The basic dimethylamino functionality at the C-15 was installed at the final stage of the whole synthesis, with those otherwise unavoidable side reactions in the conversion of the azido group effectively circumvented through using a very mild yet largely forgotten tributyltin reduction protocol.

Introduction

The name pamamycin appeared in the literature for the first time in 1979, referring to a compound isolated from the extracts of *Streptomyces alboniger* ATCC 12461 by McCann and Pogell.[1] Although the molecular formula and molecular weight of that compound were determined to be $C_{36}H_{63}NO_7$ and 621 Da, respectively, no specific chemical structure was given. The situation remained unchanged until 1988, when Marumo and co-workers reported[2a] the isolation of another compound from *Streptomyces alboniger* IFO12738, whose chemical and biological behavior is very similar to that of the pamamycin documented earlier. Because this new compound has a molecular weight of 607 Da, it was subsequently named pamamycin 607.

Extensive spectroscopic analyses were performed on pamamycin 607 (**1**, Figure 1), which allowed for the establishment of not only the molecular framework but also the relative[2b] as well as absolute[2c] configurations of the stereogenic centers. Three years later, four additional compounds, pamamycins 635A, 635B, 649A, and 649B, were isolated[2d] by the same Japanese group from the mother liquor of pamamycin 607. Then, in 1993, Gräfe and co-workers[2e] published their results on isolation of pamamycin 621 (which is now usually referred

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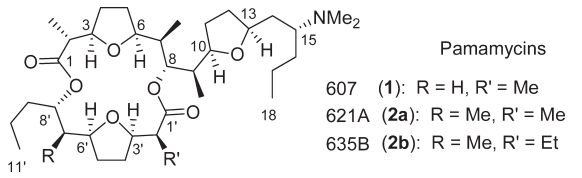

FIGURE 1. Structures of the three pamamycins that have been synthesized to date: 607 (**1a**), 621A (**2a**), and 635B (**2b**).

to as pamamycin 621A) from *Streptomyces aurantiacus* IMET 43917. A complete structure was also assigned to pamamycin 621(A) on the basis of chemical degradation and spectroscopic analyses, which made 621A the second actually fully characterized member among the whole pamamycin family to date. The other pamamycins so far documented in the literature were assigned mainly according to the MS analysis data with an inexplicit assumption that the framework and the stereochemistry are similar/comparable to those of 607 and 621A.

Another two homologues, MS-282a and MS-282b (both with MW = 635 Da),[2f] were isolated from *Streptomyces tauricus* ATCC27470 in 1994 by Nakanishi and co-workers. In the subsequent year, an additional nine pamamycins, namely, pamamycins 621B, 621C, 621D, 635A, 635B, 635C, 635D, 635E, and 635F, were identified by Natsumi et al.[2g,h] to be the components of the extracts of *Streptomyces alboniger* IFO12738. The latest four members in the family were reported by Gräfe[2i] in 1998—the pamamycins 663, 677, 691, and 705; all of them were isolated from *Streptomyces* sp. HKI-0118.

Although it has been shown, using the purified major constituent 607 or the mixtures enriched in one of the other components, that this class of compounds possesses a range of biological activities, including autoregulatory, anionophoric, antibacterial, anti-tuberculosis, and antifungal activities,[1,2a,d−i,3] further investigations are unfeasible because of the difficulty acquiring a pure individual compound. These, along with the intriguing structures, have invoked many synthetic endeavors[4] since the late 1990s.

The studies directed toward the synthesis of pamamycins began to appear in 1988.[5] However, despite the impressive efforts by a number of groups, no total synthesis was achieved throughout the whole 1990s. Then four elegant total syntheses of pamamycin 607 were completed in 2001 by Thomas,[6a] Lee,[6b,c] Metz,[6d] and Kang.[6e] In 2005, Metz disclosed the first synthesis of pamamycins 621A and 635B.[7] Recently, another efficient synthesis[6f] of pamamycin 607 along with fragments of 593 and 621D was reported by Hanquet and co-workers. In a previous publication,[8] we briefly communicated our results on pamamycin 621A. Here we wish to detail the whole work.

Results and Discussion

Our synthetic plan is outlined in Scheme 1. The target framework was disconnected into two fragments, **3** and **4**, which in turn could be related to their open-chain counterparts **5** and **6** by disconnecting the C−O bonds at the THF rings as the key steps in the whole synthesis. The linear precursor **5** was disconnected between C-2′ and C-3′ into simpler units **7** and **8**. Similarly, the precursor to the larger fragment **3** (i.e., **6**) was disconnected into three smaller fragments: **7**, **9**, and **10**.

The synthesis (Scheme 2) of the C-1′ to C-11′ fragment (**4**, the smaller/lower fragment of **2a**) emerged with an aldol reaction of Evans' *N*-propionyl oxazolidinone **7** with the known[9] enal **11** under the conditions[10] of Crimmins, which led to aldol **12** (dr 23:1). The isolated enantiopure **12** was then treated with MeNH(OMe)·HCl/$AlMe_3$ to deliver the known[11] Weinreb amide **13**. Further treatment with *n*-PrMgBr gave the corresponding ketone **14**, which on reduction with $Me_4NBH(OAc)_3$[12] in MeCN/HOAc at −20 °C produced 1,3-anti-diol **15**. No traces of the corresponding syn isomer, which was rather obvious if using $NaBH_4$ as the reducing agent, could be detected by ^1H NMR.

The diol **15** was transformed into **16** by sequential removal of the TBS (*tert*-butyldimethylsilyl) protecting group with TBAF (*n*-Bu_4NF), formation of the acetonide using $Me_2C(OMe)_2$/CSA (10-camphorsulfonic acid), and refreeing the

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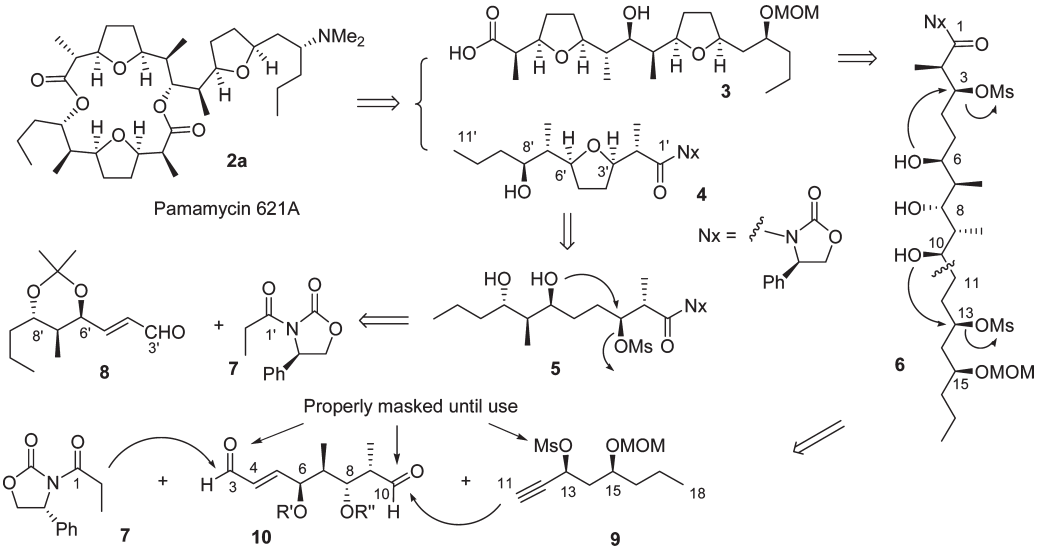
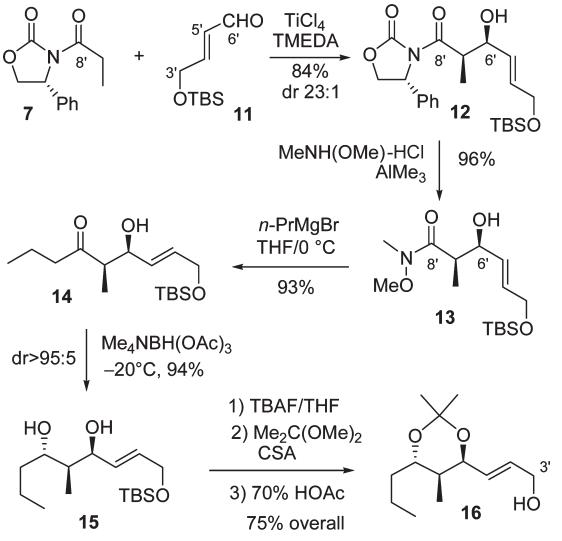
SCHEME 1. General Features of Our Retrosynthetic Analysis



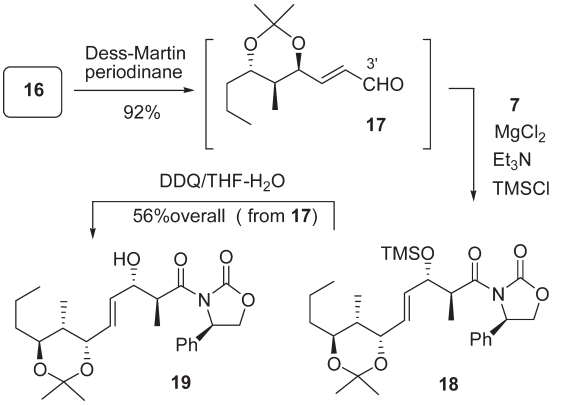
SCHEME 2



allylic OH with 70% HOAc. The seemingly more direct alternative, formation of the acetonide followed by desilylation, did not work so well, perhaps because the 1,3-anti-diol cannot form a highly thermodynamically favored acetonide as the corresponding syn diols: using either $Me_2C(OMe)_2$ or $CH_2{=}CHMe(OMe)$ in CH_2Cl_2 in the presence of weak acid catalyst PPTS (pyridium *p*-sulfonate, 0.1 equiv), the reaction was very sluggish, while stronger acid catalysts such as CSA (0.1 equiv) soon led to a complicated mixture.

Oxidation of the C-3′ alcohol into the corresponding aldehyde was readily achieved with Dess−Martin periodinane

SCHEME 3



(Scheme 3). The resulting crude enal **17** was then subjected to Evans's antiselective aldol reaction conditions ($MgCl_2$/TMSCl[13] (trimethylsilyl chloride)) to install the C-1′/C-2′. However, completely to our surprise, the anticipated condensation essentially did not occur at all under the broadly cited literature conditions (using only a catalytic amount of $MgCl_2$). We suspected that the failure might be caused by the presence of the acetonide functionality, which might consume some Mg ion and thus reduce the amount of effective content of Mg ion required for the aldol reaction, as the aldehydes in most (if not all) literature precedents were much simpler/less functionalized. Therefore, we next tried to increase the amounts of the added $MgCl_2$ and Et_3N.

The main results of the aldol reaction using stoichiometric amounts of $MgCl_2$ are outlined in Table 1. In the presence of 1 equiv (with respect to aldehyde **17**) of $MgCl_2$ and 4 equiv of Et_3N, the expected TMS protected aldol **18** was indeed formed, which on cleavage of the silyl protecting group provided aldol **19** in 31% yield (Table 1, entry 1). Addition of $NaSbF_6$ was reported[13] to have a positive effect in the literature cases. Therefore, we also attempted to improve the yield by introducing $NaSbF_6$. However, somewhat to our surprise both the yield and the diastereoselectivity declined

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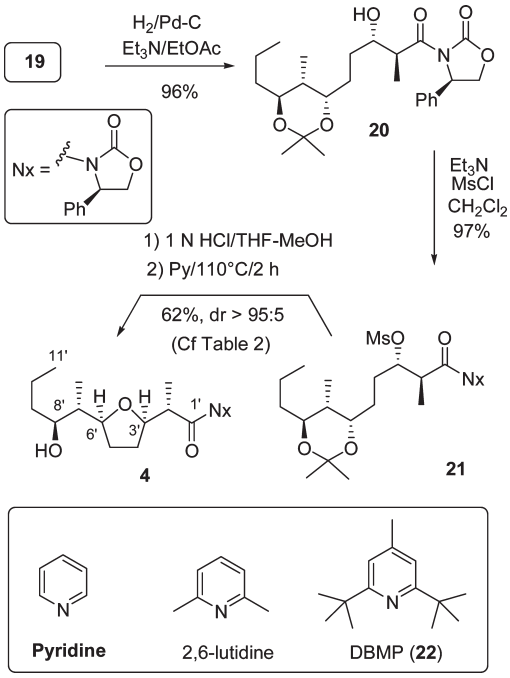
TABLE 1. Antiselective Aldol Reaction between 7 (2 equiv with respect to 17) and 17 Performed in EtOAc in the Presence of TMSCl (3 equiv with respect to 17) at Ambient Temperature with [17] = 0.5 M Unless Otherwise Stated

entry	conditions	yield of **19** (dr)
1	$MgCl_2$ (1 equiv)/Et_3N (4 equiv)	31%
2[a]	$MgCl_2$ (1 equiv)/Et_3N (5 equiv)/ $NaSbF_6$ (0.6 equiv)	25% (5:1)
3	$MgCl_2$ (1 equiv)/Et_3N (6 equiv)/4 Å MS	(traces)
4	$MgCl_2$ (2 equiv)/Et_3N (4 equiv)	45%
5	$MgCl_2$ (2 equiv)/Et_3N (5 equiv)	56% (13:1)
6[a]	$MgCl_2$ (2 equiv)/Et_3N (5 equiv)	57% (10:1)
7	$MgCl_2$ (1 equiv)/Et_3N (6 equiv)	47% (12:1)

[a][**17**] = 0.25 M.

SCHEME 4



(Table 1, entry 2). In the presence of molecular sieves, essentially no reaction occurred (Table 1, entry 3).

Use of more $MgCl_2$ (2 equiv with respect to **17**) under otherwise the same conditions as in the entry 1 raised the yield of **19** (via crude **18** without any purification) to 45% (Table 1, entry 4). If the amount of the added Et_3N increased from 4 to 5 equiv, the yield could be further raised to 56%, with a diastereomeric ratio of 13:1 (Table 1, entry 5). The amount of solvent also seemed to have an effect on the outcome of this reaction. At a lower concentration ([**17**] = 0.25 M), the dr value substantially dropped although the yield essentially remained the same (Table 1, entry 6). Finally, use of less $MgCl_2$ (1 equiv) but more Et_3N (6 equiv) gave lower yield and diastereomeric selectivity (Table 1, entry 7). Thus, the optimal conditions appeared to be those in entry 5, which were employed later in preparative runs.

The C−C double bond in **19** was saturated by hydrogenation over 10% Pd−C to deliver **20**, which was subsequently converted to the corresponding mesylate **21** via reaction with MsCl/Et_3N in CH_2Cl_2 (Scheme 4). The acetonide was then removed with 1 N HCl in THF/MeOH to release the C-6′/C-8′ diol functionality, setting up the stage for the key step of THF ring formation with concurrent configuration inversion at the C-3′.

TABLE 2. Treatment of 21 with Different Bases Leading to 4

entry	conditions	outcomes
1	2,6-lutidine/120 °C/3 h	**4** (83%, dr 11:1)
2	2,6-lutidine/140−150 °C/3 h	**4** (90%, dr 10:1)
3	2,6-luditine/rt/2 months	**4** (traces)
4	DBMP[a] (**22**)/130−140 °C/3 h	**4** (100%, dr 5:1)
5	DBMP[a] (**22**)/toluene/120 °C/3 h	**4** (88%, dr 5:1)
6	Py/110 °C/3 h	**4** (62%, dr ≥95:5)[b]
7	Py/rt/2 months	**4** (traces)

[a]DBMP = 2,6-di-*tert*-butyl-4-methylpyridine (**22**, Scheme 4). [b]No other isomer(s) could be seen by ^1H NMR.

In the beginning, the cyclization of **21** leading to **4** was thought to be very similar to that in our[14] nonactin synthesis. The most satisfactory conditions (2,6-lutidine/120 °C) developed in that work were therefore simply adopted here. However, the product thus obtained turned out to be a mixture of two diastereomers (dr 11:1, Table 2, entry 1) instead of a pure enantiomer. At a slightly higher temperature (Table 2, entry 2), the diastereomeric ratio began to drop further. If running the reaction at ambient temperature, essentially no **4** was formed even after 2 months (Table 2, entry 3).

We suspected that the presence of the minor isomer might stem from partial racemization at the stereogenic center α to the carbonyl group. If this was the case, a sterically more bulky base, which did not easily deprotonate the α-proton, might help to reduce such side reactions. With this thought in mind, we next synthesized 2,6-di-*tert*-butyl-4-methylpyridine (**22**, Scheme 4) using a literature[15] procedure. Somewhat to our surprise, when the sterically more congested base **22** was utilized as base (also as solvent) in this reaction, the diastereomeric ratio of the product declined to only 5:1 (Table 2, entry 4). Greatly reducing the amount of the added **22** by performing the reaction in toluene, also at a slightly lower temperature, did not lead to any improvement in the dr value but substantially lowered the yield of **4**. Interestingly, use of the least hindered base in the series (i.e., the pyridine itself) eliminated the isomer completely. Thus, by heating **21** in neat pyridine at 110 °C for 3 h, **4** was obtained in 63% yield as a single isomer (Table 2, entry 6). The unreacted **21** could be recovered and recycled. However, it should be noted that no **4** was formed at ambient temperature even after 2 months (Table 2, entry 7).

With the smaller fragment **4** in hand, we next turned our attention to the structurally more complex fragment **6**, a key precursor to the larger unit of pamamycin 621A (**3**). According to our general plan (Scheme 1), this linear precursor was to be assembled from its subunits **9** (the C-11 to C-19 fragment) and **10** (the C-3 to C-10 fragment). The alkyne fragment **9** was synthesized using a route shown in Scheme 5. Starting from the known epoxide **23**, which can be readily prepared[16,17] from inexpensive D-glucolactone using a practical route developed by us earlier, via reaction with EtMgBr/CuCN[18] in THF, the alcohol **24** was obtained in 97% yield.

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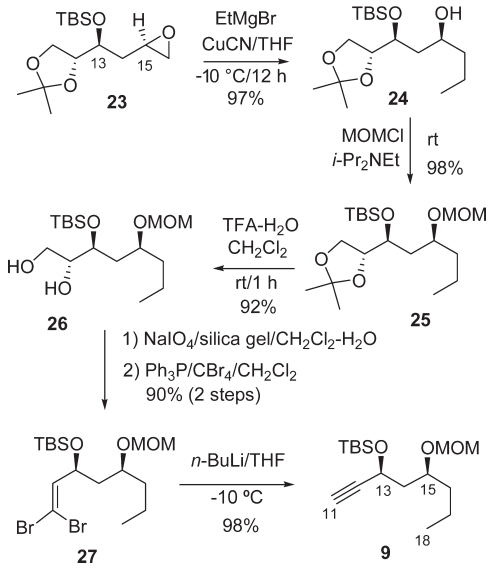
(17) It is noteworthy that in the preparation of **23** by silylation of the corresponding alcohol via treatment with TBSCl, use of the more commonly employed CH_2Cl_2 as the solvent led to extremely slow reaction at different concentrations with a large excess of the added base/silylating agent with or without DMAP. Replacement of the TBSCl with TBSOTf did not result in any improvement. In DMF, the reaction proceeded much faster, in general, but relatively high substrate concentration (ca. 1 M) is recommended.

SCHEME 5



The newly formed hydroxyl group was masked as a MOM ether by treatment with MOMCl/*i*-Pr_2NEt, giving the desired **25** in 98% yield.

Removal of the acetonide protecting group in **25** without touching the TBS group was rather difficult. A variety of conditions failed in the initial attempts (Table 3). Those most commonly employed protocols for cleavage of acetonides, such as *p*-TsOH or CSA (camphor-10-sulfonic acid)/CH_2Cl_2 (with or without added MeOH)/rt, all led to a complex mixture (Table 3, entries 1−3). Use of CAN (ceric ammonium nitrate)/$KBrO_3$[19] also resulted in a complex mixture in this case (Table 3, entries 4−6). In the presence of a borate buffer,[19] CAN failed to bring about any reactions (Table 3, entry 7).

The reaction with $FeCl_3/SiO_2/CHCl_3$[20] was better, giving the desired diol **26** in 21% yield, along with 48% of recovered starting **25** (Table 3, entry 8). Slightly higher yields were obtained with 80% aqueous HOAc (as solvent) at ambient temperature or 70% aqueous HOAc in THF at slightly elevated temperatures (Table 3, entries 9 and 10). Then we noticed a relevant example reported by Smith[21] and co-workers, which used 50% F_3CCO_2H in CH_2Cl_2 to cleave 3-pentanonide without touching the TBS in the same substrate. To our delight, this set of conditions also worked very well for us. After treatment of **25** with 50% F_3CCO_2H/CH_2Cl_2 at ambient temperature for 1 h, the desired **26** was formed in 90% yield (Table 3, entry 11).

The diol functionality was oxidatively cleaved with aq $NaIO_4/SiO_2$[22] in CH_2Cl_2. The intermediate aldehyde was treated with Ph_3P/CBr_4 to deliver the *gem*-dibromide **27**, which on further exposure to *n*-BuLi in THF at ca. −10 °C provided the terminal alkyne **9**.

TABLE 3. Removal of the Acetonide Group in 25 under Different Conditions

entry	conditions	yield for **26**
1	CSA (0.2 equiv)/CH_2Cl_2/rt	-[a]
2	CSA (0.1 equiv)/CH_2Cl_2/MeOH (10 equiv)/rt	-[a]
3	*p*-TsOH (0.1 equiv)/ CH_2Cl_2/MeOH (10 equiv)/rt	-[a]
4	CAN (0.5 equiv)/MeOH/0 °C	-[a]
5	3% CAN/$KBrO_3$ (1.5 equiv)/CH_3CN/H_2O (1:1)/60 °C	-[a]
6	3% CAN/$KBrO_3$ (1.5 equiv)/CH_3CN/H_2O (1:1)/rt	-[a]
7	3% CAN/borate buffer/CH_3CN/H_2O (1:1)/ 60 °C	(no reaction)
8	$FeCl_3-SiO_2/CHCl_3$/rt	21%[b]
9	80% aq AcOH (as solvent)/rt	30%[c]
10	70% aq AcOH/THF/rt to 50 °C	33%
11	50% aq CF_3CO_2H/CH_2Cl_2/rt/1 h[d]	90%

[a]A complex mixture was obtained. [b]Along with 48% of recovered **25**. [c]Along with 21% of recovered **25**. [d]With [**25**] = 0.03 M.

The fragment that corresponds to the C-3 to C-10 in the target structure (cf. **10** in Scheme 1) was built up using two chiral auxiliary-induced asymmetric aldol reactions[24,10] to install the four consecutive stereogenic centers. The synthesis emerged with the condensation between **28**[23] and **7**[25] under the conditions of Crimmins[10] (Scheme 6). The chiral auxiliary was then reductively cleaved with $NaBH_4/H_2O$[26] in THF to deliver the corresponding diol **30**, which was consequently transformed into the corresponding cyclic benzylidene acetal **31** before further elaboration into alcohol **33**.

Conversion of **30** into **31** was first attempted under conventional conditions (CSA/$PhCH(OMe)_2$) with CH_2Cl_2 as the solvent. The reaction was very slow. To speed up the reaction, we next performed the reaction in neat $PhCH(OMe)_2$ under aspirator vacuum (to remove any MeOH formed). Under such conditions, the desired **31** formed in 91% yield within 1 h at ambient temperature. This protocol of acetalization also allowed for direct use of the crude mixture of the diol **30** (and the concurrently generated chiral auxiliary **7**), which was rather polar and difficult to separate from **7** on silica gel.

Further elaboration of the diol via formation of the cyclic acetal **31** followed a DIBAL-H reduction afforded a pair of monoalcohols (ca. 1:13 as measured on the crude product by ^{1}H NMR) with the desired isomer as the major product. The isolated pure alcohol **33** was then oxidized with Dess−Martin periodinane to yield aldehyde **34**, which was required for a subsequent aldol condensation to introduce the C-8/C-9 stereogenic centers. To facilitate conversion of the C-10 terminal into an aldehyde at a later stage, which was required according to our synthetic plan, an oxazolidinethione auxiliary[27] (**35**) was employed because treatment of such species

(18) Smith, A. B., III; Razler, T. M.; Pettit, G. R.; Chapuis, J.-C. *Org. Lett*. **2005**, *7*, 4403–4406.
(19) Kojima, H.; Urano, Y.; Kikuchi, K.; Higuchi, T.; Hirata, Y.; Nagano, T. *Angew. Chem., Int. Ed*. **1999**, *38*, 3207–3209.
(20) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem*. **1986**, *51*, 404–407.
(21) Smith, A. B., III.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi., M. *Org. Lett*. **2002**, *4*, 783–786.
(22) Spanu, P.; Rassu, G.; Ulgheri, F.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Tetrahedron* **1996**, *52*, 4829–4838.
(23) Marshall, J. A.; Schaaf, G.; Nolting, A. *Org. Lett*. **2005**, *7*, 5331–5333.
(24) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127–2129. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc*. **1991**, *113*, 1047–1049. (c) Crimmins, M. T.; Chaudhary, K. *Org. Lett*. **2000**, *2*, 775–777. (d) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem*. **2001**, *66*, 894–902.
(25) For a practical high-yielding route to such auxiliaries, see: Wu, Y.-K.; Shen, X. *Tetrahedron: Asymmetry* **2000**, *11*, 4359–4363.
(26) Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett*. **1998**, *39*, 7067–7070.
(27) For a convenient/practical synthesis of such auxiliaries, see: Wu, Y.-K.; Yang, Y.-Q.; Hu, Q. *J. Org. Chem*. **2004**, *69*, 3390–3392.

SCHEME 6

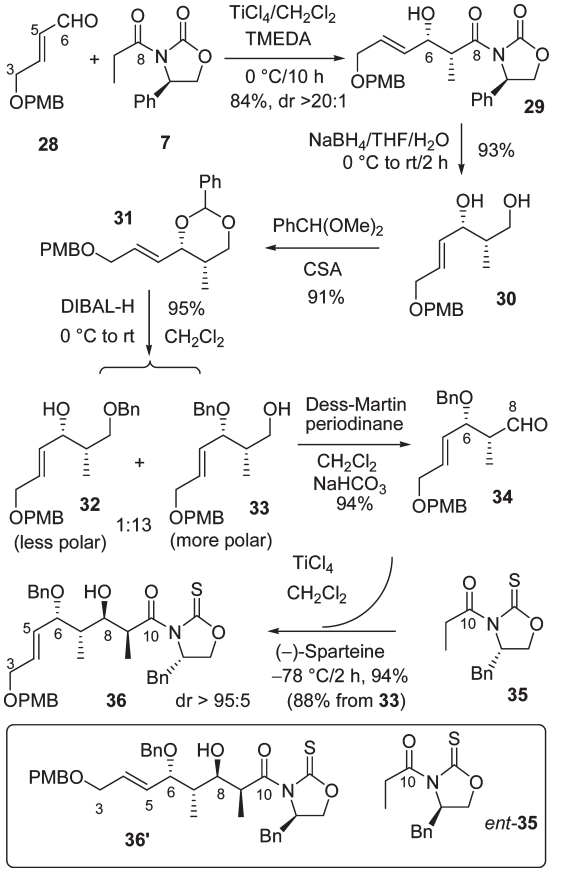


TABLE 4. Aldol Reaction of 34 with 35 or *ent*-35 at −78 °C in CH_2Cl_2 under Different Conditions

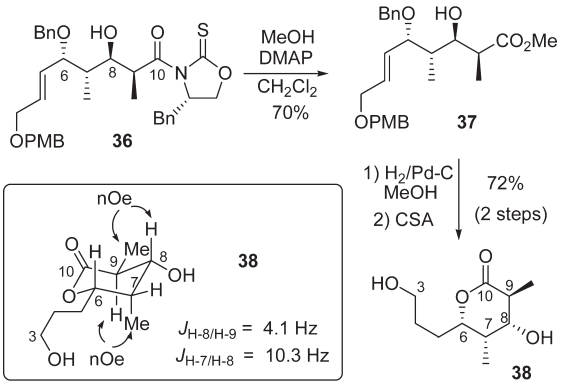
entry	auxiliary	conditions	yield of **36** (dr)
1	**35** (*R*)	$TiCl_4$ (1 equiv)/TMEDA (2.5 equiv)	traces
2	*ent*-**35** (*S*)	$TiCl_4$ (2 equiv)/*i*-Pr_2NEt (1.1 equiv)	76% [a] (13.4:1)[b]
3	*ent*-**35** (*S*)	$TiCl_4$ (2 equiv)/(−)-spartiene (1.1 equiv)	85% [a] (10:1)[b]
4	**35** (*R*)	$TiCl_4$ (1 equiv)/(−)-spartiene (2.5 equiv)	94% (>95:5)[c]

[a]Yield for **36′**. [b]As determined by HPLC on the crude oil. [c]Essentially no other diastereomers could be seen in the ^{1}H NMR of the crude product.

with DIBAL-H may directly lead to the corresponding aldehyde (with concurrent removal of the auxiliary) as shown[24c,d] by Crimmins.

The aldol reaction was first performed under the "Evans-syn" selective protocol[24c] of Crimmins, which used **35** (of *R*-configuration) and 1.0 equiv of $TiCl_4$ and 2.5 equiv of TMEDA (*N*,*N*′-tetramethylethylenediamine). However, only traces of several aldol products could be detected (Table 4, entry 1). Use of Crimmins' "non-Evans-syn" protocol gave better results. With *i*-Pr_2NEt as the base, the desired enantiopure **36′** could be obtained in 76% isolated yield with a diastereomeric ratio of ca. 13.4 (**36′**):1 (all other isomers) as determined on the crude oil by HPLC (Table 4, entry 2). Even better yield was later obtained when the *i*-Pr_2NEt was replaced by (−)-sparteine (Table 4, entry 3). Encouraged by the effect of (−)-sparteine in this run, we next switched back to the Evans-syn recipe to see if it would work equally well there. To our gratification, replacement of the TMEDA with (−)-sparteine led to a tremendously improved yield and diastereoselectivity (Table 4, entry 4).

SCHEME 7



To confirm the relative configurations of the four consecutive stereogenic centers in **36**, the chiral auxiliary was removed with MeOH/DMAP[28] in CH_2Cl_2 (Scheme 7). The resulting methyl ester (**37**) was treated with atmospheric H_2/Pd−C/MeOH followed by CSA to yield a six-membered lactone (**38**), from which clear NOEs were observed between the H-8/C-9 methyl group and the H-9/C-7 methyl group. The coupling constants were also consistent with those reported[29] in the literature for similar lactones. The stereochemistry of this fragment was thus fully secured.

To avoid potential complications in the carbanion addition reaction at a later stage of the synthesis, the hydroxyl group in **36** must be masked first with a proper protecting group. This protecting group was to be removed immediately after the catenation of the fragments containing C-11 to C-18 (**9**) and C-3 to C-10 (vide infra). Therefore, TMS (trimethylsilyl) appears to be an ideal candidate, which has a small molecular weight (and thus rather atom-economical compared with other silyl groups) and can be cleaved under very mild conditions.

The silyl protection of the C-10 OH group was readily achieved by treatment of **36** with TMSCl/2,6-lutidine in DMF (Scheme 8). However, it was noted that, if using CH_2Cl_2 as the solvent, essentially no reaction occurred. The chiral auxiliary was then removed by a DIBAL-H reduction. The resulting unstable aldehyde was directly treated with lithiated **9** at −20 °C to deliver a pair of propargyl alcohols (i.e., **41a** and **41b** in a 2:3 ratio) in 100% yield.[30] Use of zincated **9** (formed in situ through metal exchange by addition of 0.5 or 1 equiv of anhydrous $ZnBr_2$ to the above-mentioned lithiated system before introduction of the aldehyde) failed to deliver discernible amounts of **41a**/**41b**. With anhydrous $MgCl_2$ to replace $ZnBr_2$ under otherwise identical conditions, the only detectable change was loss of the TMS protecting group in aldehyde **40**. The $Zn(OTf)_2$/(−)-NME/Et_3N[31] conditions, which showed excellent enantioselectivity with other substrates, also failed to give any products in our case.

The above-mentioned two (separated) alcohols were converted (Scheme 9) into the corresponding acetonides by

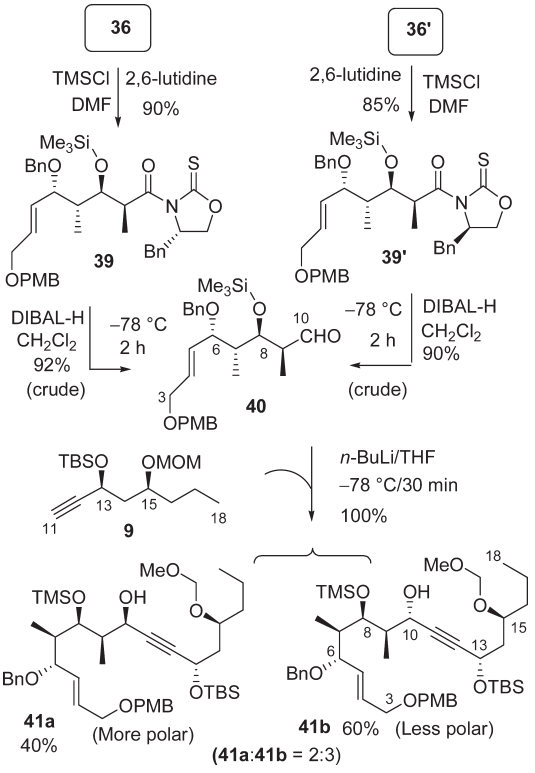
(28) For the methodology, see: (a) Su, D.-W.; Wang, Y.-C.; Yan, T.-H. *Tetrahedron Lett.* **1999**, *40*, 4197–4198. (b) Wu, Y.-K.; Sun, Y.-P.; Yang, Y.-Q.; Hu, Q.; Zhang, Q. *J. Org. Chem.* **2004**, *69*, 61410–6144.

(29) Guindon, Y.; Brazeau, J.-F. *Org. Lett.* **2004**, *6*, 2566–2602.

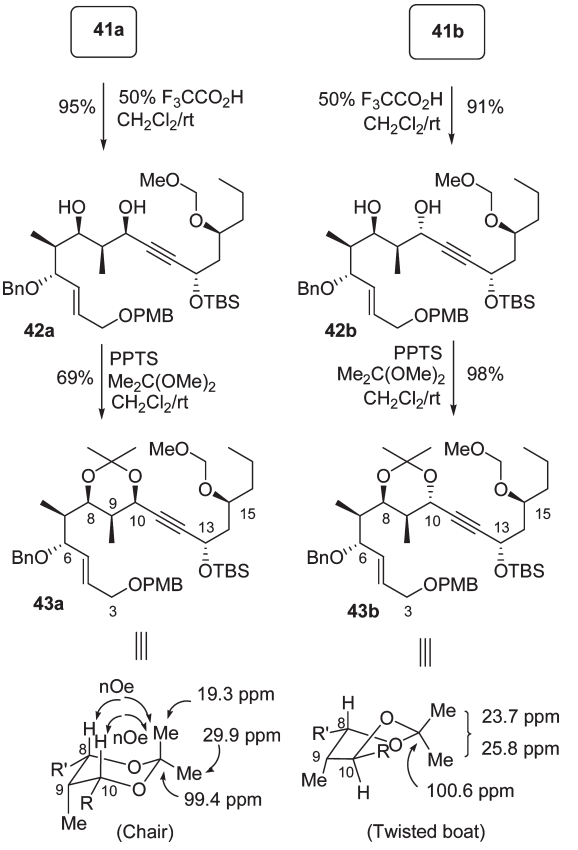
(30) Elevated temperature or prolonged reaction time all resulted in undesired desilylation of **41a**/**41b** leading to **42a**/**42b**.

(31) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.

SCHEME 8



SCHEME 9



sequential treatment, respectively, with F_3CCO_2H/CH_2Cl_2 and $Me_2C(OMe)_2$/PPTS (pyridinium *p*-sulfonate). In principle, the acetonide derived from the 1,3-syn-diol is expected to adopt a chair conformation with both substituents at the C-8 and C-10 being in an equatorial position. However, the acetonide from 1,3-anti-diol can be present only as a twisted boat. The one with a chair conformation would allow for observation of the NOEs depicted for **43a** in Scheme 9. One of the acetonides (derived from the more polar isomer of the alcohols) indeed showed such NOEs and hence was assigned to the structure of **43a**, which has a syn relationship between the C-8 and C-10 stereogenic centers. Consequently, the other acetonide was assigned to **43b** (derived from the less polar alcohol, the major component). Such assignments are also consistent with the empirical rules[32] of Rychnovsky, which says that the two methyl groups of the acetonide in a chair conformation would have a large split in the ^{13}C shifts with the ketal carbon appearing below 100 ppm, while the shifts for the two methyls in a twisted boat are rather close to each other, with the ketal carbon showing up at >100 ppm.[33a]

To make full use of the undesired isomer **41a**, the alcohol was oxidized with Dess−Martin periodinane (Scheme 10). The TMS protecting group in the resulting ketone **44** was cleaved with 50% aq F_3CCO_2H to free the hydroxyl group at the C-8. The carbonyl group was then reduced with Evans's[34] $Me_4BH(OAc)_3$, which is known to be highly 1,3-antiselective. Unfortunately, in our case, the diastereoselectivity turned out to be only 1:6. This, along with the fact that the two diols (**42a** and **42b**) are inseparable on silica gel, prompted us to seek other alternatives.

Direct reduction of **44** was also attempted[33b] (Table 5). In most cases, the major product was the desired isomer **41b**. With $LiBHEt_3$ as the reducing agent, the **41a**/**41b** ratio was only 2:3, although the yield was excellent (Table 5, entry 1). The selectivity could be raised to 1:2 by using $NaBH_4$ in THF in the presence of a small amount of water (entry 2). Better selectivity was later observed with K-Selectride ($KBH(i\text{-}Bu)_3$) at 0 °C, but the yield was substantially lower (entry 3). Interestingly, if performing the reduction at −78 °C under otherwise the same conditions, a complex mixture was obtained (entry 4). L-Selectride ($LiBH(i\text{-}Bu)_3$) gave the most satisfactory results. At −78 °C, the reduction gave alcohols **41a**/**41b** in a ratio of 1:6.4 with the total yield being 93% (entry 5). The selectivity was inverted when $LiAlH(O\text{-}t\text{-}Bu)_3$ was employed as the reductant (entry 6), while 9-BBN (9-borobicyclo[3.3.1]nonane) failed to give any reduction at all at 0 °C.

The synthesis was then continued from the enantiopure acetonide of correct configuration (**43b**), starting with a DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)-mediated oxidative removal of the PMB (*p*-methoxybenzyl) protecting group at the C-3 OH, as shown in Scheme 11. The phosphate buffer (Na_2HPO_4/citric acid, pH 7) proved to be essential for suppressing the otherwise unavoidable partial loss of the acetonide protecting group. The allyl alcohol **46** was subsequently

(32) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948. (b) Rychnovsy, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.

(33) (a) Also compare many examples in: Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100. For previous investigations on substrate-induced stereoselective reduction of propargyl ketones, see; (b) Chakraborty, T. K.; Reddy, V. R.; Reddy, T. J. *Tetrahedron* **2003**, *59*, 8613–8622.

(34) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

SCHEME 10

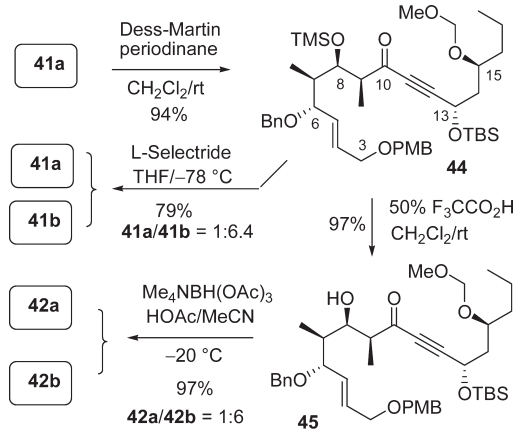


TABLE 5. Reduction of Ketone 44 with Various Reductants (cf. Scheme 10)

entry	conditions	**41a**/**41b** (% yield)
1	$LiBHEt_3$/THF/−78 °C	2:3 (96)
2	$NaBH_4$/THF/H_2O/0 °C	1:2 (94)
3	K-Selectride/THF/0 °C	1:5 (74)
4	K-Selectride/THF/−78 °C	-[a]
5	L-Selectride/THF/−78 °C	1:6.4 (93)
6	$LiAlH(O\text{-}t\text{-}Bu)_3$/THF/−78 °C	2:1 (67)
7	9-BBN/THF/0 °C to rt	-[b]

[a]Resulted in a complex mixture. [b]No reaction occurred.

oxidized with Dess−Martin periodinane to yield the corresponding aldehyde **47**. The C-2/C-3 stereogenic centers were then installed by a Crimmins[10] aldol condensation, which delivered enantiopure **48** in 90% isolated yield (along with ca. 3.9% of other diastereomers).

Cleavage of the TBS protecting group on the C-13 OH was troublesome. Many sets of conditions, including Me_4NF/THF, Me_4NF/HOAc/THF, DDQ/THF-H_2O, CAN/MeCN/aq buffer (pH 7), and KF-H_2O/TMSCl/MeCN,[35] were tried without success. Finally, the anticipated clean conversion of **48** into **49** was achieved with HF-py in THF.

The resulting alcohol **49** was subjected to H_2/Pd−C/EtOAc conditions to saturate the C−C double and triple bonds. To avoid loss of the Bn group at this stage, addition[36] of Et_3N to the hydrogenation system was necessary. The hydroxyl groups at the C-3 and C-13 were then activated with MsCl to afford dimesylate **51**.

Up to this point, the remaining task was to release the two hydroxyl groups at C-6 and C-10 before attempting the key step of construction of the two THF rings via intramolecular etherification with concurrent configuration inversion at the C-3 and C-13. This was initially attempted by removal of the acetonide group with 50% aq F_3CCO_2H in CH_2Cl_2−MeOH followed by hydrogenolysis over Pd−C in THF. The product mixture was apparently more complex than we had expected. However, heating the crude mixture in 2,6-lutidine at 120 °C for 2 h led to the desired **52a** in 93% isolated/overall yield. The F_3CCO_2H-mediated hydrolysis of the acetonide is not essential, as direct treatment of **51** with H_2/Pd−C/MeOH followed by heating in 2,6-lutidine also led to the same product, though in a slightly lower yield. More surprisingly, in the presence of added CSA, prolonged exposure of **51** to H_2/Pd−C/MeOH also gave a two THF ring containing species, which was later proved to be identical to the **52b** prepared by removal of the MOM protecting group.

The high overall yield for the transformation of **51** to **52a** or **52b** suggested that the unidentified side products in the first two steps might be those with one of the two THF rings already formed even before subjection to the basic 2,6-lutidine conditions. Such a phenomenon (i.e., formation of a THF ring from the corresponding alcohol mesylate precursor under acidic conditions) was not observed in our earlier synthesis of nonactin.[37]

With **52a** in hand, we proceeded with the remaining steps of the synthesis, as depicted in Scheme 12. The chiral auxiliary was removed with H_2O_2/LiOH in THF to deliver the corresponding acid **3**. The two fragments, **3** and **4**, were then combined with each other under Yamaguchi's[38] conditions to afford **54**. Use of MNBA (2-methyl-6-nitrobenzoyl anhydride) protocol of Shiina[39] gave a substantially lower yield (71%).

The auxiliary in **54** was subsequently cleaved with H_2O_2/LiOH, affording hydroxyl acid **55** in 94% yield. Perhaps because of the steric crowding around the C-1, the ester linkage was not affected under the given conditions. Ring closure of the 16-membered dilactone ring was much more difficult than the coupling of **3** with **4**. Under the same conditions (**53**/DMAP/4 Å MS/CH_2Cl_2/rt), no reaction seemed to occur, even if using a large excess of **53** (2−10 equiv)/DMAP (10−20 equiv)/Et_3N (12−24 equiv). If the reaction was performed in MeCN instead of CH_2Cl_2, a complex mixture that did not contain any **56** was obtained. Similar results were also obtained with the Ph_3P (4 equiv)/PySSPy (4 equiv)/AgOTf (10 equiv)/toluene/rt conditions[40] and the MNBA (2.5 equiv)/DMAP (5 equiv)/4 Å MS/toluene/rt conditions. However, when the Yamaguchi esterification was carried out in toluene at 80 °C (**53** (10 equiv)/DMAP (10 equiv)/Et_3N (12 equiv)/80 °C), the anticipated dilactone **56** was formed in 32% isolated yield. Using more reagents at higher reaction temperature (**53** (20 equiv)/DMAP (20 equiv)/Et_3N (24 equiv)/110 °C)) eventually raised the yield of **56** to 66%.

The MOM protecting group was then removed with 10% aq HBr[41] in MeCN. The resultant alcohol **57** was converted into the corresponding azide by treatment with Ph_3P/DEAD/$(PhO)_2P(O)N_3$[42] with concurrent inversion of the configuration. In their synthesis of pamamycin 607, Kang[7]

(35) Peng, Y.; Li, W.-D. Z. *Synlett* **2006**, 1165–1168.

(36) For a literature precedent of addition primary amine for similar purposes, see: Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4076–4078.

(37) Such reactions typically occur under basic conditions. For some examples (kindly provided by one of the reviewers) of related cyclization under acidic conditions, see: (a) Chakraborty, T. K.; Das, S.; Raju, T. V. *J. Org. Chem.* **2001**, *66*, 4091–4093. (b) Dehmlow, H.; Multzer, J.; Seilz, C.; Strecker, A. R.; Kohlmann, A. *Tetrahedron Lett.* **1992**, *33*, 3607–3610. For a recent review on stereoselective construction of THF rings, see: (c) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2006**, *63*, 261–290.

(38) Yamaguchi, M.; Innaga, J.; Hirata, K.; Saeki, H.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

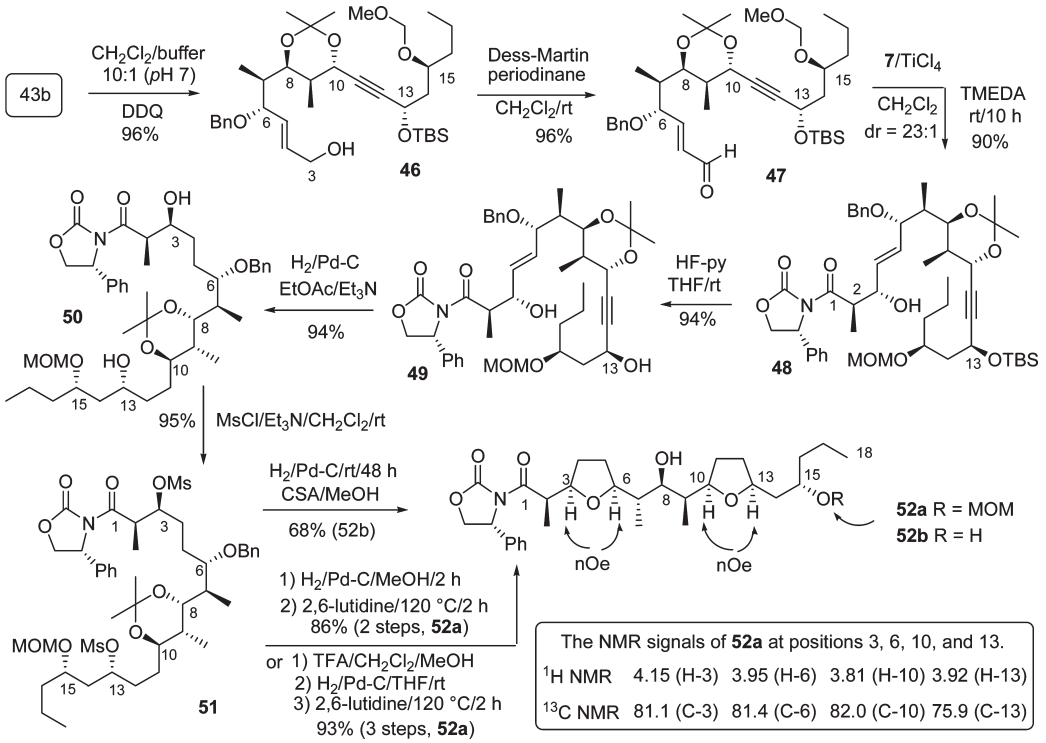
(39) (a) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535–7539. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830.

(40) Kusaka, S.-i.; Dohi, S.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 8857–8859.

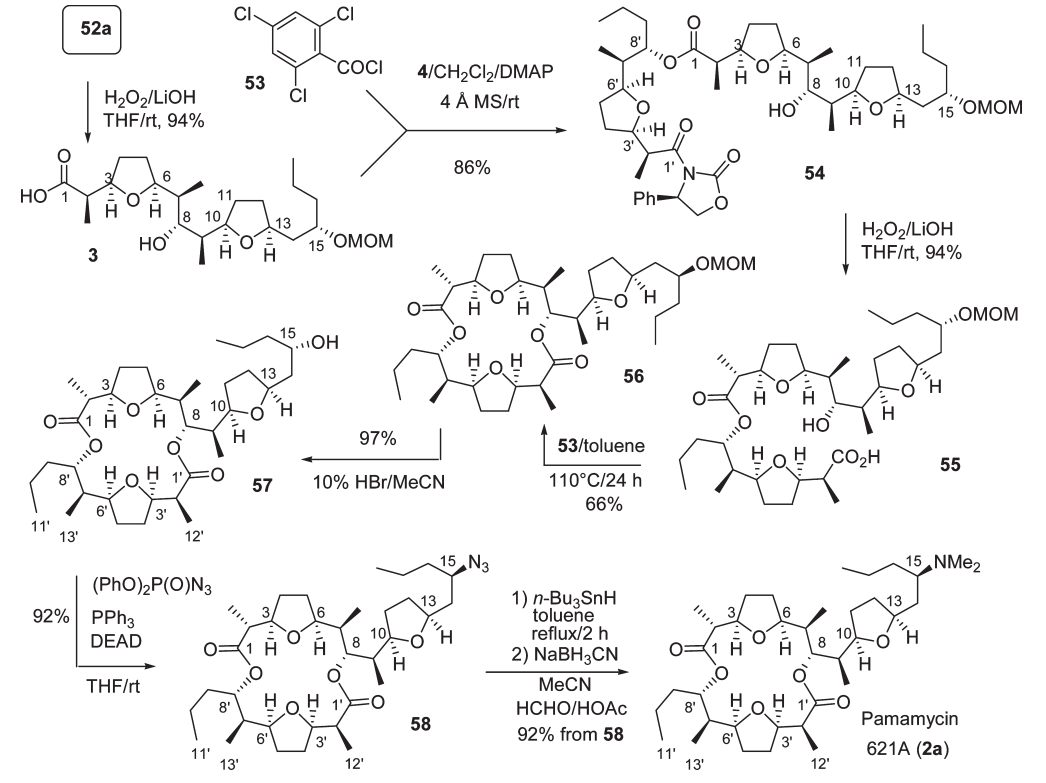
(41) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 2646–2650.

(42) Lal, B.; Pramanik, E. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977–1980.

SCHEME 11



SCHEME 12



and co-workers have succeeded in reducing a similar azido group to the corresponding dimethylamino group using hydrogenation over Pd−C in MeOH followed by treatment with 37% aq HCHO/HOAc. Unfortunately, application of such a sequence to our substrate (**58**) led to a complicated mixture that contained only traces of desired **2a**. Combing these two steps into one (i.e., performing the hydrogenation in 37% aq HCHO/HOAc/MeOH) did not lead to any

discernible improvements. Exposure of **58** to Ph_3P in THF at 60 °C followed by treatment with $NaBH_3CN$/37% aq HCHO[43] in MeCN in the presence of a NaOAc/HOAc buffer appeared to be more promising, affording the desired pamamycin 621A (**2a**) in ca. 66% yield. However, the **2a** thus obtained contained small amounts of unidentified side products, which were very difficult to get rid of. Careful monitoring of the whole process suggested that the problem most likely stemmed from the azide reduction. Therefore, we looked into the literature for other potential alternatives. Then we noticed that Redlich[44] and Roy once mentioned an individual case of *n*-Bu_3SnH-mediated reduction of a carbohydrate-derived azide.[45] Although this set of conditions does not seem to have ever been tested on any complex substrates, to our great delight, it resulted in a clean reduction of **58**. The intermediate amine was then directly treated with $NaBH_3CN$ in a mixture of 37% aq HCHO, and MeCN containing a NaOAc/HOAc buffer provided the end product **2a** in 92% overall yield.

It is noteworthy that the existence of a basic dimethylamino group in the molecule makes **2a** highly liable to protonation by traces of acids present in the NMR solvent. As a consequence, serious line broadening and appearance of "extra" signals are often observed, most notably in ^1H NMR. Such a phenomenon probably also exists with all pamamycins, which made previous investigators measure pamamycin 607's NMR in the presence of F_3CCO_2D. However, addition of an acid cannot really/completely eliminate the problem. In efforts to acquire "normal looking" spectra, we found that stirring of the $CDCl_3$ with K_2CO_3 for a few hours before the supernatant was taken for preparing the NMR solution was quite effective. After such a treatment, the spectra were essentially the same as those compounds that do not contain any basic functionalities. The optical rotation measurements of pamamycin 621A (**2a**) are also interesting, which are of opposite signs in CH_2Cl_2 and $CHCl_3$. Although it may not be surprising for two solvents of different nature/polarity (such as $CHCl_3$ and MeOH or acetone), for CH_2Cl_2 and $CHCl_3$, it is quite unexpected because they are often considered to be very similar to each other.

Conclusions

A total synthesis of natural antibiotic pamamycin 621A was achieved through a convergent route in a highly enantioselective manner. The THF rings, which are characteristic of the compounds of this family, were constructed from linear precursors via O-alkylations of hydroxyl groups with mesylates located at carbons β to a carbonyl group as the alkylating agents under carefully chosen conditions without suffering otherwise readily occurring side reactions, such as α-racemization and β-elimination.

The mesylates were derived from corresponding aldols prepared under either syn- or antiselective conditions developed by Evans and/or Crimmins. In the antiselective aldol condensation, a previously unreported effect of using stoichiometric amounts of $MgCl_2$ was observed, which was essential to the success of the given substrate. The relative configuration of the α-carbon in the aldol-derived cyclization precursors had an influence on the THF ring formation, as shown by the outcomes using pyridine bases of different steric bulkiness. In the synthesis of the larger fragment, it is noteworthy that the two THF rings could form from the mesylate alcohol precursor even under acidic conditions.

The basic amino functionality was introduced at a very late stage of the synthesis to minimize difficulties and interferences normally associated with the presence of such nitrogen atoms in the molecule. Reduction of the azido group into an amino one was achieved using *n*-Bu_3SnH in the absence of AIBN, a reduction protocol that has never been tested in any synthesis of a complex molecule.

The annoying interference (complication of the ^1H and ^{13}C NMR spectra) caused by the traces of acid in $CDCl_3$ was effectively eliminated by pretreatment of the NMR solvent with powdered K_2CO_3, which made it possible to acquire assignable "normal-looking" NMR spectra. An unusual phenomenon of opposite rotation signs in CH_2Cl_2 and $CHCl_3$ was observed for pamamycin 621A ($[\alpha]^{27}_D$ +5.4 (*c* 0.4, CH_2Cl_2) and $[\alpha]^{27}_D$ −5.4 (*c* 0.4, $CHCl_3$), respectively).

Experimental Section[46]

(4*R*)-3-[(2*R*,3*S*,4*E*)-6-*tert*-Butyldimethylsilyloxy-3-hydroxy-2-methylhex-4-enoyl]-4-phenyloxazolidin-2-one (12). $TiCl_4$ (1.87 mL, 17.1 mmol) was added (via a syringe) dropwise to a solution of **7** (3.571 g, 16.3 mmol) in dry CH_2Cl_2 (100 mL) stirred at 0 °C (ice−water bath) under N_2. After completion of the addition, the mixture was stirred at the same temperature for 10 min before dry TMEDA (6.10 mL, 40.8 mmol) was introduced dropwise. The dark red-brown mixture was stirred at 0 °C for another 30 min. A solution of aldehyde **11** (6.52 g, 32.58 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise. After completion of the addition, the mixture was stirred at the same temperature for 2 h. Aqueous NH_4Cl was added. The mixture was filtered through Celite (washing with CH_2Cl_2 three times). The filtrate and washings were combined, washed with water and brine, before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (1:4 EtOAc/PE) on silica gel gave enantiopure aldol **12** as a colorless oil (5.769 g, 13.8 mmol, 84%): $[\alpha]^{25}_D$ −60.7 (*c* 1.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.19 (m, 5H), 5.75 (dt, J = 4.1, 15.5 Hz, 1H), 5.65 (dd, J = 5.7, 15.5 Hz, 1H), 5.38 (dd, J = 3.9, 8.6 Hz, 1H), 4.62 (t, J = 8.8 Hz, 1H), 4.43 (m, 1H), 4.18 (dd, J = 3.6, 9.0 Hz, 1H), 4.11 (d, J = 4.2 Hz, 2H), 3.82 (m, 1H), 2.76 (br, 1H), 1.08 (d, J = 6.9 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 153.2, 138.8, 131.5, 129.2, 128.7, 128.6, 125.5, 71.5, 69.8, 63.0, 57.5, 42.7, 25.8, 18.3, 10.8, −5.3; FT-IR (film) 3514, 2930, 2857, 1783, 1704, 1384, 1199, 838, 777, 700 cm^{-1}; ESI-MS *m*/*z* 442.3 ($[M + Na]^+$); ESI-HRMS calcd for $C_{22}H_{33}NO_5SiNa$ ($[M + Na]^+$) 442.2020, found 442.2014.

***N*-Methoxy-*N*-methyl-(2*R*,3*S*,4*E*)-6-*tert*-butyldimethylsilyloxy-3-hydroxy-2-methylhex-4-enamide (13).** $MeAl_3$ (2.0 M in toluene, 9.0 mL, 18.0 mmol) was added slowly to a solution of MeONHMe·HCl (1.758 g, 18.0 mmol) in dry THF (10 mL) stirred at 0 °C under argon (balloon). The solid dissolved gradually with the gas evolvement. Stirring was continued at 0 °C for 15 min and at ambient temperature for 15 min before the bath was recooled to −15 °C. A solution of **12** (2.511 g, 6.0 mmol) in dry THF (5 mL) was introduced dropwsie. Stirring was continued at −15 °C until

(43) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.
(44) Redlich, H.; Roy, W. *Liebigs. Ann. Chem.* **1981**, 1215–1222.
(45) There are also other reports on *n*-Bu_3SnH reduction of azides, but they all required AIBN (2,2′-azobis(2-methylpropionitrile)) to initiate the reactions: (a) Hays, D. S.; Fu, G. *J. Org. Chem.* **1998**, *63*, 2796–2797. and the refs cited therein. (b) Poopeiko, N. E.; Pricota, T. I.; Mikhailopulo, I. A. *Synlett* **1991**, 342–342.

(46) Those steps that are not given in this section were reported in the Supporting Information for ref 8.

TLC showed completion of the reaction. The reaction mixture was poured into aq saturated potassium sodium tartrate (15 mL), followed by addition of Et_2O (50 mL). The mixture was stirred at ambient temperature until it separated into two layers. The phases were separated. The aqueous layer was back-extracted with Et_2O (3×50 mL). The combined ethereal layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (1:2 Et_2O/PE) on silica gel afforded the known Weinreb amide **13**[11] as a colorless oil (1.806 g, 5.73 mmol, 96%): $[\alpha]^{26}_D$ −17.0 (*c* 1.95, $CHCl_3$) (lit.[11] $[\alpha]^{26}_D$ −17.3 (*c* 1.96, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.67 (m, 1H), 4.44 (m, 1H), 4.20 (m, 2H), 3.78 (br, 1H), 3.71 (s, 3H), 3.20 (s, 3H), 2.96 (m, 1H), 1.17 (d, J = 7.3 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H).

(5*R*,6*S*,7*E*)-9-*tert*-Butyldimethylsilyloxy-6-hydroxy-5-methylnon-7-en-4-one (14). *n*-PrMgBr (1.5 M, in THF, 20.0 mL, 30.0 mmol) was added to a solution of the Weinreb amide **13** (3.125 g, 9.92 mmol) in dry THF (30 mL) stirred at 0 °C under argon (balloon). The mixture was stirred at the same temperature until TLC showed completion of the reaction. Aqueous saturated NH_4Cl was added. The mixture was extracted with Et_2O ($3 \times$ 50 mL). The combined ethereal layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (1:6 EtOAc/PE) on silica gave ketone **14** (2.769 g, 9.22 mmol, 93%) as a colorless oil: $[\alpha]^{28}_D$ +0.11 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.63 (m, 2H), 4.49−4.43 (m, 1H), 4.21 (dt, J = 4.3, 1.3 Hz, 2H), 2.83 (d, J = 3.5 Hz, 1H), 2.67 (dq, J = 3.9, 7.0 Hz, 1H), 2.49 (dt, J = 3.1, 7.4 Hz, 2H), 1.67−1.58 (m, 2H), 1.15 (d, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 131.3, 129.1, 71.8, 63.0, 50.6, 44.1, 25.9, 18.4, 16.9, 13.7, 10.7, −5.2; FT-IR (film) 3465, 2958, 2931, 2858, 1707, 1463, 1255, 837, 777 cm^{-1}; ESI-MS m/z 323.2 ($[M + Na]^+$); ESI-HRMS calcd for $C_{16}H_{32}O_3SiNa$ ($[M + Na]^+$) 323.2013, found 323.2011.

(4*S*,5*S*,6*S*,7*E*)-1-*tert*-Butyldimethylsilyloxy-5-methylnon-2-ene-4,6-diol (15). A solution of ketone **14** (2.365 g, 7.88 mmol) in dry CH_3CN (5 mL) was added dropwise to a solution of $Me_4NBH(OAc)_3$ (16.7 g, 63.0 mmol) in dry CH_3CN (20 mL) and glacial HOAc (20 mL) stirred at −20 °C. The mixture was stirred at the same temperature for 14 h, when TLC showed completion of the reduction. Aqueous potassium sodium tartrate (1.0 M, 50 mL) was added, followed by Et_2O. The aqueous layer was made slightly alkaline (ca. pH 8) by addition of K_2CO_3. The phases were separated. The aqueous phase was back-extracted with Et_2O (5×100 mL). The organic phases were washed with water and brine and dried over Na_2SO_4. Removal of the solvent and chromatography on silica gel (1:5 EtOAc/PE) gave diol **15** as a colorless oil (2.220 g, 7.35 mmol, 94%): $[\alpha]^{23}_D$ −20.1 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78−5.72 (m, 2H), 4.43 (m, 1H), 4.20 (s, 2H), 3.62 (m, 1H), 3.08 (br, 1H), 2.84 (br, 1H), 1.70 (m, 1H), 1.59−1.24 (m, 4H), 0.95−0.82 (m, 15H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 130.6, 130.1, 74.9, 74.0, 63.2, 42.3, 37.6, 25.9, 18.6, 18.4, 14.1, 12.1, −5.2; FT-IR (film) 3398, 1463, 1254, 838, 776 cm^{-1}; ESI-MS m/z 325.3 ($[M + Na]^+$); ESI-HRMS calcd for $C_{16}H_{34}O_3SiNa$ ($[M + Na]^+$) 325.2169, found 325.2166.

(2*E*)-3-((4*S*,5*S*,6*S*)-2,2,5-Trimethyl-6-propyl-1,3-dioxan-4-yl)-prop-2-en-1-ol (16). A solution of TBAF (1.0 M in THF, 6.0 mL, 6.0 mmol) and diol **15** (906 mg, 3.0 mmol) in dry THF (6.0 mL) was stirred at ambient temperature until TLC showed completion of the reaction. The mixture was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (EtOAc) to give the intermediate triol as a yellowish oil (551 mg, 2.93 mmol), to which were added $Me_2C(OMe)_2$ (10 mL) and CSA (65 mg, 0.287 mmol). The mixture was stirred at ambient temperature for 48 h. Et_3N (2 mL) was added. Stirring was continued at ambient temperature for 10 min before the mixture was concentrated on a rotary evaporator. The residue was chromatographed (EtOAc) on silica gel to give a colorless oil, which was directly dissolved in THF (6 mL). With stirring, aq HOAc (70%) was added in portions. The reaction (removal of the undesired $Me_2C(OMe)$ group on the allylic OH) was monitored by TLC. When the reaction was complete, aq saturated $NaHCO_3$ was added to neutralize the acid. The mixture was extracted with Et_2O (3×100 mL). The organic phase was washed in turn with water and brine and dried over Na_2SO_4. Removal of the solvent and chromatography on silica gel (1:13 EtOAc/PE) gave alcohol **16** as a colorless oil (512 mg, 2.24 mmol, 75% from **15**): $[\alpha]^{24}_D$ +9.8 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (dt, J = 15.6, 5.3 Hz, 1H), 5.68 (dd, J = 6.1, 15.5 Hz, 1H), 4.43 (t, J = 5.8 Hz, 1H), 4.14 (d, J = 5.0 Hz, 2H), 3.29−3.25 (m, 1H), 1.72−1.61 (m, 2H), 1.51−1.41 (m, 3H), 1.35 (s, 6H), 0.92 (t, J = 7.0 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.7, 129.2, 100.6, 74.3, 69.9, 63.2, 40.8, 36.7, 25.3, 23.9, 19.1, 14.0, 12.7; FT-IR (film) 3416, 2986, 2873, 1380, 1222, 929 cm^{-1}; ESI-MS m/z 251.3 ($[M + Na]^+$); ESI-HRMS calcd for $C_{13}H_{24}O_3Na$ ($[M + Na]^+$) 251.1618, found 251.1628.

(4*R*)-3-[(2*S*,3*S*,4*E*)-3-Hydroxy-2-methyl-5-((4*S*,5*S*,6*S*)-2,2,5-trimethyl-6-propyl-1,3-dioxan-4-yl)-pent-4-enoyl]-4-phenyloxazolidin-2-one (19). Dess−Martin periodinane (1.742 g, 4.11 mmol) and $NaHCO_3$ (518 mg, 6.17 mmol) were added in turn to a solution of alcohol **16** (469 mg, 2.06 mmol) in dry CH_2Cl_2 (10 mL) stirred at 0 °C. Stirring was continued until TLC showed completion of the reaction. Et_2O was added. The mixture was filtered through Celite. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (1:8 EtOAc/PE) on silica gel to afford the intermediate unstable aldehyde **17** (428 mg, 1.89 mmol, 92%) as a yellowish oil, on which a diagnostic ^{1}H NMR was briefly acquired before performing the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, J = 7.9 Hz, 1H), 6.73 (dd, J = 4.3, 15.9 Hz, 1H), 6.35 (dd, J = 7.8, 16.0 Hz, 1H), 4.70 (m, 1H), 3.29 (m, 1H), 1.88 (m, 1H), 1.61−1.44 (m, 2H), 1.37 (s, 3H), 1.36 (s, 3H), 0.93 (t, J = 7.0 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H).

Et_3N (0.35 mL, 2.50 mmol) was added dropwise to a solution of the acyloxazolidinone **7** (219 mg, 1.0 mmol) and anhydrous $MgCl_2$ (105 mg, 1.0 mmol) in dry EtOAc (1.0 mL) stirred at ambient temperature. To the resulting mixture a solution of aldehyde **17** (142 mg, 0.63 mmol) obtained above in dry EtOAc (1.0 mL) was added, followed by Me_3SiCl (0.19 mL, 1.50 mmol). The mixture was stirred at ambient temperature for 24 h before being diluted with Et_2O and filtered through Celite (washing with Et_2O). The filtrate and washings were combined and concentrated on a rotary evaporator. The residue (crude TMS ether **18**) was dissolved in THF (18 mL) and H_2O (2 mL). To this solution was added DDQ (30 mg, 0.136 mmol). The mixture was stirred at ambient temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was then added. The mixture was extracted with Et_2O (3×50 mL). The combined ethereal layers were washed with aq saturated $NaHSO_3$ (twice), H_2O, and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation left a yellowish oil, which was chromatographed (1:3 EtOAc/PE) on silica gel to give aldol **19** as a colorless oil (156 mg, 0.351 mmol, 56% from **17**, 52% from **16**).

Data for **18** (purified by chromatography (1:6 EtOAc/PE) on silica gel): $[\alpha]^{24}_D$ −11.5 (*c* 1.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 5.50 (m, 2H), 5.43 (dd, J = 4.4, 9.0 Hz, 1H), 4.67 (t, J = 9.0 Hz, 1H), 4.36−4.26 (m, 2H), 4.21 (dd, J = 4.0, 8.8 Hz, 1H), 3.93 (m, 1H), 3.23 (m, 1H), 1.63 (m, 1H), 1.59−1.50 (m, 4H), 1.32 (s, 3H), 1.31 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H), −0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 153.4, 139.2, 131.6, 130.7, 129.1, 128.5, 126.2, 100.4, 75.3, 74.2, 70.0, 69.7, 57.7, 44.6, 41.0, 36.6, 25.1, 23.8, 19.1, 14.0, 13.9, 12.8, 0.08; FT-IR (film)

2959, 2874, 1783, 1708, 1495, 1457, 1382, 1250, 842 cm^{-1}; ESI-MS *m*/*z* 540.2 ($[M + Na]^+$); ESI-HRMS calcd for $C_{28}H_{43}NO_6SiNa$ ($[M + Na]^+$) 540.2752, found 540.2781.

Data for **19**: $[\alpha]^{26}_D$ −19.2 (*c* 0.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.63−5.61 (m, 2H), 5.44 (dd, *J* = 3.9, 8.7 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, 1H), 4.37 (t, *J* = 4.0 Hz, 1H), 4.24 (dd, *J* = 4.0, 8.8 Hz, 1H), 4.18 (m, 1H), 3.99 (m, 1H), 3.24 (m, 1H), 2.38 (d, *J* = 6.3 Hz, 1H), 1.64−1.58 (m, 2H), 1.45−1.38 (m, 3H), 1.33 (s, 6H), 1.14 (d, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 153.7, 138.7, 131.2, 131.0, 129.1, 128.6, 125.7, 100.6, 75.4, 74.2, 69.9, 69.7, 58.0, 43.5, 40.8, 36.6, 25.2, 23.8, 19.1, 14.3, 13.9, 12.6; FT-IR (film) 3503, 3033, 2935, 2874, 1782, 1705, 1382, 1222, 700 cm^{-1}; ESI-MS *m*/*z* 468.3 ($[M + Na]^+$); ESI-HRMS calcd for $C_{25}H_{35}NO_6Na$ ($[M + Na]^+$) 468.2357, found 468.2355.

(1*S*,3*S*)-1-*tert*-Butyldimethylsilyloxy-1-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-hexan-3-ol (24). PrMgBr (1.3 M in THF, 8.6 mL, 11.2 mmol) was added to a suspension of CuCN (10 mg, 0.11 mmol) in dry THF (7 mL) stirred at 0 °C under N_2. The stirring was continued at 0 °C for 10 min, which led to a clear solution. The bath was then cooled to −10 °C. A solution of epoxide **23** (1.190 g, 3.93 mmol) in THF (7 mL) was introduced dropwise. After completion of the addition, the stirring was continued at the same temperature for 12 h. Aqueous saturated NH_4Cl was added. The mixture was extracted with Et_2O (4 × 50 mL). The organic layers were combined and washed in turn with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 Et_2O/PE) on silica gel gave alcohol **24** as a colorless oil (1.266 g, 3.81 mmol, 97%): $[\alpha]^{25}_D$ +21.9 (*c* 2.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.11−4.03 (m, 2H), 3.92−3.78 (m, 3H), 2.59 (br s, 1H), 1.74−1.67 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H),1.48−1.36 (m, 4H), 0.93 (t, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.4, 78.7, 71.4, 67.9, 67.3, 42.7, 40.1, 26.6, 25.8, 25.4, 18.8, 17.9, 14.1, −4.1, −4.5; FT-IR (film) 3585, 2956, 2932, 838, 776 cm^{-1}; ESI-MS *m*/*z* 355.1 ($[M + Na]^+$); ESI-HRMS calcd for $C_{17}H_{36}SiO_4Na$ ($[M + Na]^+$) 355.2275, found 355.2275.

(1*S*,3*S*)-1-*tert*-Butyldimethylsilyloxy-1-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methoxymethoxyhexane (25). MOMCl (1.52 mL, 19 mmol) was introduced dropwise to a solution of alcohol **24** (1.250 g, 3.80 mmol), DMAP (114 mg, 0.95 mmol), and *i*-Pr_2NEt (6.6 mL, 38.0 mmol) in dry CH_2Cl_2 (13 mL) stirred at 0 °C under N_2. The stirring was continued at ambient temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ (10 mL) was added. The mixture was extracted with Et_2O (4 × 50 mL). The organic layers were combined and washed in turn with water and brine, before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:15 Et_2O/PE) on silica gel gave the MOM ether **25** as a yellowish oil (1.392 g, 3.70 mmol, 98%): $[\alpha]^{25}_D$ +11.8 (*c* 2.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (d, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.09 (m, 1H), 3.98 (t, *J* = 6.8 Hz, 1H), 3.91−3.74 (m, 3H), 3.38 (s, 3H), 1.77−1.66 (m, 2H), 1.64−1.59 (m, 2H), 1.52−1.34 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 0.92 (t, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.9, 95.4, 78.8, 74.2, 69.7, 66.1, 55.6, 40.3, 37.2, 26.6, 25.9, 25.4, 18.3, 18.0, 14.2, −4.2, −4.4; FT-IR (film) 2955, 2930, 1256, 1045, 838, 777 cm^{-1}; ESI-MS *m*/*z* 399.2 ($[M + Na]^+$); ESI-HRMS calcd for $C_{19}H_{40}SiO_5Na$ ($[M + Na]^+$) 399.2537, found 399.2555.

(2*R*,3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-methoxymethoxy-octane-1,2-diol (26). A solution of acetonide **25** (890 mg, 2.37 mmol) and CF_3CO_2H (50% aq solution, 3.4 mL) in CH_2Cl_2 (78 mL) was stirred at ambient temperature for 1 h. The mixture was diluted with Et_2O (300 mL), washed with aq saturated $NaHCO_3$ (20 mL), water, and brine, and dried over anhydrous Na_2SO_4. Removal of the organic solvent on a rotary evaporator and column chromatography (1:3 EtOAc/PE) on silica gel gave diol **26** as a colorless oil (730 mg, 2.17 mmol, 92%): $[\alpha]^{25}_D$ +28.7 (*c* 4.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (d, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 3.85 (m, 1H), 3.81−3.70 (m, 2H), 3.62 (m, 2H), 3.40 (s, 3H), 3.39 (m, 1H), 2.42 (m, 1H), 1.92−1.62 (m, 2H), 1.52 (m, 2H), 1.40 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.90 (s, 9H), 0.09 (d, *J* = 3.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.6, 74.3, 73.6, 71.0, 63.6, 55.9, 38.4, 37.0, 25.7, 18.2, 17.9, 14.2, −4.4, −4.8; FT-IR (film) 3446, 2920, 2861, 2822, 1471, 836, 778 cm^{-1}; ESI-MS *m*/*z* 359.2 ($[M + Na]^+$); ESI-HRMS calcd for $C_{16}H_{36}O_5SiNa$ ($[M + Na]^+$) 359.2224, found 359.2234.

(3*R*,5*S*)-1,1-Dibromo-3-*tert*-butyldimethylsilyloxy-5-methoxy-methoxyoctene (27). An aqueous solution of $NaIO_4$ (0.65 M, 37.27 mmol) was added dropwise to a mixture of diol **26** (8.364 g, 24.9 mmol) and silica gel (300−400 mesh, 15.0 g) in CH_2Cl_2 (150 mL) and was vigorously stirred at ambient temperature. After completion of the addition, stirring was continued for 1 h at the same temperature before another portion of $NaIO_4$ solution (same as above, 37.27 mmol) was introduced dropwise. When TLC showed completion of the reaction, the mixture was filtered through Celite (washing with CH_2Cl_2). The filtrate and washings were combined and washed in turn with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography on silica gel (1:4 Et_2O/PE) yielded the unstable intermediate aldehyde (7.255 g, 23.9 mmol, 96%) as a colorless oil, which was used immediately dissolved in dry CH_2Cl_2 (20 mL) and added dropwsie to a solution of PPh_3 (37.88 g, 143.0 mmol) and CBr_4 (23.73 g, 71.5 mmol) in dry CH_2Cl_2 (120 mL) stirred at 0 °C. When the reaction was complete as shown by TLC, the mixture was poured into hexanes (1000 mL) and then filtered through Celite. The solvents were removed by rotary evaporation. The residual was filtered through Celite again. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (1:30 Et_2O/PE) on silica gel to afford the *gem*-dibromide **27** as a colorless oil (10.25 g, 22.4 mmol, 94%): $[\alpha]^{24}_D$ −27.2 (*c* 3.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (d, *J* = 7.4 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.43−4.35 (m, 1H), 3.67−3.59 (m, 1H), 3.38 (s, 3H), 1.90−1.81 (m, 1H), 1.64−1.58 (m, 1H), 1.57−1.45 (m, 2H), 1.44−1.32 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.08 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 95.8, 88.6, 74.3, 70.9, 55.6, 41.5, 36.7, 25.7, 18.3, 17.9, 14.2, −4.4, −5.0; FT-IR (film) 2956, 2930, 2821, 1621, 837, 777 cm^{-1}; ESI-MS *m*/*z* 481.1 ($[M + Na]^+$); ESI-HRMS calcd for $C_{16}H_{32}SiO_3Br_2Na$ ($[M + Na]^+$) 481.0380, found 481.0387.

(3*R*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-methoxymethoxyoctyne (9). *n*-BuLi (2.5 M, in hexanes, 20.9 mL, 52.2 mmol) was added via syringe to a solution of the *gem*-dibromide **27** (9.57 g, 20.9 mmol) in dry THF (100 mL) stirred at −10 °C under N_2. After completion of the addition, stirring was continued at the same temperature for 30 min before aq saturated NH_4Cl was introduced. The mixture was extracted with Et_2O (3 × 100 mL). The organic phases were combined and washed with water and brine and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (1:15 Et_2O/PE) on silica gel gave the alkyn **9** (6.14 g, 20.5 mmol, 98%) as a yellowish oil: $[\alpha]^{24}_D$ −16.8 (*c* 3.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.66 (s, 2H), 4.54 (ddd, *J* = 2.1, 6.0, 8.1 Hz, 1H), 4.82−4.72 (m, 1H), 3.39 (s, 3H), 2.44 (d, *J* = 2.0 Hz, 1H), 1.99−1.77 (m, 2H), 1.60−1.44 (m, 2H), 1.42−1.30 (m, 2H), 0.93 (t, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.14 (d, *J* = 8.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.6, 85.1, 74.6, 72.8, 60.5, 55.6, 43.6, 36.8, 25.7, 18.3, 18.1, 14.1, −4.6, −5.1; FT-IR (film) 3312, 2958, 2823, 1472, 838, 778 cm^{-1}; EI-MS *m*/*z* (%) 255 ($[M - CH_2OCH_3]^+$, 0.82), 211 (6), 161 (9), 143 (19), 89 (99), 45 (100); EI-HRMS calcd for $C_{14}H_{27}O_2Si$ ($[M - CH_2OCH_3]^+$) 255.1780, found 255.1789.

(4*R*)-3-[(2*R*,3*S*,4*E*)-3-Hydroxy-2-methyl-6-(4-methoxybenzyloxy)-hex-4-enoyl]-4-phenyloxazolidin-2-one (29). Freshly distilled $TiCl_4$ (5.7 mL, 52.0 mmol) was added (via a syringe) dropwise to a solution of acyloxazolidinone **7** (10.95 g, 50.0 mmol) in dry CH_2Cl_2 (300 mL) stirred at 0 °C under N_2. The resulting yellow solution was stirred the same temperature for 10 min before neat TMEDA (20.8 mL, 130.0 mmol) was added dropwise (resulting in a dark red-brown solution). After stirring at 0 °C for another 20 min, a solution of aldehyde **28** (10.4 g, 50.5 mmol) in dry CH_2Cl_2 (20 mL) was introduced via a syringe. The stirring was continued at 0 °C for 10 h. Aqueous NH_4Cl was added. The voluminous yellow precipitates were filtered off through Celite. The filtrate was washed in turn with water and brine and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (1:2 EA/PE) on silica gel afforded the aldol **29** (17.9 g, 42.1 mmol, 84%) as a yellowish oil: $[\alpha]^{29}_D$ −58.9 (*c* 3.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 7H), 6.87 (d, J = 8.8 Hz, 2H), 5.86 (dt, J = 15.7, 5.3 Hz, 1H), 5.76 (dd, J = 15.7, 5.4 Hz, 1H), 5.40 (dd, J = 8.9, 3.7 Hz, 1H), 4.65 (t, J = 8.9 Hz, 1H), 4.50 (m, 1H), 4.44 (s, 2H), 4.21 (dd, J = 8.9, 3.8 Hz, 1H), 4.00 (d, J = 5.4 Hz, 2H), 3.93−3.91 (m, 1H), 3.80 (s, 3H), 2.90 (br, 1H), 1.15 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 159.1, 153.3, 138.8, 131.8, 130.2, 129.3, 129.2, 128.7, 128.6, 125.5, 113.7, 71.72, 71.65, 69.8, 69.6, 57.5, 55.2, 42.6, 11.0; FT-IR (film) 3504, 2936, 1775, 1702, 1513, 1383, 1248, 1034, 978, 705 cm^{-1}; ESI-MS m/z 448.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{24}H_{27}NO_6Na$ ([M + Na]$^+$) 448.1731, found 448.1731.

(2*S*,3*S*,4*E*)-2-Methyl-6-(4-methoxybenzyloxy)-hex-4-ene-1,3-diol (30). A solution of $NaBH_4$ (6.001 g, 158.0 mmol) in H_2O (20 mL) was added dropwise to a solution of (16.8 g, 39.5 mmol) in THF stirred at 0 °C. After completion of the addition, the cooling bath was removed and the stirring was continued at ambient temperature for 2 h. The reaction was quenched with aq HCl (2 M). The volatiles were removed by rotary evaporation. The residue was extracted with EtOAc. The organic phase was washed in turn with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation led to precipitation of a white solid (the acyloxazolidinone **7**), which was collected by filtrate (5.4 g, 33.1 mmol, 84%). The filtrate was concentrated on a rotary evaporator. The residue was purified by column chromatography (1:1 EtOAc/PE) on silica gel to yield the diol **30** (9.8 g, 36.8 mmol, 93%) as a colorless oil: $[\alpha]^{24}_D$ −4.3 (*c* 2.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 7.9 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.84−5.72 (m, 2H), 4.45 (s, 2H), 4.29 (m, 1H), 4.01 (d, J = 4.4 Hz, 2H), 3.79 (s, 3H), 3.64−3.52 (m, 2H), 3.39 (br, 1H), 3.27 (br, 1H), 1.96−1.82 (m, 1H), 0.84 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 133.3, 130.0, 129.4, 127.6, 113.7, 74.6, 71.8, 69.8, 65.8, 55.2, 39.5, 11.2; FT-IR (film) 3423, 2875, 1670, 1612, 1514, 1248, 1032, 821, 758 cm^{-1}; ESI-MS m/z 289.1 ([M + Na]$^+$); ESI-HRMS calcd for $C_{15}H_{22}O_4Na$ ([M + Na]$^+$) 289.1410, found 289.1417.

(4*R*,5*S*)-5-Methyl-4-[(1*E*)-3-(4-methoxybenzyloxy)-propenyl]-2-phenyl-1,3-dioxane (31). A solution of diol **30** (9.8 g, 36.8 mmol) and CSA (853 mg, 3.68 mmol) in $PhCH(OMe)_2$ (12 mL) was stirred at ambient temperature under aspirator vacuum. When TLC showed completion of the reaction, the mixture was chromatographed (1:30 to 1:7 EtOAc/PE) on silica gel to yield acetonide **31** (11.93 g, 33.6 mmol, 91%) as a yellowish oil: $[\alpha]^{24}_D$ −2.5 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.25 (m, 7H), 6.88 (d, J = 8.7 Hz, 2H), 5.90 (dt, J = 5.6, 15.7 Hz, 1H), 5.80 (dd, J = 4.9, 15.8 Hz, 1H), 5.57 (s, 1H), 4.56 (m, 1H), 4.46 (s, 2H), 4.17−4.05 (m, 2H), 4.02 (d, J = 5.6 Hz, 2H), 3.80 (s, 3H), 1.69−1.65 (m, 1H), 1.24 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 159.2, 138.7, 131.2, 130.4, 129.3, 128.8, 128.2, 127.8, 126.2, 113.8, 101.7, 79.4, 73.3, 71.8, 69.9, 55.2, 32.9, 11.5; FT-IR (film) 3064, 2963, 2851, 1612, 1586, 1513, 1465, 820, 755 cm^{-1}; ESI-MS m/z 377.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{22}H_{26}O_4Na$ ([M + Na]$^+$) 377.1723, found 377.1733. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.52; H, 7.44.

(2*S*,3*S*,4*E*)-1-Benzyloxy-2-methyl-6-(4-methoxybenzyloxy)-hex-4-en-3-ol (32) and (2*S*,3*S*,4*E*)-3-Benzyloxy-2-methyl-6-(4-methoxybenzyloxy)-hex-4-en-1-ol (33). DIBAL-H (1.0 M, in cyclohexane, 134.8 mL, 134.8 mmol) was added dropwise to a solution of (11.93 g, 33.6 mmol) in dry CH_2Cl_2 (80 mL) stirred at 0 °C under N_2. After completion of the addition, the cooling bath was removed and the stirring was continued at ambient temperature until TLC showed completion of the reaction. Aqueous saturated potassium sodium tartrate (100 mL) was added, followed by Et_2O (300 mL). The mixture was stirred at ambient temperature for 2 h. The phases were separated. The aqueous layer was back-extracted with Et_2O. The organic phases were combined and washed in turn with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation followed by column chromatography (1:4 EtOAc/PE) on silica gel gave **32** (less polar) and **33** (more polar) (1:13 as determined by ^{1}H NMR before chromoatography, 11.4 g altogether after chromatography, 32.1 mmol, 95% in total). The two alcohols are separable on silica gel; on preparative scales, one chromatography normally could afford 85−91% of the enantiopure **32**, along with a mixture of **32** and **33**.

Data for **32** (the less polar component, yellowish oil): $[\alpha]^{27}_D$ +3.2 (*c* 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.25 (m, 7H), 6.87 (d, J = 8.6 Hz, 2H), 5.88−5.71 (m, 2H), 4.50 (s, 2H), 4.44 (s, 2H), 4.29−4.25 (m, 1H), 4.00 (d, J = 5.1 Hz, 2H), 3.80 (s, 3H), 3.50 (m, 2H), 2.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.0, 133.4, 130.5, 129.4, 128.5, 127.8, 127.7, 113.8, 74.5, 73.8, 73.5, 71.7, 70.0, 55.3, 38.5, 11.8; FT-IR (film) 3448, 2933, 2856, 1612, 1513, 1454, 1248, 820, 699 cm^{-1}; ESI-MS m/z 379.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{22}H_{28}O_4Na$ ([M + Na]$^+$) 379.1880, found 379.1894.

Data for **33** (the more polar component, yellowish oil): $[\alpha]^{26}_D$ +35.1 (*c* 4.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.24 (m, 7H), 6.88 (d, J = 9.0 Hz, 2H), 5.88−5.71 (m, 2H), 4.61 (d, J = 12.2 Hz, 1H), 4.46 (s, 2H), 4.33 (d, J = 12.3 Hz, 1H), 4.05 (d, J = 5.1 Hz, 2H), 3.93 (dd, J = 4.5, 7.2 Hz, 1H), 3.78 (s, 3H), 3.65 (dd, J = 7.5, 10.8 Hz, 1H), 3.50 (dd, J = 4.5, 10.9 Hz, 1H), 2.58 (br, 1H), 2.02−1.91 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 138.2, 131.0, 130.3, 130.0, 129.3, 128.3, 127.54, 127.50, 113.7, 82.2, 71.8, 70.3, 69.6, 65.5, 55.1, 39.7, 12.1; FT-IR (film) 3448, 2933, 2861, 1612, 1513, 1454, 1248, 820, 699 cm^{-1}; ESI-MS m/z 379.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{22}H_{28}O_4Na$ ([M + Na]$^+$) 379.1880, found 379.1874.

(2*S*,3*R*,4*R*,5*S*,6*E*)-5-Benzyloxy-1-((4*S*)-4-benzyl-2-thioxo-oxazolidin-3-yl)-3-hydroxy-2,4-dimethyl-8-(4-methoxybenzyloxy)-oct-6-en-1-one (36). Dess−Martin periodinane (596 mg, 1.40 mmol) and $NaHCO_3$ (252 mg, 3.0 mmol) were added in turn to a solution of **33** (356 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL) stirred at ambient temperature. The mixture was stirred until TLC showed completion of the reaction. Et_2O (100 mL) was added. The solids were filtered off through Celite. The filtrate was concentrated on a rotary evaporator. The residue was purified by column chromatography (1:8 EtOAc/PE) to afford the intermediate aldehyde **34** (334 mg, 0.94 mmol, 94%) as a yellowish oil.

Freshly distilled $TiCl_4$ (155 μL, 1.42 mmol) was added dropwise to a solution of acyloxazolidinethione **35** (337 mg, 1.35 mmol) in dry CH_2Cl_2 (7 mL) stirred at 0 °C under N_2. The resulting yellow solution was stirred for 10 min before neat (−)-sparteine (0.78 mL, 3.38 mmol) was added dropwise. The resulting dark red-brown mixture was stirred at 0 °C for 20 min before a solution of the above-mentioned aldehyde **34** (319 mg, 0.90 mmol) in dry CH_2Cl_2 (1.2 mL) was introduced via syringe. The stirring was continued at the same temperature for 2 h.

Aqueous NH_4Cl was added. The resulting mixture was filtered through Celite. The filtrate was washed in turn with water and brine and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (1:4 EtOAc/PE) on silica gel afforded the aldol **36** (509 mg, 0.843 mmol, 94% from **34** or 88% from **33**) as a yellow oil: $[\alpha]^{26}_D$ +30.1 (*c* 4.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.19 (m, 12H), 6.86 (d, J = 8.4 Hz, 2H), 5.88−5.72 (m, 2H), 4.92−4.79 (m, 2H), 4.60 (d, J = 11.8 Hz, 1H), 4.45 (s, 2H), 4.36 (d, J = 11.6 Hz, 1H), 4.27−4.16 (m, 3H), 4.10 (m, 1H), 4.05 (d, J = 4.4 Hz, 2H), 3.84 (d, J = 2.8 Hz, 1H), 3.78 (s, 3H), 3.29 (dd, J = 3.2, 13.0 Hz, 1H), 2.74 (dd, J = 10.4, 13.1 Hz, 1H), 1.90 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 177.4, 159.1, 138.0, 135.2, 131.0, 130.1, 130.0, 129.30, 129.27, 128.9, 128.3, 127.52, 127.50, 127.3, 113.7, 81.4, 72.9, 71.8, 70.7, 70.0, 69.6, 60.4, 55.1, 40.5, 40.1, 37.4, 11.5, 10.0; FT-IR (film) 3503, 2920, 2851, 1737, 1697, 1513, 1454, 1364, 1191, 957 cm^{-1}; ESI-MS m/z 626.4 ($[M + Na]^+$); ESI-HRMS calcd for $C_{35}H_{41}NO_6SNa$ ($[M + Na]^+$) 626.2547, found 626.2532.

(2*S*,3*R*,4*R*,5*S*,6*E*)-5-Benzyloxy-1-((4*R*)-4-benzyl-2-thioxo-oxazolidin-3-yl)-3-hydroxy-2,4-dimethyl-8-(4-methoxybenzyloxy)-oct-6-en-1-one (36′). Freshly distilled $TiCl_4$ (150 μL, 1.41 mmol) was added dropwise to a solution of acyloxazolidinethione *ent*-**35** (176 mg, 0.707 mmol) in dry CH_2Cl_2 (6 mL) stirred at 0 °C under N_2. The resulting yellow solution was stirred for 10 min before neat (−)-sparteine (180 μL, 0.78 mmol) was added dropwise. The resulting dark red-brown mixture was stirred at 0 °C for 20 min before a solution of the above-mentioned aldehyde **34** (167 mg, 0.471 mmol) in dry CH_2Cl_2 (1 mL) was introduced via syringe. The stirring was continued at the same temperature for 2 h. Aqueous NH_4Cl was added. The resulting mixture was filtered through Celite. The filtrate was washed in turn with water and brine and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (1:3 EtOAc/PE) on silica gel afforded **36′** as a colorless oil (242 mg, 0.40 mmol, 85%). If the (−)-sparteine was replaced by *i*-Pr_2NEt (140 μL, 0.78 mmol), **36′** was obtained in 76% yield under the otherwise identical conditions.

Data for **36′**: $[\alpha]^{26}_D$ −54.6 (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.21 (m, 12H), 6.89 (d, J = 8.6 Hz, 2H), 5.89−5.71 (m, 2H), 4.96 (m, 1H), 4.92 (m, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.49 (s, 2H), 4.41 (d, J = 11.8 Hz, 1H), 4.31−4.23 (m, 4H), 4.09 (d, J = 4.4 Hz, 2H), 3.81 (s, 3H), 3.80 (br, 1H), 3.30 (dd, J = 3.1, 13.3 Hz, 1H), 2.68 (dd, J = 10.3, 13.3 Hz, 1H), 1.95 (m, 1H), 1.25 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 177.3, 159.1, 138.0, 135.2, 131.1, 130.1, 130.0, 129.31, 129.29, 128.9, 128.3, 127.6, 127.3, 113.7, 81.6, 72.6, 71.8, 70.8, 70.1, 69.7, 59.9, 55.2, 40.7, 40.2, 37.7, 11.6, 10.0; FT-IR (film) 3477, 3062, 3028, 2973, 2858, 1702, 1612, 1513, 1454, 1369, 958, 821, 752 cm^{-1}; ESI-MS m/z 626.4 ($[M + Na]^+$); ESI-HRMS calcd for $C_{35}H_{41}NO_6SNa$ ($[M + Na]^+$) 626.2547, found 626.2575.

Methyl (2*S*,3*R*,4*R*,5*S*,6E)-5-Benzyloxy-3-hydroxy-8-(4-methoxybenzyloxy)-2,4-dimethyloct-6-enate (37). A solution of **36** (80 mg, 0.133 mmol) and DMAP (3.2 mg, 0.027 mmol) in dry CH_2Cl_2 (2 mL) and MeOH (0.1 mL) was stirred at ambient temperature until TLC showed completion of the reaction. The mixture was diluted with CH_2Cl_2 (20 mL), washed in turn with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:3 EtOAc/PE) on silica gel yielded the methyl ester **37** (42 mg, 0.10 mmol, 70%) as a colorless oil: $[\alpha]^{26}_D$ +32.1 (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.26 (m, 7H), 6.89 (d, J = 8.4 Hz, 2H), 5.88−5.74 (m, 2H), 4.61 (d, J = 11.6 Hz, 1H), 4.47 (s, 2H), 4.34 (d, J = 11.7 Hz, 1H), 4.22 (m, 1H), 4.06 (d, J = 4.3 Hz, 2H), 3.97 (dt, J = 8.4, 4.0 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.53 (d, J = 3.9 Hz, 1H), 2.51 (m, 1H), 1.81 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 176.2, 159.2, 138.0, 131.0, 130.3, 130.2, 129.4, 128.4, 127.8, 127.7, 113.8, 80.9, 73.6, 71.9, 70.7, 69.7, 55.3, 51.8, 42.3, 39.9, 11.6, 9.7; FT-IR (film) 3495, 2939, 1736, 1612, 1513, 1455, 1248, 1066, 976, 700 cm^{-1}; ESI-MS m/z 465.2 ($[M + Na]^+$); ESI-HRMS calcd for $C_{26}H_{34}O_6Na$ ($[M + Na]^+$) 465.2248, found 465.2256.

(3*S*,4*R*,5*R*,6*S*)-4-Hydroxy-6-(3-hydroxypropyl)-3,5-dimethyltetrahydropyran-2-one (38). A solution of **37** (13 mg, 30.8 μmol) and 10% Pd−C (33 mg) in MeOH (1 mL) was stirred at ambient temperature under H_2 (1 atm) atmosphere for 24 h. The solid was filtered off. The filtrate was concentrated on a rotary evaporator. The residue was dissolved in toluene (1 mL). CSA (3.6 mg, 15.4 μmol) was added. The mixture was stirred at ambient temperature for 2 h. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with EtOAc (3 × 5 mL). The organic phases were combined and washed in turn with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (4:1 EtOAc/PE) on silica gel yielded the lactone **38** (4.5 mg, 22.3 μmol, 72%) as a colorless oil: $[\alpha]^{26}_D$ −92.2 (*c* 0.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.31 (d, J = 4.3 Hz, 1H), 4.29 (m, 1H), 3.84 (dt, J = 10.3, 4.1 Hz, 1H), 3.59−3.52 (m, 2H), 3.50 (t, J = 5.2 Hz, 1H), 2.33 (dq, J = 10.2, 6.8 Hz, 1H), 2.19−2.10 (m, 1H), 1.80−1.70 (m, 1H), 1.70−1.61 (m, 2H), 1.60−1.52 (m, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.6, 80.1, 73.8, 62.1, 40.6, 38.3, 29.8, 29.7, 14.6, 4.7; FT-IR (film) 3398, 2942, 1719, 1218, 1039, 983 cm^{-1}; ESI-MS m/z 225.0 ($[M + Na]^+$); ESI-HRMS calcd for $C_{10}H_{18}O_4Na$ ($[M + Na]^+$) 225.1097, found 225.1107.

(4*S*,5*R*,6*R*,7*S*,8*R*,2*E*)-4-Benzyloxy-11-*tert*-butyldimethylsilyloxy-1-(4-methoxybenzyloxy)-13-methoxymethoxy-5,7-dimethyl-6-trimethylsilyloxyhexadec-2-en-9-yn-8-ol (41a) and (4*S*,5*R*,6*R*,7*S*,8*S*,4*E*)-4-Benzyloxy-11-*tert*-butyldimethylsilyloxy-1-(4-methoxybenzyloxy)-13-methoxymethoxy-5,7-dimethyl-6-trimethylsilyloxyhexadec-2-en-9-yn-8-ol (41b). TMSCl (1.20 mL, 9.49 mmol) was added dropwise to a solution of **36** (2.293 g, 3.80 mmol) and 2,6-lutidine (1.44 mL, 11.4 mmol) in dry DMF (15 mL) stirred at 0 °C under N_2. After completion of the addition, the cooling bath was removed. The stirring was continued at ambient temperature for 2 h. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3 × 50 mL). The organic phases were combined and washed in turn with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (1:8 EtOAc/PE) gave the unstable TMS-ether **39** (2.309 g, 3.42 mmol, 90%) as a colorless oil, which was used immediately in the next step: FT-IR (film) 2957, 2853, 1699, 1612, 1513, 1364, 841, 746 cm^{-1}; ESI-MS m/z 698.4 ($[M + Na]^+$); ESI-HRMS calcd for $C_{38}H_{49}NO_6NaSSi$ ($[M + Na]^+$) 698.2942, found 698.2957.

DIBAL-H (1.0 M, in cyclohexane, 8.5 mL, 8.5 mmol) was added dropwise to a solution of the above-mentioned **39** (2.30 g, 3.41 mmol) in dry CH_2Cl_2 (10 mL) stirred at −78 °C under argon. The mixture was stirred at the same temperature for 2 h. Aqueous saturated potassium sodium tartrate (10 mL) was added, followed by Et_2O (100 mL). The mixture was stirred at ambient temperature until the phases were clear and separated. The aqueous layer was back-extracted with Et_2O (3 × 50 mL). The organic phases were combined and washed in turn with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation followed by column chromatography (1:4 EtOAc/PE) on silica gel gave the intermediate aldehyde **40** (1.525 g, 3.14 mmol, 92%) as a colorless oil, which was used immediately in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.24−7.25 (m, 7H), 6.90 (d, J = 8.4 Hz, 2H), 5.90−5.75 (m, 2H), 4.61 (d, J = 12 Hz, 1H), 4.50−4.40 (m, 1H), 4.47 (s, 2H), 4.31 (br d, J = 12 Hz, 1H), 4.22−4.17 (m, 1H), 4.07−4.02 (br s, 2H), 3.81 (s, 3H), 2.50 (m, 1H), 1.70 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.07 (s, 9H).

n-BuLi (2.5 M in hexanes, 1.44 mL, 3.60 mmol) was added to a solution of the alkyne (1.081 g, 3.60 mmol) in dry THF (20 mL)

stirred at −20 °C under N_2. The stirring was continued at that temperature for 30 min before a solution of aldehyde **40** (1.579 g, 3.26 mmol) in dry THF (3 mL) was introduced dropwise over 30 min. After completion of the addition, the mixture was stirred at the same temperature for another 15 min. Aqueous saturated NH_4Cl was added. The mixture was extracted with Et_2O (3 × 100 mL). The organic phases were combined, washed in turn with water and brine, and dried over $NaSO_4$. Removal of the solvent and chromatography on silica gel (1:8 EtOAc/PE) yielded the less polar isomer **41b** (1.539 g, 1.96 mmol, 60%) and the more polar **41a** (1.012 g, 1.29 mmol, 40%).

Data for **41a** (a yellowish oil, the more polar component, (10*R*)-isomer): $[\alpha]^{24}_D$ −21.8 (*c* 2.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.25 (m, 7H), 6.88 (d, J = 8.6 Hz, 2H), 5.82−5.80 (m, 2H), 4.63 (t, J = 7.0 Hz, 1H), 4.58−4.53 (m, 3H), 4.45 (s, 2H), 4.33 (d, J = 12 Hz, 1H), 4.21 (m, 1H), 4.14 (m, 1H), 4.07−4.02 (m, 3H), 3.84−3.76 (m, 1H), 3.80 (s, 3H), 3.35 (s, 3H), 2.59 (m, 1H), 1.92−1.80 (m, 3H), 1.71 (m, 1H), 1.52−1.43 (m, 2H), 1.41−1.30 (m, 2H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 0.86 (s, 9H), 0.15 (s, 9H), 0.07 (d, J = 1.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 139.1, 133.2, 130,.2, 129.5, 129.3, 128.1, 127.0, 126.9, 113.7, 95.1, 87.2, 85.5, 78.9, 74.9, 74.3, 71.8, 69.9, 69.7, 65.9, 60.8, 55.4, 55.2, 43.5, 43.4, 42.7, 37.4, 25.7, 18.4, 18.0, 14.1, 10.4, 8.8, 1.0, −4.4, −5.2; FT-IR (film) 3438, 2956, 2857, 1676, 1612, 1514, 838 cm^{-1}; ESI-MS m/z 807.5 ([M + Na]$^+$); ESI-HRMS calcd for $C_{44}H_{72}Si_2O_8Na$ ([M + Na]$^+$) 807.4658, found 807.4673.

Data for **41b** (a yellowish oil, the less polar component, (10*S*)-isomer): $[\alpha]^{24}_D$ −20.9 (*c* 2.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.27 (m, 7H), 6.89 (d, J = 8.4 Hz, 2H), 5.83−5.81 (m, 2H), 4.69 (d, J = 6.9 Hz, 1H), 4.65 (d, J = 6.9 Hz, 1H), 4.61−4.58 (m, 2H), 4.47 (s, 2H), 4.34 (d, J = 12.2 Hz, 1H), 4.23 (d, J = 9.1 Hz, 1H), 4.18 (d, J = 4.3 Hz, 1H), 4.12 (dd, J = 5.5, 8.8 Hz, 1H), 3.86−3.81 (m, 1H), 3.81 (s, 3H), 3.40 (s, 3H), 2.41 (m, 1H), 1.98−1.90 (m, 1H), 1.90−1.78 (m, 2H), 1.66 (m, 1H), 1.52 (m, 2H), 1.41 (m, 2H), 0.95−0.91 (m, 18H), 0.16 (s, 9H), 0.14 (d, J = 9.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 139.2, 133.4, 130.2, 129.4, 128.1, 127.04, 127.00, 113.8, 95.0, 86.3, 79.0, 74.1, 71.8, 71.7, 69.9, 64.3, 60.9, 55.5, 55.2, 43.5, 43.2, 42.3, 37.3, 25.7, 18.4, 18.1, 14.1, 10.0, 9.7, 0.9, −4.5, −5.1; FT-IR (film) 3438, 2956, 2857, 1676, 1612, 1514, 838 cm^{-1}; ESI-MS m/z 807.5 ([M + Na]$^+$); ESI-HRMS calcd for $C_{44}H_{72}Si_2O_8Na$ ([M + Na]$^+$) 807.4658, found 807.4658.

(4*S*,5*R*,6*R*,7*S*,8*R*,2*E*)-4-Benzyloxy-11-*tert*-butyldimethylsilyloxy-1-(4-methoxybenzyloxy)-13-methoxymethoxy-5,7-dimethylhexadec-2-en-9-yne-6,8-diol (42a). The procedure was the same as described below for converting **41b** into **42b**. Data for **42a** (a colorless oil, 91% from **41a**): $[\alpha]^{24}_D$ −18.8 (*c* 1.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 7H), 6.90 (d, J = 8.6 Hz, 2H), 5.91−5.75 (m, 2H), 4.68−4.60 (m, 4H), 4.57 (t, J = 7.8 Hz, 1H), 4.48 (s, 2H), 4.36 (d, J = 11.8 Hz, 1H), 4.09−4.07 (m, 4H), 3.91 (d, J = 9.7 Hz, 1H), 3.83−3.75 (m, 1H), 3.81 (s, 3H), 3.72 (br, 1H), 3.37 (s, 3H), 2.06−1.96 (m, 1H), 1.92−1.84 (m, 1H), 1.83−1.79 (m, 1H), 1.79−1.70 (m, 1H), 1.56−1.43 (m, 2H), 1.42−1.30 (m, 2H), 1.07 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.76 (d, J = 7.4 Hz, 3H), 0.12 (d, J = 9.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 137.8, 131.9, 130.1, 129.4, 129.0, 128.5, 127.7, 127.6, 113.8, 95.4, 85.6, 85.0, 82.7, 74.5, 72.0, 70.7, 69.6, 67.7, 60.7, 55.5, 55.2, 43.6, 40.3, 39.8, 37.0, 25.7, 18.3, 18.1, 14.1, 12.2, 5.8, −4.5, −5.1; FT-IR (film) 3445, 2930, 2857, 1613, 1463, 1037, 837, 778 cm^{-1}; ESI-MS m/z 735.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{41}H_{64}O_8SiNa$ ([M + Na]$^+$) 735.4263, found 735.4256.

(4*S*,5*R*,6*R*,7*S*,8*S*,2*E*)-4-Benzyloxy-11-*tert*-butyldimethylsilyloxy-1-(4-methoxybenzyloxy)-13-methoxymethoxy-5,7-dimethylhexadec-2-en-9-yne-6,8-diol (42b). Aqueous CF_3CO_2H (50%, 1.0 mL) was added to a solution of alcohol **41b** (1.771 g, 2.26 mmol) in CH_2Cl_2 (30 mL) stirred at ambient temperature. After complete addition, stirring was continued at the same temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3 × 100 mL). The organic phases were combined, washed with water and brine, and dried over anhydrous $NaSO_4$. Removal of the solvent and chromatography on silica gel (1:4 EtOAc/PE) gave diol **42b** (1.526 g, 2.14 mmol, 95%) as a colorless oil: $[\alpha]^{24}_D$ −20.8 (*c* 1.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.27 (m, 7H), 6.89 (d, J = 8.5 Hz, 2H), 5.85 (m, 2H), 4.66−4.61 (m, 4H), 4.47 (s, 2H), 4.40 (t. J = 7.1 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 4.24 (m, 1H), 4.05 (m, 3H), 3.85 (br s, 1H), 3.82−3.78 (m, 1H), 3.81 (s, 3H), 3.54 (m, 1H), 3.37 (s, 3H), 2.06−1.84 (m, 2H), 1.82−1.70 (m, 2H), 1.58−1.44 (m, 2H), 1.40−1.31 (m, 2H), 1.02 (d, J = 6.4 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.75 (d, J = 6.9 Hz, 3H), 0.12 (d, J = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 137.8, 132.2, 130.1, 129.4, 129.3, 128.5, 127.73, 127.67, 113.8, 95.3, 86.3, 85.7, 83.1, 74.4, 72.3, 71.9, 70.5, 69.8, 66.2, 60.8, 55.5, 55.2, 43.6, 40.2, 39.6, 37.0, 25.8, 18.4, 18.1, 14.1, 12.4, 9.4, −4.4, −5.1; FT-IR (film) 3446, 2928, 1614, 1514, 1097, 969, 837 cm^{-1}; ESI-MS m/z 735.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{41}H_{64}O_8SiNa$ ([M + Na]$^+$) 735.4263, found 735.4257.

(4*S*,5*R*,2*E*)-4-Benzyloxy-1-(4-methoxy-benzyloxy)-5-[(4*R*,5*S*,6*R*)-6-(3-*tert*-butyldimethylsilyl-5-methoxymethoxyoctyn-1-yl)-2,2,5-trimethyl-1,3-dioxinan-4-yl]-2-hexene (43a). The procedure was the same as described below for converting **42b** into **43b**. Data for **43a** (a colorless oil, 63% over two steps from **41a**): $[\alpha]^{28}_D$ −21.1 (*c* 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.23 (m, 7H), 6.88 (d, J = 8.5 Hz, 2H), 5.82−5.75 (m, 2H), 4.76 (s, 1H), 4.58 (d, J = 6.8 Hz, 2H), 4.56 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 4.55 (t, J = 9.0 Hz, 1H), 4.45 (s, 2H), 4.39−4.37 (m, 1H), 4.28 (d, J = 6.4 Hz, 1H), 4.24 (dd, J = 2.7, 10.3 Hz, 1H), 4.03 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.71−3.69 (m, 1H), 3.32 (s, 3H), 1.93−1.79 (m, 3H), 1.63−1.60 (m, 1H), 1.51−1.47 (m, 2H), 1.37−1.26 (m, 2H), 1.48 (s, 3H), 1.34 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.87 (s, 9H), 0.86 (t, J = 7.0 Hz, 3H), 0.09 (d, J = 4.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 139.2, 132.8, 130.5, 129.3, 128.8, 128.2, 127.2, 127.1, 113.9, 100.6, 95.8, 86.9, 85.1, 77.1 (revealed by HMQC), 74.9, 71.8, 70.9, 70.0, 68.2, 67.5, 60.8, 55.5, 55.3, 43.7, 39.7, 36.9, 36.2, 28.6, 25.8, 23.7, 18.3, 18.1, 14.2, 11.3, 8.1, −4.4, −5.0; FT-IR (film) 2930, 2856, 1613, 1513, 1459, 1010, 837, 778 cm^{-1}; ESI-MS m/z 775.5 ([M + Na]$^+$); ESI-HRMS calcd for $C_{44}H_{68}O_8SiNa$ ([M + Na]$^+$) 775.4576, found 775.4594.

(4*S*,5*R*,2*E*)-4-Benzyloxy-1-(4-methoxybenzyloxy)-5-[(4*R*,5*S*,6*S*)-6-(3-*tert*-butyldimethylsilyl-5-methoxymethoxyoctyn-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl]-2-hexene (43b). A solution of diol **42b** (1.526 g, 2.14 mmol), PPTS (55 mg, 0.214 mmol), and $Me_2C(OMe)_2$ (15 mL) in CH_2Cl_2 (15 mL) was stirred at ambient temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3 × 100 mL). The organic phases were combined, washed with water and brine, and dried over anhydrous $NaSO_4$. Removal of the solvent and chromatography on silica gel (1:8 EtOAc/PE) gave acetonide **43b** (1.571 g, 2.09 mmol, 98%) as a colorless oil: $[\alpha]^{28}_D$ −15.8 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.23 (m, 7H), 6.88 (d, J = 8.6 Hz, 2H), 5.82−5.75 (m, 2H), 4.64−4.55 (m, 4H), 4.46 (part of an AB system, d, J = 11.8 Hz, 1H), 4.44 (part of an AB system, d, J = 11.8 Hz, 1H), 4.39−4.37 (m, 1H), 4.28 (d, J = 6.4 Hz, 1H), 4.24 (dd, J = 2.7, 10.3 Hz, 1H), 4.03 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.71−3.69 (m, 1H), 3.32 (s, 3H), 1.93−1.79 (m, 3H), 1.63−1.60 (m, 1H), 1.51−1.47 (m, 2H), 1.37−1.26 (m, 2H), 1.48 (s, 3H), 1.34 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.87 (s, 9H), 0.86 (t, J = 7.0 Hz, 3H), 0.09 (d, J = 4.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 139.2, 132.8, 130.5, 129.3, 128.8, 128.2, 127.2, 127.1, 113.9, 100.6, 95.8, 86.9, 85.1, 77.1 (revealed by HMQC), 74.9, 71.8, 70.9, 70.0, 68.2, 67.5, 60.8, 55.5, 55.3, 43.7, 39.7, 36.9, 36.2, 28.6, 25.8, 23.7, 18.3, 18.1, 14.2,

11.3, 8.1, −4.4, −5.0; FT-IR (film) 2930, 2856, 1613, 1513, 1459, 1010, 837, 778 cm^{-1}; ESI-MS *m*/*z* 775.5 ($[M + Na]^+$); ESI-HRMS calcd for $C_{44}H_{68}O_8SiNa$ ($[M + Na]^+$) 775.4576, found 775.4594.

(4*S*,5*R*,6*R*,7*S*,11*S*,13*S*,2*E*)-4-Benzyloxy-11-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-14-methoxymethoxy-5,7-dimethyl-6-trimethylsilanyloxyheptadec-2-en-9-yn-8-one (44). Dess−Martin periodinane (465 mg, 1.095 mmol) and $NaHCO_3$ (138 mg, 1.644 mmol) were added to a solution of alcohol **41a** (430 mg, 0.548 mmol) in dry CH_2Cl_2 (5 mL) stirred at ambient temperature. The mixture was stirred at ambient temperature until TLC showed completion of the reaction before being diluted with Et_2O, filtered through Celite, and concentrated on a rotary evaporator. The residue was purified by column chromatography (1:8 EtOAc/PE) to afford ketone **44** (402 mg, 0.513 mmol, 94%) as a light yellow oil: $[\alpha]^{24}_D$ −8.4 (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 7H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.90−5.75 (m, 2H), 4.68 (t, *J* = 7.1 Hz, 1H), 4.60 (s, 2H), 4.63−4.57 (m, 1H), 4.50 (dd, *J* = 2.1, 9.1 Hz, 1H), 4.46 (s, 2H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.19 (br d, *J* = 4.4 Hz, 1H), 4.03 (d, *J* = 9.5 Hz, 2H), 3.81 (s, 3H), 3.73−3.65 (m, 1H), 3.33 (s, 3H), 2.72 (m, 1H), 2.01−1.80 (m, 2H), 1.62 (m, 1H), 1.58−1.40 (m, 2H), 1.39−1.21 (m, 2H), 1.11 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 159.2, 139.1, 132.9, 134.2, 129.6, 129.4, 128.2, 127.0, 126.9, 113.7, 95.8, 93.6, 83.6, 78.3, 76.6, 74.5, 73.0, 71.9, 69.8, 60.5, 55.5, 55.2, 51.1, 43.5, 43.0, 36.7, 25.6, 18.2, 18.0, 14.2, 10.0, 7.9, 0.8, −4.5, −5.2; FT-IR (film) 3065, 2956, 2932, 2858, 2207, 1679, 1613, 1514, 1464, 839, 779 cm^{-1}; ESI-MS *m*/*z* 805.4 ($[M + Na]^+$); ESI-HRMS calcd for $C_{44}H_{70}O_8Si_2Na$ ($[M + Na]^+$) 805.4502, found 805.4486.

L-Selectride Reduction of Ketone 44 Giving 41a and 41b. L-Selectride (1.0 M, in THF, 2.75 mL, 2.75 mmol) was added to a solution of ketone **44** (431 mg, 0.55 mmol) in dry THF (4 mL) stirred at −78 °C under argon. After completion of the addition, stirring was continued at −78 °C for 3 h. MeOH (2 mL) was added, followed by aq saturated potassium sodium tartrate (5 mL) and Et_2O (50 mL). The mixture was then stirred at ambient temperature for another 2 h, resulting in a two-phase clear mixture. The phases were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The organic phases were combined, washed with water and brine, and dried over anhydrous $NaSO_4$. Removal of the solvent and chromatography (1:8 EtOAc/PE) on silica gel yielded the less polar isomer **41b** (340 mg, 0.433 mmol, 79%) and the more polar isomer **41a** (56 mg, 0.071 mmol, 13%) as yellowish oils. Data for **41a** and **41b** are given above (prepared via coupling of alkyne **9** with aldehyde **40**).

(4*S*,5*R*,6*R*,7*S*,11*S*,13*S*,2*E*)-4-Benzyloxy-11-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-14-methoxymethoxy-5,7-dimethyl-6-hydroxyheptadec-2-en-9-yn-8-one (45). Aqueous CF_3CO_2H (50%, 0.67 mL) was added to a solution of TMS ether **44** (620 mg, 0.792 mmol) in CH_2Cl_2 (25 mL) stirred at ambient temperature. After complete of the addition, stirring was continued at the same temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3 × 50 mL). The organic phases were combined, washed with water and brine, and dried over anhydrous $NaSO_4$. Removal of the solvent and chromatography on silica gel (1:4 EtOAc/PE) gave alcohol **45** (547 mg, 0.769 mmol, 97%) as a yellowish oil: $[\alpha]^{24}_D$ −3.0 (*c* 2.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 7H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.86−5.79 (m, 2H), 4.70 (t, *J* = 7.0 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.63 (s, 2H), 4.47 (s, 2H), 4.21 (m, 1H), 4.16 (m, 1H), 4.05 (d, *J* = 4.9 Hz, 2H), 3.81 (s, 3H), 3.72 (m, 1H), 3.36 (s, 3H), 3.28 (d, *J* = 4.2 Hz, 1H), 2.59 (m, 1H), 1.97−1.80 (m, 3H), 1.54−1.47 (m, 2H), 1.40−1.32 (m, 2H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.93−0.85 (m, 15H), 0.12 (d, *J* = 9.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 159.2, 138.0, 131.0, 130.3, 130.1, 129.4, 128.4, 127.72, 127.68, 113.8, 95.7, 93.7, 82.9, 80.3, 74.3, 72.6, 71.9, 70.6, 69.7, 60.5, 55.6, 55.2, 51.1, 42.9, 40.0, 36.7, 25.6, 18.2, 18.0, 14.1, 11.4, 8.9, −4.6, −5.1; FT-IR (film) 3487, 2956, 2857, 2209, 1677, 1612, 1513, 1464, 1250, 838, 780, 699 cm^{-1}; ESI-MS *m*/*z* 733.4 ($[M + Na]^+$); ESI-HRMS calcd for $C_{41}H_{62}SiO_8Na$ ($[M + Na]^+$) 733.4106, found 733.4084.

(4*S*,5*R*,2*E*)-4-Benzyloxy-1-(4-methoxy-benzyloxy)-5-[(4*R*,5*S*,6*S*)-6-(3-*tert*-butyldimethylsilyl-5-methoxymethoxyoctyn-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl]-hex-2-en-1-ol (46). DDQ (51 mg, 0.223 mmol) was added in one portion to a solution of **43b** (140 mg, 0.186 mmol) in a two-phase mixture of CH_2Cl_2 (10 mL) and a pH 7 aq buffer ($NaHPO_4/Na_2HPO_4$, 1 mL) stirred at ambient temperature. The mixture was stirred at the same temperature for 1 h before another portion of DDQ (51 mg, 0.223 mmol) was added. Stirring was continued until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3 × 100 mL). The organic phases were combined, washed with water and brine, and dried over anhydrous $NaSO_4$. Removal of the solvent and chromatography on silica gel (1:4 EtOAc/PE) afforded alcohol **46** (110 mg, 0.174 mmol, 93%) as a colorless oil: $[\alpha]^{28}_D$ −26.0 (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.26 (m, 5H), 5.88 (dt, *J* = 16.1, 5.3 Hz, 1H), 5.72 (dd, *J* = 16.3, 6.3 Hz, 1H), 4.61 (d, *J* = 6.5 Hz, 1H), 4.58 (d, *J* = 6.5 Hz, 1H), 4.55 (m, 1H), 4.54 (d, *J* = 10.0 Hz, 1H), 4.41−4.39 (m, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.29−4.22 (m, 2H), 4.17 (d, *J* = 5.4 Hz, 2H), 3.72 (m, 1H), 3.33 (s, 3H), 1.98−1.74 (m, 3H), 1.64−1.58 (m, 1H), 1.54−1.40 (m, 2H), 1.48 (s, 3H), 1.40−1.26 (m, 2H), 1.34 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.09 (d, *J* = 2.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 131.3, 131.2, 128.2, 127.3, 127.2, 100.6, 95.8, 86.9, 85.0, 74.8, 70.9, 68.2, 67.4, 63.2, 60.8, 55.6, 43.6, 39.7, 36.9, 36.2, 28.6, 25.8, 23.7, 18.3, 18.1, 14.2, 11.3, 8.1, −4.3, −5.0; FT-IR (film) 3481, 2957, 2858, 1462, 1380, 1257, 837, 778 cm^{-1}; ESI-MS *m*/*z* 655.6 ($[M + Na]^+$); ESI-HRMS calcd for $C_{36}H_{60}O_7SiNa$ ($[M + Na]^+$) 655.4001, found 655.4009.

(4*R*)-3-{(2*R*,3*S*,6*S*,7*R*,4*E*)-6-Benzyloxy-7-[(4*R*,5*S*,6*S*)-6-((3*S*,5*S*)-3-*tert*-butyldimethylsilyloxy-5-methoxymethoxyoctyn-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl]-3-hydroxy-2-methyl-oct-4-enoyl}-4-phenyloxazolidin-2-one (48). Dess−Martin periodinane (795 mg, 1.86 mmol) and $NaHCO_3$ (234 mg, 2.79 mmol) were added in turn to a solution of **46** (588 mg, 0.93 mmol) in dry CH_2Cl_2 (5 mL) stirred at ambient temperature. The mixture was stirred until TLC showed completion of the reaction. Et_2O (100 mL) was added. The solids were filtered off through Celite. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (1:6 EtOAc/PE) on silica gel to afford the unstable aldehyde **47** (566 mg, 0.90 mmol, 96%) as a yellowish oil, which was immediately used in the next step of aldol condensation.

Freshly distilled $TiCl_4$ (0.23 mL, 2.10 mmol) was added dropwise to a solution of the acyloxazolidinone **7** (438 mg, 2.0 mmol) in dry CH_2Cl_2 (12 mL) stirred at 0 °C under N_2. The resulting yellow solution was stirred for 10 min before neat TMEDA (0.80 mL, 5.0 mmol) was added dropwise. The dark red-brown mixture was stirred at 0 °C for 30 min before a solution of the above-mentioned aldehyde **47** (566 mg, 0.90 mmol) in dry CH_2Cl_2 (2 mL) was introduced via syringe. The stirring was continued at ambient temperature for 10 h. Aqueous NH_4Cl was added. The resulting mixture was filtered through Celite. The filtrate was washed in turn with water and brine and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (1:3 EtOAc/PE) on silica gel afforded enantiopure aldol **48** (691 mg, 0.813 mmol, 90% from aldehyde **47** or 86% from alcohol **46**) as a colorless oil: $[\alpha]^{28}_D$ −35.2 (*c* 1.90, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.23 (m, 10H), 5.80 (dd, *J* = 6.4, 15.6 Hz, 1H), 5.70 (dd, *J* = 4.9, 15.7 Hz, 1H), 5.40 (dd, *J* = 3.8, 8.7 Hz, 1H), 4.65 (t, *J* = 8.8 Hz, 1H), 4.58−4.53 (m, 5H), 4.39 (m, 1H), 4.32−4.22 (m, 4H), 3.93−3.90 (m, 1H), 3.70 (m, 1H), 3.33 (s, 3H), 2.75 (br, 1H), 1.93−1.77 (m, 3H), 1.64−1.59 (m, 1H), 1.52−1.47 (m, 2H), 1.50 (s, 3H), 1.39−1.26 (m, 2H), 1.35

(s, 3H), 1.14 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.85 (d, J = 7.0 Hz, 3H), 0.08 (d, J = 4.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 153.4, 139.2, 138.8, 131.8, 131.1, 129.3, 128.8, 128.2, 127.3, 127.1, 125.6, 100.6, 95.8, 86.9, 85.0, 74.8, 71.7, 71.0, 69.9, 68.2, 67.5, 60.8, 57.7, 55.5, 43.7, 42.8, 39.7, 36.9, 36.2, 28.6, 25.8, 23.7, 18.3, 18.1, 14.2, 11.3, 11.0, 8.1, −4.4, −5.0; FT-IR (film) 3490, 3032, 2957, 2932, 2858, 1783, 1705, 1465, 1382, 1361, 1201, 838, 778 cm^{-1}; ESI-MS m/z 872.5 ([M + Na]$^+$); ESI-HRMS calcd for $C_{48}H_{71}NO_{10}SiNa$ ([M + Na]$^+$) 872.4740, found 872.4742.

(4*R*)-3-{(2*R*,3*S*,6*S*,7*R*,4*E*)-6-Benzyloxy-7-[(4*R*,5*S*,6*S*)-6-((3*S*,5*S*)-3-hydroxy-5-methoxymethoxyoctyn-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl]-3-hydroxy-2-methyloct-4-enoyl}-4-phenyloxazolidin-2-one (49). Aqueous HF·py (70%, 0.25 mL, 1.74 mmol) was added to a solution of **48** (296 mg, 0.348 mmol) in THF (8 mL) stirred at ambient temperature. Stirring was continued at the same temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3 × 50 mL). The organic phases were combined, washed in turn with aq saturated $CuSO_4$, water and brine, and dried over anhydrous $NaSO_4$. Removal of the solvent and chromatography (2:3 EtOAc/PE) on silica gel gave diol **49** (241 mg, 0.328 mmol, 94%) as a colorless foam: $[\alpha]^{28}_D$ −32.2 (c 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 10H), 5.79 (dd, J = 6.0, 15.3 Hz, 1H), 5.72 (dd, J = 5.3, 15.8 Hz, 1H), 5.41 (dd, J = 3.9, 8.8 Hz, 1H), 4.71−4.54 (m, 6H), 4.33−4.20 (m, 5H), 3.93−3.90 (m, 1H), 3.70 (m, 1H), 3.36 (s, 3H), 2.92 (d, J = 2.7 Hz, 1H), 2.69 (d, J = 4.2 Hz, 1H), 2.02−1.80 (m, 3H), 1.60 (m, 1H), 1.54−1.44 (m, 2H), 1.47 (s, 3H), 1.40−1.22 (m, 2H), 1.36 (s, 3H), 1.16 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 175.7, 153.2, 138.8, 138.6, 131.2, 131.1, 129.0, 128.5, 128.0, 127.04, 126.98, 125.3, 100.6, 95.2, 86.3, 84.7, 76.9, 75.4, 71.5, 70.6, 69.7, 68.0, 66.9, 60.4, 57.4, 55.4, 42.6, 42.2, 39.2, 36.7, 36.4, 27.6, 23.5, 17.9, 14.0, 11.0, 10.9, 8.0; FT-IR (film) 3449, 2959, 2933, 1782, 1702, 1458, 1382, 1201, 1040, 700 cm^{-1}; ESI-MS m/z 758.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{42}H_{57}NO_{10}Na$ ([M + Na]$^+$) 758.3875, found 758.3867.

(4*R*)-3-{(2*R*,3*S*,6*S*,7*R*)-6-Benzyloxy-7-[(4*R*,5*S*,6*S*)-6-((3*S*,5*S*)-3-hydroxy-5-methoxymethoxyoctyl)-2,2,5-trimethyl-1,3-dioxan-4-yl]-3-hydroxy-2-methyloctyl}-4-phenyloxazolidin-2-one (50). A solution of enyne **49** (311 mg, 0.423 mmol), 10% Pd−C (311 mg), and Et_3N (0.15 mL, 1.06 mmol) in EtOAc (8 mL) was stirred at ambient temperature under H_2 (1 atm) for 24 h. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was purified by column chromatography (1:1 EtOAc/PE) on silica gel to afford the saturated diol **50** (295 mg, 0.398 mmol, 94%) as a colorless oil: $[\alpha]^{28}_D$ −25.9 (c 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.24 (m, 10H), 5.40 (dd, J = 3.8, 8.9 Hz, 1H), 4.71 (d, J = 6.9 Hz, 1H), 4.66 (t, J = 8.8 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.64 (d, J = 6.7 Hz, 1H), 4.41 (d, J = 11.3 Hz, 1H), 4.22 (dd, J = 3.6, 8.9 Hz, 1H), 3.90−3.77 (m, 6H), 3.49 (br, 1H), 3.39 (s, 3H), 3.30−3.21 (m, 1H), 2.96 (d, J = 2.7 Hz, 1H), 2.08−1.94 (m, 1H), 1.72−1.42 (m, 12H), 1.41−1.31 (m, 3H), 1.32 (s, 3H), 1.27 (s, 3H), 1.17 (d, J = 7.1 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H), 0.87 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 176.9, 153.2, 139.4, 138.7, 129.2, 128.7, 128.0, 126.9, 126.7, 125.4, 100.7, 94.9, 77.2, 77.1, 75.3, 71.3, 71.1, 70.4, 69.8, 69.1, 57.4, 55.6, 42.1, 41.4, 38.1, 36.4, 36.3, 34.2, 30.8, 30.3, 27.6, 25.2, 23.8, 18.0, 14.2, 11.7, 10.2, 8.3; FT-IR (film) 3481, 2932, 2874, 1782, 1704, 1456, 1382, 1040, 699 cm^{-1}; ESI-MS m/z 764.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{42}H_{63}NO_{10}Na$ ([M + Na]$^+$) 764.4344, found 764.4350.

(4*R*)-3-{(2*R*,3*S*,6*S*,7*R*)-6-Benzyloxy-7-[(4*R*,5*S*,6*S*)-6-((3*S*,5*S*)-3-methanesulfonyloxy-5-methoxymethoxyoctyl)-2,2,5-trimethyl-1,3-dioxan-4-yl]-3-methanesulfonyloxy-2-methyloctyl}-4-phenyloxazolidin-2-one (51). MsCl (61 μL, 0.742 mmol) was added to a solution of diol **50** (110 mg, 0.148 mmol) and Et_3N (0.10 mL, 0.742 mmol) in CH_2Cl_2 (5 mL) stirred at ambient temperature under N_2 atmosphere. Stirring was continued at the same temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3 × 20 mL). The organic phases were combined, washed in turn with water and brine, and dried over anhydrous $NaSO_4$. Removal of the solvent and chromatography (1:32 EtOAc/PE) on silica gel gave dimesylate **51** (126 mg, 0.140 mmol, 95%) as a colorless oil: $[\alpha]^{28}_D$ −37.8 (c 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 10H), 5.32 (dd, J = 3.0, 8.5 Hz, 1H), 5.14 (m, 1H), 4.92 (m, 1H), 4.72−4.60 (m, 4H), 4.46 (AB, J = 11.4 Hz, 1H), 4.26 (dd, J = 3.1, 8.7 Hz, 1H), 4.08 (m, 1H), 3.90−3.78 (m, 2H), 3.64 (m, 1H), 3.38 (s, 3H), 3.24 (m, 1H), 3.02 (s, 3H), 2.99 (s, 3H), 2.07−1.92 (m, 2H), 1.90−1.71 (m, 4H), 1.70−1.44 (m, 6H), 1.43−1.25 (m, 4H), 1.32 (s, 3H), 1.28 (s, 3H), 1.15 (d, J = 7.2 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 153.7, 139.1, 138.9, 128.9, 128.4, 128.0, 126.9, 126.8, 125.6, 100.5, 95.1, 81.2, 80.6, 77.2, 74.5, 73.8, 71.3, 70.2, 69.0, 57.9, 55.5, 41.3, 39.3, 38.4, 38.2, 38.0, 36.42, 36.38, 31.0, 29.5, 29.3, 27.0, 25.1, 23.7, 18.0, 13.9, 11.5, 9.4, 8.3; FT-IR (film) 2935, 1778, 1709, 1456, 1357, 1335, 1173, 910 cm^{-1}; ESI-MS m/z 920.6 ([M + Na]$^+$); ESI-HRMS calcd for $C_{44}H_{67}NO_{14}S_2Na$ ([M+ Na]$^+$) 920.3895, found 920.3921.

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Supporting Information Available: General information for the Experimental Section, physical and spectroscopic data listing, ^{1}H as well as ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.