Systematic Construction of a Monotetrahydrofuran-Ring Library in *Annonaceous* Acetogenins by Asymmetric Alkynylation and Stereodivergent Tetrahydrofuran-Ring Formation

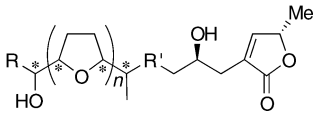
Naoto Kojima, Naoyoshi Maezaki,* Hiroaki Tominaga, Mikito Asai, Minori Yanai, and Tetsuaki Tanaka*[a]

Abstract: All eight diastereoisomers of the monotetrahydrofuran-ring cores of *annonaceous* acetogenins have been synthesized through utilization of asymmetric alkynylation and stereodivergent one-pot tetrahydrofuran-ring formation. In all cases, the asymmetric alkynylation proceeded with very high diastereoselectivity to give eight kinds of optically pure tetrahydrofuran core from a common α-oxyaldehyde. We also describe a comparison of the ^{1}H NMR, ^{13}C NMR, and CD spectral data of the eight isomers and give full details of the tetrahydrofuran-ring construction including a model study of asymmetric alkynylation.

Keywords: alkynylations · cyclization · polyketides · stereodivergent synthesis · synthetic methods

Introduction

Annonaceous acetogenins (Scheme 1) are a new class of natural polyketides that have attracted worldwide attention due to their broad spectrum of biological activity; this activity includes cytotoxic, antitumor, immunosuppressive, antimalarial, and antifeedant effects.[1, 2] Some of these compounds are promising candidates for new types of antitumor drugs possessing potent inhibitory activity against NADH:ubiquinone oxidoreductase of the respiratory chain (mitochondrial complex I), the main gate of energy production in the cell (NADH = nicotinamide adenine dinucleotide, reduced form).[3] Furthermore, it is known that some acetogenins inhibit multidrug-resistant cancer cells with an ATP-driven transporter system (ATP = adenosine triphosphate).[4] Over 350 acetogenins have been isolated from various *annonaceae* plants so far. Most of them are characterized by having one to three tetrahydrofuran (THF) ring(s) with various stereochemistries in the center of a long hydrocarbon chain with an α,β-unsaturated γ-lactone moiety at the end. The number and stereochemistry of the THF rings are known to affect the kind of effective tumor cell lines for growth inhibition.[1] Therefore, systematic synthesis of the poly-THF-ring core would be important to establish a structure – activity relationship.



Scheme 1. Representative structure of *annonaceous* acetogenins, where $n = 1-3$ and R, R′ = hydrocarbon chains with oxygenated moieties and/or double bonds.

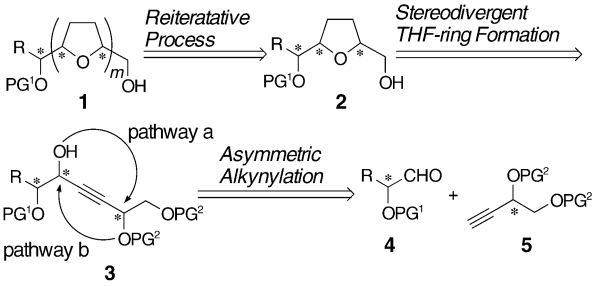
Reiterative strategy is an effective approach to synthesize the poly-THF-ring cores, because of their repeated structure. This methodology is advantageous in terms of economics (reuse of the same reagents) and ease of operation. Pioneering works have been reported by the groups of Figadère, Casiraghi, and Koert. Figadère et al. and Casiraghi and coworkers independently reported a unique reiterative procedure through Lewis acid promoted *C*-glycosydation with a 2-(trimethylsilyloxy)furan-type C_4 unit.[5] Although their procedure was useful to construct varied collections of the poly-THF-ring cores, it lacked stereoselectivity. Koert et al. developed a reiterative method with use of nucleophilic addition of a 3,4-isopropylidenedioxybutyl anion to α-oxyaldehyde.[6] Both *syn* and *anti* adducts were synthesized with good diastereoselectivities by changing the metal species. However, the non-chelation-controlled addition with an organozinc reagent gave low yields due to decomposition of the reagent under the Lewis acidic reaction conditions. In addition, the diastereoselectivity was low in the cases where the α-oxyaldehyde was mismatched with the C_4 unit.[6b]

[a] Dr. N. Maezaki, Prof. Dr. T. Tanaka, N. Kojima, H. Tominaga, M. Asai, M. Yanai
Graduate School of Pharmaceutical Sciences
Osaka University, 1-6 Yamadaoka, Suita
Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-8214
E-mail: maezaki@phs.osaka-u.ac.jp, t-tanaka@phs.osaka-u.ac.jp

Supporting information for this article is available on the WWW under http://www.chemeurj.org or from the author.

DOI: 10.1002/chem.200305185

During the course of our synthetic study of *annonaceous* acetogenins,[7] we planned a systematic synthesis of the poly-THF-ring cores based on asymmetric alkynylation of α-oxyaldehyde with a 3-butyne-1,2-diol derivative, as depicted in Scheme 2. In a preliminary communication, we demonstrated a highly stereodivergent and stereoselective synthesis of monoTHF-ring cores.[7c] Herein, we report the systematic synthesis of all eight isomers of the THF-ring core with two flanking secondary alcohols, and we discuss the comparison of their ^{1}H NMR, ^{13}C NMR, and CD spectral data.



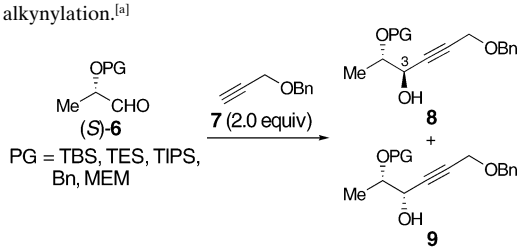
Scheme 2. Strategy of systematic synthesis of poly-THF ring cores. PG = Protecting group.

Results and Discussion

Our strategy for the systematic synthesis of the THF cores is outlined in Scheme 2. One key step is asymmetric alkynylation of the α-oxyaldehyde **4** with the chiral alkyne C_4 unit **5**, both enantiomers of which are readily prepared from natural products in enantiomerically pure form. We expected high diastereoselectivity from the prominent stereodifferentiating ability of the method of Carreira and co-workers, and convenient stereocontrol was also anticipated by changing the chiral ligand.[8] The employment of alkynylation is advantageous since the unreacted acetylide can be reused even if the reaction requires excess reagent. Such reuse is impossible in the case of an organometallic reagent generated by halogen–metal exchange reaction. Another key step is the stereodivergent THF-ring formation, by which four kinds of THF-ring core can be synthesized from two common precursors by changing the protocol (pathways a and b). Moreover, the terminal alcohol in the resulting THF-ring core **2** becomes a junction with the next C_4 unit **5** by oxidation to an aldehyde. Therefore, our strategy can potentially be applied to the synthesis of poly-THF-ring cores **1**.[9]

Initially, we examined the effect of the protecting group of the α-oxyaldehyde on the reagent-controlled asymmetric alkynylation with the benzyl ether of propargyl alcohol **7**[10] (Table 1). We selected silyl ethers[11a] (TBS, TES, and TIPS) and alkyl ethers[11b] (Bn and MEM) as protecting groups for (*S*)-**6** (PG = H), taking into account its application to the total synthesis of the *annonaceous* acetogenins. The asymmetric alkynylation was carried out by using $Zn(OTf)_2$, and Et_3N in the presence of (1*R*,2*S*)- or (1*S*,2*R*)-NME according to the protocol of Carreira and co-workers. As a result, we found that the stereochemistry of the asymmetric alkynylation was controlled by the chirality of the reagent rather than that of the α-oxyaldehyde in all cases.[12–14] The TBS-protected α-oxyaldehyde afforded the best results in terms of both yield and diastereoselectivity. Thus, we decided to employ the TBS group as the protecting group of the α-oxyaldehyde in further investigations.

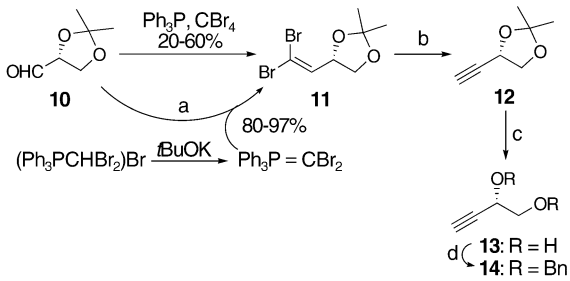
Table 1. Effect of the protecting group of the α-oxyaldehyde on asymmetric alkynylation.[a]



PG	Yield [%] (*anti*:*syn*)[b] (1*R*,2*S*)-NME	(1*S*,2*R*)-NME
TBS	92 (80:20)	86 (8:92)
TES	52 (69:31)	82 (20:80)
TIPS	79 (53:47)	76 (18:82)
Bn	85 (61:39)	85 (24:76)
MEM	70 (59:41)	58 (19:81)

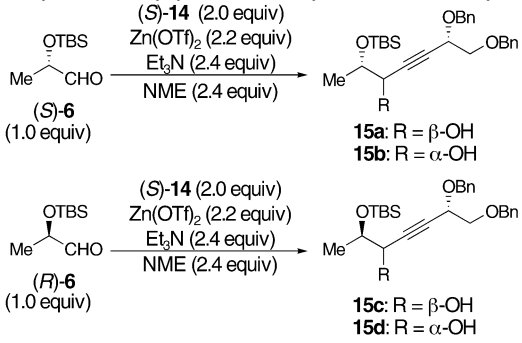
[a] Conditions: $Zn(OTf)_2$ (2.2 equiv), Et_3N (2.4 equiv), NME (2.4 equiv), toluene, RT. Abbreviations: TBS = *tert*-Butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl, Bn = benzyl, MEM = (2-methoxyethoxy)methyl, OTf = trifluoromethanesulfonate, NME = *N*-methylephedrine. [b] Determined from ^{1}H NMR spectroscopic data (500 MHz, $CDCl_3$).

We attempted to prepare the C_4 unit, 3-butyne-1,2-diol (**13**), from D-mannitol by the procedure reported by Gooding, Cooper and co-workers.[15] However, the yield of the Wittig reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde (**10**) in the Corey–Fuchs sequence was poor and not reproducible (Scheme 3). The problem was overcome by adopting Rassat's procedure. Thus, C_1-elongation of the aldehyde **10** was accomplished by using $(Ph_3PCHBr_2)Br$ and *t*BuOK,[16] to give dibromoolefin **11** in good yield and with excellent reproducibility.[17] Next, the resulting **11** was converted into the diol **13** without isolation of volatile acetonide **12** by the modified Gooding protocol.[15a] Diol **13** was protected with dibenzyl ethers to give a protected alkyne **14**, which has the advantage of reducing the number of steps since the deprotection and reduction of the triple bond can take place simultaneously.



Scheme 3. Preparation of the C_4 unit **14**. a) THF, 0 °C; b) *n*BuLi, THF, −78 °C → RT; c) Dowex 50W, MeOH, 35 °C, 83% over 2 steps; d) BnBr, NaH, nBu_4NI, THF, 0 °C → RT, 84%.

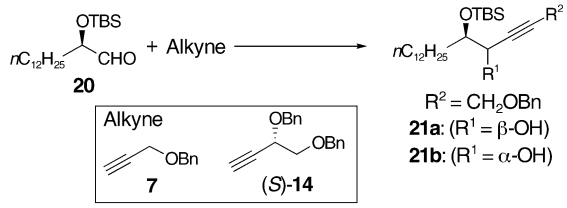
Table 2. Asymmetric alkynylation of aldehyde **6** with chiral alkyne (*S*)-**14**.



Aldehyde	NME	Major product	Yield [%]	*anti*:*syn*[a]
(*S*)-**6**	1*R*,2*S*	**15a**	58	84:16
(*S*)-**6**	1*S*,2*R*	**15b**	15	39:61
(*R*)-**6**	1*R*,2*S*	**15c**	66	8:92
(*R*)-**6**	1*S*,2*R*	**15d**	25	73:27

[a] Determined from ^{1}H NMR spectroscopic data (500 MHz, $CDCl_3$).

Table 3. Asymmetric alkynylation of aldehyde **20** with alkynes **7** or (*S*)-**14**.[a]

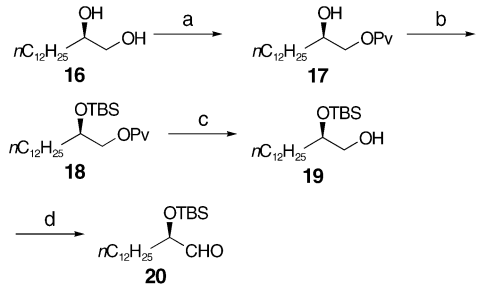


Entry	Alkyne	NME	Yield [%]	*anti*:*syn*[b]
1	**7**	1*R*,2*S*	54	3:>97
2	**7**	1*S*,2*R*	25	64:36
3	(*S*)-**14**	1*R*,2*S*	trace	–
4	(*S*)-**14**	1*S*,2*R*	trace	–

[a] Conditions: Alkyne (2.0 equiv), $Zn(OTf)_2$ (2.2 equiv), Et_3N (2.4 equiv), NME (2.4 equiv), toluene, RT. [b] Determined from ^{1}H NMR spectroscopic data (500 MHz, $CDCl_3$).

We next investigated the asymmetric alkynylation with the chiral C_4 unit **14** (Table 2). The stereochemistry of the major product was mainly subject to the chirality of the chiral ligand rather than that of the aldehyde or the alkyne.[12, 13] In particular, a combination of the alkyne (*S*)-**14** with (*R*)-**6** provided better yield and selectivity than the corresponding combination of (*S*)-**14** with (*S*)-**6**.[18]

(*R*)-2-Silyloxytetradecanal **20** was prepared as shown in Scheme 4. Optically pure (*R*)-tetradecane-1,2-diol (**16**) was prepared by kinetic resolution of (±)-tetradecene oxide with



Scheme 4. Preparation of aldehyde **20**. a) PvCl, pyridine, CH_2Cl_2, 0 °C → RT, 85%; b) TBSCl, imidazole, DMF, 0 °C → RT, quantitative; c) DIBAL-H, CH_2Cl_2, −78 °C, quantitative; d) Dess–Martin periodinane, CH_2Cl_2, RT, 96%. Pv = Pivalate, DMF = *N*,*N*-dimethylformamide, DIBAL-H = diisobutylaluminum hydride.

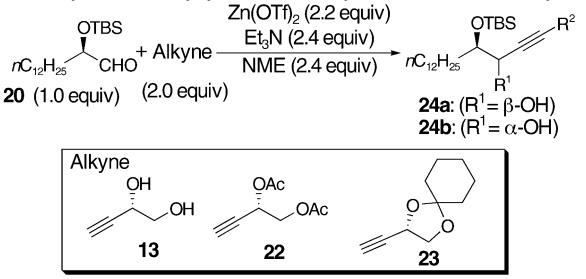
Jacobsen's salen–manganese catalyst.[19] The diol **16** was converted into **18** by selective protection of the primary alcohol to give pivalate **17** followed by silylation of the secondary alcohol. Treatment of **18** with DIBAL-H at −78 °C furnished primary alcohol **19** in quantitative yield. This was then oxidized to form α-oxyaldehyde **20** in 96% yield.

Next, asymmetric alkynylation with the long-chain aldehyde **20** was investigated. The stereochemistry of the asymmetric alkynylation depended on the chirality of the reagent (Table 3, entries 1 and 2).[20] Aldehyde (*R*)-**20** and (1*R*,2*S*)-NME seem to be a matched pair, as expected from the results shown in Table 1. However, the yield was low to moderate compared with the yield of alkynylation of the aldehyde **6**. Based on the model study, a combination of the *R*-configured aldehyde and *S*-configured alkyne was adopted. However, the reaction became sluggish when the substrates **20** and (*S*)-**14** were employed. In spite of the matched pair, only a trace amount of the adduct was obtained, and most of **20** decomposed during the long reaction time (entries 3 and 4).

We assumed that steric bulkiness of the dibenzyl moiety in alkyne (*S*)-**14** impeded the reaction. Therefore, we tried a coupling reaction of the aldehyde **20** and various 3-butyn-1,2-diol derivatives with lesser steric demands (Table 4). Unprotected diol **13** (entry 1) and diacetyl derivative **22** (entry 2)[21] afforded no adduct. On the other hand, cyclohexylidene acetal **23**[22] afforded the *syn* adduct **24a** in good yield and with high diastereoselectivity, but the yield and selectivity for the *anti*-adduct **24b** were only moderate (entries 3 and 4).[20] Furthermore, selective deacetalization of **24** was difficult due to the presence of the acid-sensitive TBS group.

Eventually, we found that a benzylidene acetal is the best protecting group. The benzylidene acetal **25** was readily prepared by an acetal-exchange reaction of 3-butyne-1,2-diol

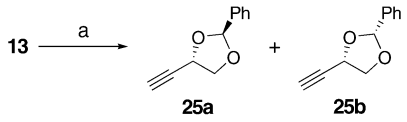
Table 4. Asymmetric alkynylation of aldehyde **20** with various alkynes.



Entry	Alkyne	NME	Yield [%]	*anti*:*syn*[a]
1	**13**	1*R*,2*S*	no reaction	–
2	**22**	1*R*,2*S*	trace	–
3	**23**	1*R*,2*S*	93	3:>97
4	**23**	1*S*,2*R*	43	85:15

[a] Determined from ^{1}H NMR spectroscopic data (500 MHz, $CDCl_3$).

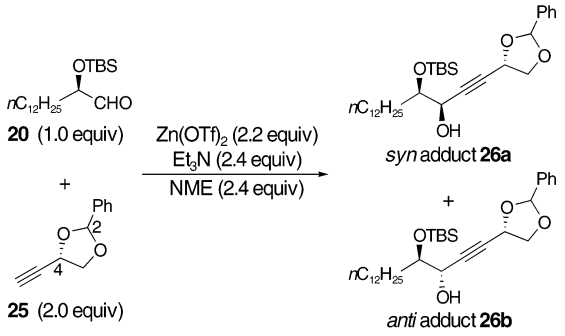
(**13**) in good yield to give an approximately 1:1 mixture of diastereomeric isomers **25a** and **25b**,[23] which can be separated by column chromatography (Scheme 5).



Scheme 5. Preparation of alkyne **25**. a) $PhCH(OMe)_2$, CSA, THF, reflux, 88%. CSA = (+)-10-camphorsulfonic acid.

Table 5 shows the results of the asymmetric alkynylation of the aldehyde **20** with the alkynes **25a** and **25b**. The C_2 stereogenic centers in the alkynes **25a** and **25b** did not show remarkable effects on either the yield or the selectivity (entries 1 and 2). In both reactions, the *syn* adduct **26a**

Table 5. Asymmetric alkynylation of aldehyde **20** with alkynes **25a** and **25b**.



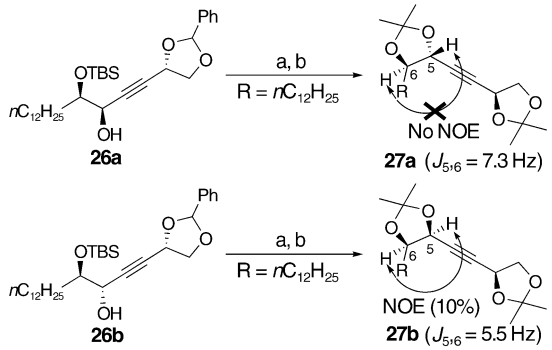
Entry	Alkyne	NME	Yield [%]	*anti*:*syn*[a]
1	2*S*,4*S*	1*R*,2*S*	74	3:>97
2	2*R*,4*S*	1*R*,2*S*	86	5:95
3	2*RS*,4*S*	1*R*,2*S*	96	3:>97
4	2*RS*,4*S*	1*S*,2*R*	quantitative	94:6

[a] Determined from ^1H NMR spectroscopic data (500 MHz, $CDCl_3$).

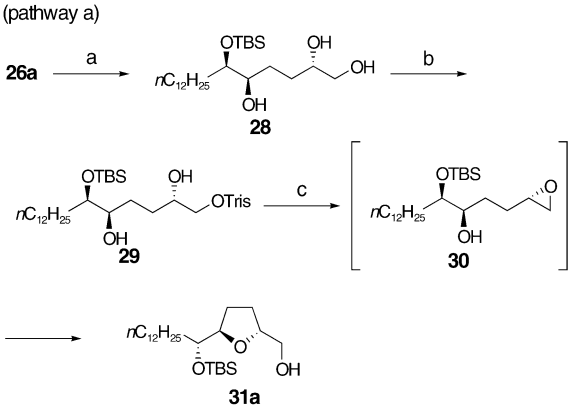
predominated over the *anti* adduct **26b**. The results indicate that separation of **25a** and **25b** is not required in a practical operation. In fact, the *syn* adduct **26a** was obtained in excellent yield with very high diastereoselectivity by using a mixture of **25a** and **25b** (entry 3).[24, 25] We also found that the *anti* adduct **26b** can be obtained in good yield and with acceptable diastereoselectivity by using the antipode of NME (entry 4).[26]

The stereochemistry of the coupling products **26a** and **26b** was determined by comparison of the coupling constants with related compounds (Scheme 6).[13] The adducts **26a** and **26b** were respectively converted into diacetonides **27a** and **27b** by desilylation and subsequent acetalization. The coupling constants ($J_{5,6}$ = 7.3 Hz in **27a** and $J_{5,6}$ = 5.5 Hz in **27b**) were identical with those of the related substrates.[27] Moreover, an NOE was observed between the two protons at the C5 and C6 positions in **27b**, but not in **27a**.

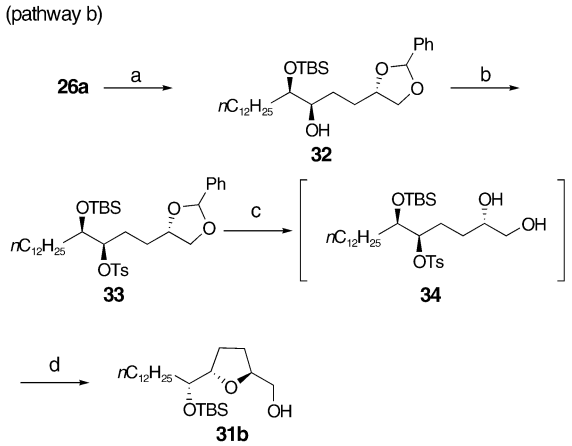
With the *syn* and *anti* adducts **26a** and **26b** in hand, we examined the stereodivergent THF-ring formation. The synthesis of the 2,5-*trans*-fused THF ring with **26a** by pathways a and b is depicted in Schemes 7 and 8.



Scheme 6. Synthesis of acetals **27a** and **27b**. a) TBAF, THF, RT; b) $Me_2C(OMe)_2$, pTsOH · H_2O, CH_2Cl_2, RT, 94% over 2 steps from **26a**, 97% over 2 steps from **26b**. TBAF = tetrabutylammonium fluoride, pTs = 4-toluenesulfonyl = tosyl.



Scheme 7. Synthesis of THF-ring moiety **31a**. a) H_2, 10% Pd/C, EtOAc, RT, 94%; b) TrisCl, pyridine, CH_2Cl_2, 0 °C → RT, 87%; c) K_2CO_3, MeOH, 0 °C → RT, 70%. Tris = 2,4,6-triisopropylbenzenesulfonyl.



Scheme 8. Synthesis of THF-ring moiety **31b**. a) H_2, 10% Pd/C, Et_3N, EtOAc, RT, quantitative; b) pTsCl, pyridine, 0 °C → RT, 96%; c) H_2, 10% Pd/C, EtOAc, RT; d) NaH, THF, 0 → 40 °C, 78% over 2 steps.

Hydrogenation of the triple bond accompanied by deprotection of the benzylidene acetal with 10% Pd/C in EtOAc afforded a saturated alcohol **28** in good yield. Selective sulfonylation of the primary alcohol with TrisCl furnished the sulfonate **29** in 87% yield. Upon treatment of **29** with K_2CO_3 in MeOH, THF-ring formation proceeded smoothly via

epoxide **30** in a one-pot reaction, to give the *trans*/*threo* isomer **31a** in 70% yield (Scheme 7, pathway a).[28]

Alternatively, the *trans*/*erythro* isomer **31b** was synthesized through pathway b (Scheme 8). An attempt to obtain **34** by tosylation of **26a** accompanied by simultaneous reduction of the triple bond and the benzylidene acetal was unsuccessful, presumably due to hydrogenolysis of the tosyl group. Selective hydrogenation of the triple bond in the presence of Et_3N as a catalyst poison[29] followed by tosylation of the secondary alcohol transformed **26a** into tosylate **33** in 96% yield over two steps. Reductive deacetalization and subsequent intramolecular Williamson reaction with NaH in THF promoted THF-ring formation rather than tetrahydropyran-ring formation and led to the production of **31b** in 78% yield over two steps.[30]

The deprotection of the benzylidene acetal and the THF-ring formation can also be performed in a one-pot operation with a comparative yield by changing the solvent of hydrogenation to THF (Table 6, entry 2). We found that the yield was remarkably improved when **34** was present in high concentration, and **31b** could be obtained in quantitative yield (entry 3).

Table 6. One-pot THF-ring formation of **33**.

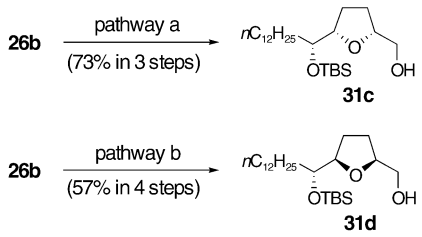
Entry	Conditions	Concentration [M][a]	Yield [%]
1	1) Pd/C, H_2, EtOAc 2) NaH, THF	0.025	78
2	Pd/C, H_2, THF then NaH	0.025	75
3	Pd/C, H_2, THF then NaH	0.049	quantitative

[a] Concentration of **34** in the THF-ring formation step.

In a similar manner, a *cis*/*erythro* isomer **31c** and a *cis*/*threo* isomer **31d** were synthesized from the common *anti* adduct **26b** in 73 and 57% overall yield, respectively (Scheme 9).

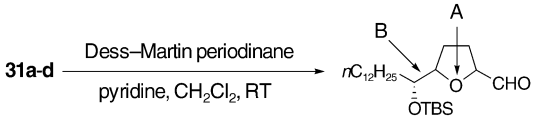
Next, we examined the conversion of **31a–d** into the THF cores with two flanking secondary alcohols, whose structure is frequently found in natural monoTHF-ring acetogenins. Oxidation of the terminal primary alcohol of **31a–d** was carried out with Dess–Martin periodinane[31] to furnish the α-tetrahydrofuranic aldehydes **35a–d** in good yield (Table 7).

Trimethylsilylacetylene was then diastereoselectively introduced to the α-tetrahydrofuranic aldehydes **35a–d** (Table 8). The reaction proceeded with predictable selectivities, and the diastereoselectivity was very high in all cases, giving all eight diastereomers **36–39a** and **36–39b** with high optical purity.[32] The stereochemistry of the adducts was confirmed



Scheme 9. Synthesis of THF-ring moieties **31c** and **31d** by pathways a or b, as depicted in Schemes 7 and 8.

Table 7. Oxidation of alcohols **31a–d** to aldehydes **35a–d**.



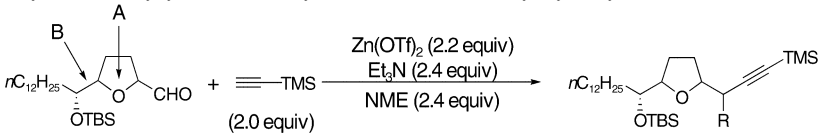
Alcohol	Product	Yield [%]
31a	**35a**	86
31b	**35b**	85
31c	**35c**	93
31d	**35d**	76

by the modified Mosher method.[12] Since selective deprotection of the TMS group is possible, these adducts would be useful for the synthesis of various monoTHF-ring acetogenins.

Representative chemical shifts in the ^1H and ^{13}C NMR spectral data of **36–39a** and **36–39b** are summarized in Tables 9 and 10. These eight compounds exhibited a characteristic signal pattern and their signals are distinguishable. Almost no signal due to other diastereomeric isomers was observed in each spectrum, a fact which indicates the high purity of these products.

Figure 1 shows a comparison of the CD spectra of the eight diastereoisomers. The difference in stereochemistry affects the maximum wavelength and the intensity, so the diaster-

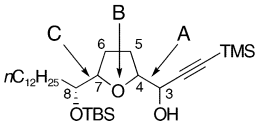
Table 8. Asymmetric alkynylation of aldehydes **35a–d** with trimethylsilylacetylene.[a]



Aldehyde A	Aldehyde B	NME	Product	Yield [%]	Selectivity[b] α-OH:β-OH
trans	*threo*	1*R*,2*S*	**36a**	70	3:>97
trans	*threo*	1*S*,2*R*	**36b**	72	>97:3
trans	*erythro*	1*R*,2*S*	**37a**	75	3:>97
trans	*erythro*	1*S*,2*R*	**37b**	69	>97:3
cis	*erythro*	1*R*,2*S*	**38a**	61	3:>97
cis	*erythro*	1*S*,2*R*	**38b**	71	>97:3
cis	*threo*	1*R*,2*S*	**39a**	79	3:>97
cis	*threo*	1*S*,2*R*	**39b**	66	94:6[c]

[a] TMS = trimethylsilyl. [b] Determined from ^1H NMR spectroscopic data (500 MHz, $CDCl_3$). [c] Calculated from yield of product.

Table 9. Representative ^{1}H NMR spectral data of **36**–**39a** and **36**–**39b** (500 MHz, $CDCl_3$).



Stereochemistry A/B/C	OH	C3-H	C4-H	C7-H	C8-H
threo/*trans*/*threo* (**36a**)	2.47	4.18	4.04	3.91	3.57
erythro/*trans*/*threo* (**36b**)	2.35	4.39	4.12	4.04	3.56
erythro/*trans*/*erythro* (**37a**)	2.33	4.36	4.10	4.03	3.78
threo/*trans*/*erythro* (**37b**)	2.43	4.18	4.03	3.92	3.78–3.81
threo/*cis*/*erythro* (**38a**)	2.67	4.17	3.99	3.90	3.79
erythro/*cis*/*erythro* (**38b**)	2.87	4.48	4.09	3.92	3.85
erythro/*cis*/*threo* (**39a**)	3.05	4.50	4.11	3.97	3.62
threo/*cis*/*threo* (**39b**)	2.85	4.18	4.03	3.98	3.58

Table 10. Representative ^{13}C NMR spectral data of **36**–**39a** and **36**–**39b** (75 MHz, $CDCl_3$).

Stereochemistry A/B/C	C3	C4	C7	C8
threo/*trans*/*threo* (**36a**)	65.6	82.0	82.9	74.9
erythro/*trans*/*threo* (**36b**)	65.0	81.4	83.5	75.0
erythro/*trans*/*erythro* (**37a**)	65.2	81.5	83.6	73.0
threo/*trans*/*erythro* (**37b**)	65.4	82.0	82.6	72.9
threo/*cis*/*erythro* (**38a**)	66.5	81.9	82.8	73.0
erythro/*cis*/*erythro* (**38b**)	65.4	81.3	82.4	73.0
erythro/*cis*/*threo* (**39a**)	65.3	81.3	81.9	74.6
threo/*cis*/*threo* (**39b**)	65.8	81.7	82.4	74.5

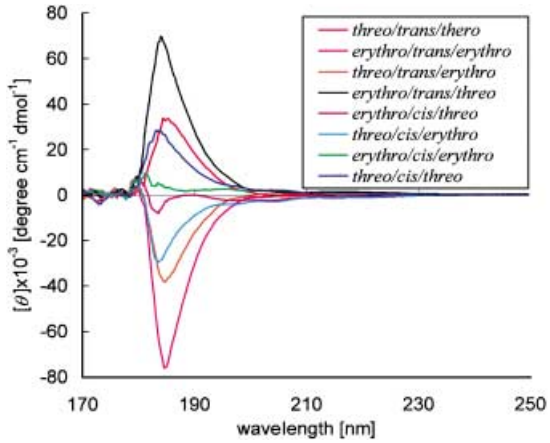


Figure 1. CD spectral data for **36**–**39a** and **36**–**39b**.

eomers can thereby be differentiated. The maximum wavelength of the *trans* isomers and the *cis* isomers was observed at about 184.4 and 183.4 nm, respectively. The intensity of the spectra for the *trans* isomers was generally stronger than that of the *cis* isomers.

Conclusion

We have developed a highly stereoselective and stereodivergent synthesis of the cores of monoTHF-ring acetogenins based on asymmetric alkynylation of a chiral α-oxyaldehyde with a C_4 unit. We have also demonstrated the stereodivergent synthesis of eight diastereomeric isomers. The asymmetric alkynylation proceeded, almost exclusively, to give *syn* and *anti* adducts with predictable selectivity by changing the chiral ligand. Since the antipodes of all chiral materials (alkyne, aldehyde, NME) are available, the antipodes of each isomer could theoretically be synthesized. Thus, our methodology could be widely used for the synthesis of various annonaceous acetogenins. Application of our strategy to the synthesis of biologically active acetogenins is under way. Those results will be reported elsewhere.

Experimental Section

General: Melting points are uncorrected. Optical rotations were measured by using a JASCO DIP-360 digital polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-GX500 spectrometer (500 MHz). ^{13}C NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-AL300 spectrometer (75 MHz). All signals are expressed as ppm downfield from tetramethylsilane as an internal standard (δ value). The following abbreviations are used: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sep = septet, and m = multiplet. IR absorption spectra (FT: diffuse reflectance spectroscopy) were recorded with KBr powder with a Horiba FT-210 IR spectrometer, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were obtained with a JEOL JMS-600H and a JEOL JMS-700 mass spectrometer. Column chromatography was carried out by using Kanto Chemical silica gel 60N (spherical, neutral, 63–210 μm). Flash column chromatography was carried out by using Merck silica gel 60 (40–63 μm). All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of Ar or N_2. All solvents were dried and distilled according to standard procedures. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator under reduced pressure. Known compounds (*S*)-**6**,[11] **7**,[10] **10**,[15] **16**,[19] **22**,[21] and **23**[22] were synthesized according to the literature methods. Experimental procedures and characterization data for **8**, **9**, **14**, **15**, **21**, **24a**, and **24b** are included in the Supporting Information.

Preparation of 11 with (Ph_3PCHBr_2)Br: *t*BuOK (6.42 g, 57.2 mmol) was added to a solution of (Ph_3PCHBr_2)Br (31.0 g, 60.2 mmol) in THF (250 mL) with stirring at 0 °C. After 10 min at RT, a solution of **10** (3.92 g, 30.1 mmol) in THF (50 mL) was added to the mixture at 0 °C. After 10 min, the reaction was quenched with brine. The solvent was evaporated prior to extraction with *n*-hexane. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (5:1)) yielded **11** (8.32 g, 97 %) as a yellow oil. The spectral data were identical with those previously reported.[15a]

Preparation of 13: *n*BuLi (88.8 mL, 1.56 M in *n*-hexane, 139 mmol) was added to a solution of **11** (18.0 g, 62.9 mmol) in THF (180 mL) with stirring at −78 °C over 1 h, then the mixture was allowed to warm to 10 °C over 1 h. Et_2O (110 mL) and water (110 mL) were added to the mixture at RT. After 15 min, the aqueous layer was extracted with Et_2O. Dowex 50W (18.0 g) and MeOH (150 mL) were added to the combined organic layers with stirring at RT, and the whole reaction mixture was stirred at 35 °C for 15 h. Dowex 50W was filtered off and the filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/EtOAc (3:2 → 2:3)) yielded **13** (4.49 g, 83 %). The spectral data were identical with those previously reported.[15a]

(*R*)-2-Hydroxytetradecanyl pivalate (17): Pivaloyl chloride (5.55 mL, 45.0 mmol) was added to a solution of **16** (6.91 g, 30.0 mmol) in pyridine (30 mL) and CH_2Cl_2 (30 mL) with stirring at 0 °C. After 5 min, the whole mixture was stirred at RT for 15 h. Concentration followed by azeotropic removal of pyridine with toluene was repeated three times. Purification by column chromatography on silica gel (hexane/EtOAc (5:1)) yielded **17** (8.01 g, 85 %) as a white powder. M.p. 40.1–42.2 °C (*n*-hexane/EtOAc); $[\alpha]_D^{26} = -2.3$ ($c = 1.59$, $CHCl_3$); ^{1}H NMR: $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.22 (s, 9H), 1.26–1.31 (m, 20H), 1.43–1.52 (m, 2H), 2.00 (br s, 1H), 3.81–3.85 (m, 1H), 3.97 (dd, $J = 11.6$, 6.7 Hz, 1H), 4.13 (dd, $J = 11.6$, 3.1 Hz,

1H) ppm; ^{13}C NMR: $\delta = 14.1$, 22.7, 25.3, 27.2 (3C), 29.3, 29.5, 29.55 (2C), 29.63 (2C), 29.7, 31.9, 33.4, 38.9, 68.6, 70.2, 178.7 ppm; IR (KBr): $\tilde{\nu} = 3535$, 1703 cm^{-1}; MS (FAB): *m/z*: 315 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{39}O_3$: 315.2899; found: 315.2909 $[M+H]^+$.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)tetradecanyl pivalate (18): Imidazole (3.40 g, 50.0 mmol) was added to a solution of **17** (7.86 g, 25.0 mmol) in DMF (25 mL) with stirring at 0 °C. After 5 min, TBSCl (7.54 g, 50.0 mmol) was added to the mixture with stirring at 0 °C. After 2 h at RT, the mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (10:1)) yielded **18** (11.7 g, quantitative) as a colorless oil. $[\alpha]_D^{26} = +1.7$ ($c = 1.28$, $CHCl_3$); ^{1}H NMR: $\delta = 0.06$ (s, 3H), 0.07 (s, 3H), 0.87 (t, $J =$ 6.4 Hz, 3H), 0.88 (s, 9H), 1.20 (s, 9H), 1.25–1.39 (m, 20H), 1.42–1.52 (m, 2H), 3.83 (qn, $J = 5.5$ Hz, 1H), 3.94 (dd, $J = 11.0$, 5.5 Hz, 1H), 3.97 (dd, $J =$ 11.0, 5.5 Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.7$, -4.6, 14.1, 18.0, 22.7, 24.9, 25.8 (3C), 27.2 (3C), 29.3, 29.5, 29.55, 29.63 (2C), 29.66, 29.70, 31.9, 34.6, 38.7, 68.1, 70.1, 178.5 ppm; IR (KBr): $\tilde{\nu} = 1734$ cm^{-1}; MS (FAB): *m/z*: 429 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{25}H_{53}O_3Si$: 429.3764; found: 429.3774 $[M+H]^+$.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)tetradecanol (19): DIBAL-H (1.0 M in toluene, 40.0 mL, 40.0 mmol) was added to a solution of **18** (8.58 g, 20.0 mmol) in CH_2Cl_2 (210 mL) with stirring at -78 °C. After 25 min, saturated Rochelle salt was gradually added to the mixture, and the whole mixture was stirred at RT for 0.5 h. After solvent evaporation, the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (5:1)) yielded **19** (6.96 g, quantitative) as a colorless oil. $[\alpha]_D^{26} = -8.4$ ($c = 1.34$, $CHCl_3$); ^{1}H NMR: $\delta = 0.07$ (s, 6H), 0.86 (t, $J = 7.0$ Hz, 3H), 0.89 (s, 9H), 1.25–1.30 (m, 20H), 1.43–1.50 (m, 2H), 2.01 (br s, 1H), 3.42 (dd, $J = 11.0$, 5.5 Hz, 1H), 3.53 (dd, $J = 11.0$, 3.7 Hz, 1H), 3.70 (m, 1H) ppm; ^{13}C NMR: $\delta =$ -4.6, -4.5, 14.1, 18.0, 22.7, 25.3, 25.8 (3C), 29.3, 29.5, 29.55, 29.62 (2C), 29.64, 29.8, 31.9, 34.0, 66.2, 72.9 ppm; IR (KBr): $\tilde{\nu} = 3329$ cm^{-1}; MS (FAB): *m/z*: 345 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{45}O_2Si$: 345.3189; found: 345.3185 $[M+H]^+$.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)tetradecanal (20): Dess–Martin periodinane (1.48 g, 3.48 mmol) was added to a solution of **19** (800 mg, 2.32 mmol) in CH_2Cl_2 (12 mL) with stirring at 0 °C. After 15 min at RT, the mixture was filtered through silica gel and the filtrate was evaporated. Purification by column chromatography on silica gel (hexane/EtOAc (10:1)) yielded **20** (765 mg, 96 %) as a colorless oil. $[\alpha]_D^{24} = +24.5$ ($c = 1.69$, $CHCl_3$); ^{1}H NMR: $\delta = 0.04$ (s, 3H), 0.05 (s, 3H), 0.85 (t, $J = 6.7$ Hz, 3H), 0.90 (s, 9H), 1.23–1.42 (m, 20H), 1.53–1.63 (m, 2H), 3.93 (td, $J = 6.1$, 1.2 Hz, 1H), 9.55 (dd, $J = 1.8$, 1.2 Hz, 1H) ppm; ^{13}C NMR: $\delta = -5.1$, -4.7, 14.1, 18.1, 22.6, 24.6, 25.7 (3C), 29.3, 29.40, 29.41, 29.5, 29.59, 29.61, 29.64, 31.9, 32.6, 77.6, 204.0 ppm; IR (KBr): $\tilde{\nu} = 1738$ cm^{-1}; MS (FAB): *m/z*: 365 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{42}NaO_2Si$: 365.2852; found: 365.2873 $[M+Na]^+$.

(2*RS*,4*S*)-4-Ethynyl-2-phenyl-1,3-dioxolane (25): Benzaldehyde dimethyl acetal (0.175 mL, 1.16 mmol) and (+)-10-camphorsulfonic acid (13.5 mg, 0.058 mmol) were added to a solution of **13** (50.0 mg, 0.581 mmol) in THF (4 mL) with stirring at RT. After 1 h under reflux conditions, the reaction was quenched with Et_3N and the solvent was evaporated. $NaBH_4$ (33.0 mg, 0.872 mmol) was added to the solution of the residue in MeOH (3.0 mL) with stirring at 0 °C. After 30 min at RT, the reaction was quenched with water and the solvent was evaporated. The residue was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (100:1 → 10:1)) yielded **25** (89.2 mg, 88 %, **25a**:**25b** = 1:1). Analytical samples of **25a** and **25b** were purified by column chromatography on silica gel (hexane/EtOAc (100:1 → 10:1)). **25a**: Colorless powder; m.p. 51.0–53.0 °C; $[\alpha]_D^{26} = +86.3$ ($c = 1.17$, $CHCl_3$); ^{1}H NMR: $\delta = 2.63$–2.64 (m, 1H), 4.04 (dd, $J = 7.9$, 6.1 Hz, 1H), 4.38 (dd, $J = 7.9$, 6.7 Hz, 1H), 4.93 (td, $J = 6.4$, 1.8 Hz, 1H), 6.05 (s, 1H), 7.43–7.46 (m, 3H), 7.54–7.55 (m, 2H) ppm; ^{13}C NMR: $\delta = 65.3$, 70.8, 74.7, 80.9, 103.4, 126.4 (2C), 128.1 (2C), 129.3, 136.3 ppm; IR (KBr): $\tilde{\nu} = 2119$, 1066 cm^{-1}; MS (EI): *m/z*: (%): 174 (37.2) $[M]^+$, 173 (48.4) $[M-H]^+$, 97 (14.6) $[M-C_6H_5]^+$, 78 (100); HRMS (EI): *m/z* calcd for $C_{11}H_{10}O_2$: 174.0681; found: 174.0683 $[M]^+$. **25b**: Colorless oil; $[\alpha]_D^{26} = +37.5$ ($c = 1.21$, $CHCl_3$); ^{1}H NMR: $\delta = 2.57$ (d, $J = 1.8$ Hz, 1H), 4.15 (dd, $J = 8.2$, 5.2 Hz, 1H), 4.20 (dd, $J = 8.2$, 6.7 Hz, 1H), 4.87 (ddd, $J = 6.7$, 5.2, 1.8 Hz, 1H), 5.87 (s, 1H), 7.40–7.44 (m, 3H), 7.55–7.58 (m, 2H) ppm; ^{13}C NMR: $\delta = 65.9$, 70.8, 74.3, 80.8, 105.1, 126.8 (2C), 128.3 (2C), 129.4, 136.8 ppm; IR (KBr): $\tilde{\nu} = 2121$, 1070 cm^{-1}; MS (EI): *m/z*: (%): 174 (27.9) $[M]^+$, 173 (36.0) $[M-H]^+$, 78 (100); HRMS (EI): *m/z* calcd for $C_{11}H_{10}O_2$: 174.0681; found: 174.0688 $[M]^+$.

General procedure of the asymmetric alkynylation (Table 5, Entry 3): A flask was charged with $Zn(OTf)_2$ (2.18 g, 6.01 mmol). Vacuum (5 mmHg) was applied and heated to 120 °C for 12 h. After the flask was cooled to RT, the vacuum was released. *N*-Methylephedrine (1.17 g, 6.55 mmol), toluene (6 mL), and Et_3N (0.912 mL, 6.55 mmol) were added to the flask with stirring at RT. After 3 h, a solution of **25** (951 mg, 5.46 mmol, **25a**:**25b** = 1:1) in toluene (0.3 mL) was added to the mixture at RT. After 15 min, a solution of **20** (935 mg, 2.73 mmol) in toluene (0.3 mL) was added to the mixture with stirring at RT. The reaction mixuture was stirred for 43 h. The reaction was quenched with saturated NH_4Cl and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica (hexane/EtOAc (50:1 → 20:1)) yielded (2*RS*,4*S*,3′*R*,4′*R*)-**26a** (1.36 g, 96 %, *anti*:*syn* = 3: > 97) as a colorless oil.

(2*S*,4*S*)-4-[(3′*R*,4′*R*)-4′-(*tert*-Butyldimethylsilyloxy)-3′-hydroxy-1′-hexadecynyl]-2-phenyl-1,3-dioxolane [(2*S*,4*S*,3′*R*,4′*R*)-26a]: The procedure was same as that used for preparation of (2*RS*,4*S*,3′*R*,4′*R*)-**26a**. Colorless oil; $[\alpha]_D^{25} = +34.7$ ($c = 1.17$, $CHCl_3$); ^{1}H NMR: $\delta = 0.12$ (s, 3H), 0.15 (s, 3H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 1.26–1.31 (s, 20H), 1.50–1.69 (m, 2H), 2.56 (d, $J = 7.3$ Hz, 1H), 3.76 (td, $J = 6.1$, 4.3 Hz, 1H), 3.99 (dd, $J = 7.9$, 6.4 Hz, 1H), 4.29–4.31 (m, 1H), 4.36 (dd, $J = 7.9$, 6.7 Hz, 1H), 4.93 (ddd, $J = 6.7$, 6.4, 1.8 Hz, 1H), 5.96 (s, 1H), 7.36–7.40 (m, 3H), 7.46–7.48 (m, 2H) ppm; ^{13}C NMR: $\delta = -4.52$, -4.45, 14.0, 18.0, 22.6, 25.0, 25.8 (3C), 29.2, 29.4, 29.46, 29.54 (2C), 29.57, 29.64, 31.8, 33.6, 64.7, 65.8, 71.1, 75.2, 81.9, 86.6, 103.5, 126.5 (2C), 128.2 (2C), 129.3, 136.6 ppm; IR (KBr): $\tilde{\nu} = 3510$, 2251, 1107 cm^{-1}; MS (FAB): *m/z*: 539 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{31}H_{52}NaO_4Si$: 539.3533; found: 539.3540 $[M+Na]^+$.

(2*R*,4*S*)-4-[(3′*R*,4′*R*)-4′-(*tert*-Butyldimethylsilyloxy)-3′-hydroxy-1′-hexadecynyl]-2-phenyl-1,3-dioxolane [(2*R*,4*S*,3′*R*,4′*R*)-26a]: The procedure was same as that used for preparation of (2*RS*,4*S*,3′*R*,4′*R*)-**26a**. Colorless oil; $[\alpha]_D^{24} = +7.5$ ($c = 1.40$, $CHCl_3$); ^{1}H NMR: $\delta = 0.10$ (s, 3H), 0.13 (s, 3H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.91 (s, 9H), 1.26–1.31 (m, 20H), 1.47–1.65 (m, 2H), 2.51 (d, $J = 7.3$ Hz, 1H), 3.73 (td, $J = 6.1$, 4.3 Hz, 1H), 4.07 (dd, $J = 7.9$, 5.5 Hz, 1H), 4.18 (dd, $J = 7.9$, 6.7 Hz, 1H), 4.26 (ddd, $J = 7.3$, 4.3, 1.2 Hz, 1H), 4.88 (ddd, $J = 6.7$, 5.5, 1.2 Hz, 1H), 5.86 (s, 1H), 7.36–7.40 (m, 3H), 7.51–7.53 (m, 2H) ppm; ^{13}C NMR: $\delta = -4.5$, -4.4, 14.1, 18.1, 22.6, 25.0, 25.8 (3C), 29.3, 29.47, 29.50, 29.57 (2C), 29.61, 29.7, 31.9, 33.6, 64.7, 66.4, 70.6, 75.2, 81.6, 86.2, 104.9, 126.8 (2C), 128.2 (2C), 129.3, 137.0 ppm; IR (KBr): $\tilde{\nu} = 3489$, 2243, 1066 cm^{-1}; MS (FAB): *m/z*: 539 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{31}H_{52}NaO_4Si$: 539.3533; found: 539.3546 $[M+Na]^+$.

(2*RS*,4*S*)-4-[(3′*S*,4′*R*)-4′-(*tert*-Butyldimethylsilyloxy)-3′-hydroxy-1′-hexadecynyl]-2-phenyl-1,3-dioxolane (26b): The procedure was same as that used for preparation of (2*RS*,4*S*,3′*R*,4′*R*)-**26a**. Colorless oil; $[\alpha]_D^{26} = +33.6$ ($c = 1.09$, $CHCl_3$); ^{1}H NMR: $\delta = 0.10$ (s, 3H), 0.11 (s, 3H), 0.88 (t, $J =$ 6.7 Hz, 3H), 0.91 (s, 4.5H), 0.92 (s, 4.5H), 1.28–1.43 (m, 20H), 1.56–1.69 (m, 2H), 2.32 (d, $J = 5.5$ Hz, 0.5H), 2.37 (d, $J = 6.1$ Hz, 0.5H), 3.75 (ddd, $J = 7.3$, 5.5, 3.7 Hz, 0.5H), 3.78 (ddd, $J = 7.3$, 5.5, 3.7 Hz, 0.5H), 3.99 (dd, $J =$ 7.9, 6.1 Hz, 0.5H), 4.07 (dd, $J = 7.9$, 5.5 Hz, 0.5H), 4.19 (dd, $J = 7.9$, 6.7 Hz, 0.5H), 4.367 (dd, $J = 7.9$, 6.7 Hz, 0.5H), 4.374–4.42 (m, 1H), 4.91 (ddd, $J =$ 6.7, 5.5, 1.2 Hz, 0.5H), 4.96 (ddd, $J = 6.7$, 6.1, 1.2 Hz, 0.5H), 5.87 (s, 0.5H), 5.96 (s, 0.5H), 7.37–7.39 (m, 3H), 7.47–7.49 (m, 1H), 7.52–7.54 (m, 1H) ppm; ^{13}C NMR: (2*R*)-**26b**: $\delta = -4.6$, -4.4, 14.0, 18.0, 22.6, 25.27, 25.8 (3C), 29.3, 29.46, 29.50 (2C), 29.55, 29.59, 29.64, 31.8, 32.4, 65.8, 66.0, 71.1, 74.8, 82.9, 83.1, 103.5, 126.5 (2C), 128.2 (2C), 129.4, 136.5 ppm; (2*S*)-**26b**: $\delta = -4.6$, -4.4, 14.0, 18.0, 22.6, 25.33, 25.8 (3C), 29.3, 29.46, 29.50 (2C), 29.55, 29.59, 29.64, 31.8, 32.3, 66.0, 66.3, 70.7, 74.8, 84.2, 84.8, 104.9, 126.8 (2C), 128.2 (2C), 129.3, 137.1 ppm; IR (KBr): $\tilde{\nu} = 3462$, 2241, 1097 cm^{-1}; MS (FAB): *m/z*: 517 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{31}H_{53}O_4Si$: 517.3713; found: 517.3705 $[M+H]^+$.

(2*S*,5*R*,6*R*)-1,2:5,6-Di-*O*-isopropylidene-octadec-3-yne-1,2,5,6-tetrol (27a): TBAF (1.0 M in THF, 0.192 mL, 0.192 mmol) was added to a solution of **26a** (50.0 mg, 0.0967 mmol) in THF (0.5 mL) with stirring at RT. After 1.5 h, water (0.7 mL) and Et_2O (1.7 mL) were added to the reaction mixture, and the aqueous layer was extracted with Et_2O. The combined

organic layers were washed with water and brine prior to drying and solvent evaporation. $Me_2C(OMe)_2$ (9.6 mL, 78.0 mmol) and a catalytic amount of pTsOH·H_2O were added to the solution of the crude product in CH_2Cl_2 (6 mL) with stirring at RT. After 18 h, saturated $NaHCO_3$ and CH_2Cl_2 were added, and the organic layer was washed with brine prior to drying and solvent evaporation. Purification by flash column chromatography on silica gel (hexane/EtOAc (30:1)) yielded **27a** (36.0 mg, 94%) as a pale yellow oil. $[\alpha]_D^{28} = +26.8$ ($c = 1.55$, $CHCl_3$); ^{1}H NMR: $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.20–1.51 (m, 20H), 1.38 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.48 (s, 3H), 1.60–1.64 (m, 2H), 3.93 (dd, $J = 7.9$, 6.1 Hz, 1H), 4.00 (td, $J = 7.3$, 6.4 Hz, 1H), 4.16 (dd, $J = 7.9$, 6.1 Hz, 1H), 4.24 (dd, $J = 7.3$, 1.2 Hz, 1H), 4.76 (td, $J = 6.1$, 1.2 Hz, 1H) ppm; ^{13}C NMR: $\delta = 14.1$, 22.7, 25.7, 25.9, 26.13, 26.16, 27.1, 29.3, 29.46, 29.54, 29.60, 29.63 (2C), 29.64, 31.9, 32.4, 65.5, 69.8, 70.4, 81.4, 82.7, 83.9, 109.7, 110.4 ppm; IR (KBr): $\tilde{\nu} = 1063$ cm^{-1}; MS (FAB): m/z: 395 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{24}H_{43}O_4$: 395.3161; found: 395.3167 $[M+H]^+$.

(2*S*,5*S*,6*R*)-1,2:5,6-Di-*O*-isopropylidene-octadec-3-yne-1,2,5,6-tetrol (27b): The procedure was the same as that used for preparation of **27a**. Pale yellow oil; $[\alpha]_D^{28} = -6.6$ ($c = 1.35$, $CHCl_3$); ^{1}H NMR: $\delta = 0.88$ (t, $J =$ 6.7 Hz, 3H), 1.26–1.54 (m, 20H), 1.34 (s, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 1.51 (s, 3H), 1.63–1.70 (m, 1H), 1.73–1.79 (m, 1H), 3.92 (dd, $J = 7.9$, 6.1 Hz, 1H), 4.06 (td, $J = 6.7$, 5.8 Hz, 1H), 4.16 (dd, $J = 7.9$, 6.1 Hz, 1H), 4.76 (dd, $J = 5.8$, 1.2 Hz, 1H), 4.77 (td, $J = 6.1$, 1.2 Hz, 1H) ppm; ^{13}C NMR: $\delta =$ 14.1, 22.7, 25.90, 25.93, 26.1 (2C), 27.9, 29.3, 29.48, 29.54, 29.62 (2C), 29.64 (2C), 30.7, 31.9, 65.5, 69.2, 69.9, 78.1, 82.0, 85.0, 109.5, 110.3 ppm; IR (KBr): $\tilde{\nu} = 1065$ cm^{-1}; MS (FAB): m/z: 395 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{24}H_{43}O_4$: 395.3161; found: 395.3162 $[M+H]^+$.

(2*S*,5*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)octadecane-1,2,5-triol (28): A solution of **26a** (1.21 g, 2.34 mmol) in EtOAc (23 mL) was hydrogenated on 10% Pd/C (60.5 mg) with stirring at RT for 24 h. The Pd/C was filtered off and the filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/EtOAc (1:4)) yielded **28** (1.14 g, 94%) as a colorless oil. $[\alpha]_D^{26} = -5.7$ ($c = 1.60$, $CHCl_3$); ^{1}H NMR: $\delta = 0.08$ (s, 3H), 0.09 (s, 3H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 1.26–1.31 (m, 20H), 1.38–1.69 (m, 6H), 2.65 (br s, 1H), 3.23 (br s, 1H), 3.47 (dd, $J =$ 11.0, 7.6 Hz, 1H), 3.48–3.53 (m, 2H), 3.63 (dd, $J = 11.0$, 3.1 Hz, 1H), 3.74 (ddd, $J = 11.0$, 7.3, 4.3 Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.2, 14.1, 18.1, 22.7, 24.8, 25.8 (3C), 29.3, 29.55, 29.57, 29.61 (3C), 29.64, 29.8, 29.9, 31.9, 33.7, 66.6, 72.0, 73.0, 75.4 ppm; IR (KBr): $\tilde{\nu} = 3358$, 1080 cm^{-1}; MS (FAB): m/z: 433 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{24}H_{53}O_4Si$: 433.3713; found: 433.3726 $[M+H]^+$.

(2*S*,5*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,5-dihydroxyoctadecanyl 2′,4′,6′-triisopropylbenzenesulfonate (29): 2,4,6-Triisopropylbenzenesulfonyl chloride (1.05 g, 3.48 mmol) was added to a solution of **28** (500 mg, 1.16 mmol) in pyridine (2 mL) and CH_2Cl_2 (3 mL) at 0 °C with stirring. After 20 h at RT, water was added to the reaction mixture, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (5:1)) yielded **29** (704 mg, 87%) as a colorless oil. $[\alpha]_D^{24} = +0.12$ ($c = 0.96$, $CHCl_3$); ^{1}H NMR: $\delta = 0.07$ (s, 3H), 0.08 (s, 3H), 0.87–0.89 (m, 12H), 1.25 (m, 39H), 1.36–1.65 (m, 4H), 1.70–1.75 (m, 1H), 2.41 (d, $J = 5.5$ Hz, 1H), 2.87 (br s, 1H), 2.88–2.94 (m, 1H), 3.43–3.45 (m, 1H), 3.47–3.50 (m, 1H), 3.92–3.96 (m, 2H), 4.04 (dd, $J = 12.8$, 7.3 Hz, 1H), 4.14 (sep, $J = 6.7$ Hz, 2H), 7.19 (s, 2H) ppm; ^{13}C NMR: $\delta = -4.7$, -4.2, 14.1, 18.0, 22.6, 23.5, 24.66 (2C), 24.69 (2C), 24.74 (2C), 25.8 (3C), 29.3, 29.5 (3C), 29.6 (5C), 29.8 (2C), 31.9, 33.7, 34.2, 69.4, 72.6, 72.8, 75.4, 123.8 (2C), 129.1, 150.8 (2C), 153.8 ppm; IR (KBr): $\tilde{\nu} =$ 3379, 1425, 1076 cm^{-1}; MS (FAB): m/z: 699 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{39}H_{75}O_6SSi$: 699.5054; found: 699.5059 $[M+H]^+$.

(2*R*,5*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,5-epoxyoctadecan-1-ol (31a): K_2CO_3 (71.9 mg, 0.520 mmol) was added to a mixture of **29** (72.4 mg, 0.104 mmol) with stirring at 0 °C. The whole mixture was stirred at 0 °C for 2 h and at RT for 39 h. Water was added to the reaction mixture. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (10:1)) yielded **31a** (30.2 mg, 70%) as a colorless oil. $[\alpha]_D^{26} = +4.4$ ($c = 0.76$, $CHCl_3$); ^{1}H NMR: $\delta = 0.06$ (s, 3H), 0.07 (s, 3H), 0.87–0.89 (m, 12H), 1.26 (m, 22H), 1.60–1.74 (m, 2H), 1.88–1.97 (m, 2H), 3.48 (dd, $J = 11.6$, 6.1 Hz, 1H), 3.57 (ddd, $J =$ 7.0, 6.1, 4.0 Hz, 1H), 3.65 (dd, $J = 11.6$, 2.7 Hz, 1H), 3.91 (dt, $J = 7.3$, 6.1 Hz, 1H), 4.05–4.10 (m, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.2, 14.1, 18.3, 22.7, 25.6, 26.0 (3C), 27.7, 27.8, 29.3, 29.59 (2C), 29.63 (2C), 29.7, 29.8, 31.9, 33.0, 64.9, 75.0, 79.4, 82.1 ppm; IR (KBr): $\tilde{\nu} = 3421$, 1068 cm^{-1}; MS (FAB): m/z: 415 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{24}H_{51}O_3Si$: 415.3608; found: 415.3600 $[M+H]^+$.

(2*RS*,4*S*)-4-[(3′*R*,4′*R*)-4′-(*tert*-Butyldimethylsilyloxy)-3′-hydroxyoctadecanyl]-2-phenyl-1,3-dioxolane (32): A mixture of **26a** (300 mg, 0.580 mmol) and Et_3N (0.040 mL, 0.290 mmol) in EtOAc (6 mL) was hydrogenated on 10% Pd/C (15 mg) with stirring at RT for 2.5 h. The Pd/C was filtered off and the filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/EtOAc (7:1)) yielded **32** (301 mg, quantitative) as a colorless oil. $[\alpha]_D^{24} = +2.5$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR: $\delta = 0.07$–0.09 (m, 6H), 0.87–0.90 (m, 12H), 1.26 (m, 21H), 1.38–1.51 (m, 1.58H), 1.60–1.68 (m, 1.42H), 1.72–1.95 (m, 2H), 2.21 (d, $J = 6.7$ Hz, 0.42H), 2.23 (d, $J = 6.7$ Hz, 0.58H), 3.44–3.53 (m, 2H), 3.64 (t, $J = 6.7$ Hz, 0.58H), 3.70 (t, $J = 7.3$ Hz, 0.42H), 4.12 (t, $J = 7.0$ Hz, 0.42H), 4.20–4.28 (m, 1.58H), 5.81 (s, 0.42H), 5.93 (s, 0.58H), 7.35–7.39 (m, 3H), 7.46–7.50 (m, 2H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.1, 14.1, 18.1, 22.6, 25.0, 25.9 (3C), 29.3, 29.5 (2C), 29.59 (2C), 29.63, 29.8, 30.0 (0.58C), 30.2 (0.42C), 30.57 (0.42C), 30.64 (0.58C), 31.9, 33.8, 70.1 (0.42C), 70.7 (0.58C), 72.6 (0.58C), 72.7 (0.42C), 75.26 (0.42C), 75.29 (0.58C), 76.8 (0.58C), 77.6 (0.42C), 103.0 (0.58C), 104.0 (0.42C), 126.3 (1.16C), 126.6 (0.84C), 128.3 (2C), 129.0 (0.42C), 129.2 (0.58C), 137.8 (0.42C), 138.4 (0.58C) ppm; IR (KBr): $\tilde{\nu} = 3562$, 1070 cm^{-1}; MS (FAB): m/z: 521 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{31}H_{57}O_4Si$: 521.4026; found: 521.4015 $[M+H]^+$.

(2*RS*,4*S*)-4-[(3′*R*,4′*R*)-4′-(*tert*-Butyldimethylsilyloxy)-3′-(*p*-toluenesulfonoxyl)octadecanyl]-2-phenyl-1,3-dioxolane (33): pTsCl (522 mg, 2.74 mmol) was added to a solution of **32** (285 mg, 0.548 mmol) in pyridine (2 mL) with stirring at 0 °C. The stirring was continued at RT for 7 h. The reaction was quenched with saturated NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (10:1)) yielded **33** (354 mg, 96%) as a colorless oil. $[\alpha]_D^{25} = +13.1$ ($c = 0.73$, $CHCl_3$); ^{1}H NMR: $\delta = -0.01$ (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 0.88 (t, $J = 7.0$ Hz, 3H), 1.26 (m, 22H), 1.40–1.59 (m, 3H), 1.97–2.04 (m, 1H), 2.42 (s, 1.26H), 2.44 (s, 1.74H), 3.49 (dd, $J = 7.9$, 6.7 Hz, 0.58H), 3.55 (dd, $J = 7.9$, 6.7 Hz, 0.42H), 3.65–3.76 (m, 1H), 4.03 (dd, $J = 7.3$, 6.7 Hz, 0.42H), 4.06–4.14 (m, 1H), 4.18 (dd, $J = 7.9$, 6.1 Hz, 0.58H), 4.38 (ddd, $J = 9.2$, 4.3, 3.1 Hz, 0.42H), 4.41–4.44 (m, 0.58H), 5.75 (s, 0.42H), 5.82 (s, 0.58H), 7.30–7.37 (m, 5H), 7.42–7.44 (m, 2H), 7.79 (t, 2H, $J = 8.2$ Hz) ppm; ^{13}C NMR: $\delta = -4.8$, -4.6, 14.1, 17.9, 21.6, 22.6, 24.2 (0.42C), 24.3 (0.58C), 25.7 (3C), 25.9, 29.3, 29.5 (2C), 29.56, 29.61 (2C), 29.65, 29.43, 30.2, 31.9, 69.9 (0.42C), 70.5 (0.58C), 71.9 (0.58C), 72.0 (0.42C), 76.2 (0.58C), 76.8 (0.42C), 84.8, 102.9 (0.58C), 103.9 (0.42C), 126.3 (1.16C), 126.5 (0.84C), 127.8 (2C), 128.2 (0.84C), 128.3 (1.16C), 129.0 (0.58C), 129.2 (0.42C), 129.7 (2C), 134.2 (0.42C), 134.3 (0.58C), 137.6 (0.42C), 138.2 (0.58C), 144.7 ppm; IR (KBr): $\tilde{\nu} = 1068$ cm^{-1}; MS (FAB): m/z: 697 $[M+Na]^+$; HRMS (FAB): m/z calcd for $C_{38}H_{62}NaO_6SSi$: 697.3934; found: 697.3907 $[M+Na]^+$.

(2*S*,5*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,5-epoxyoctadecan-1-ol (31b): A solution of **33** (55.0 mg, 0.0815 mmol) in EtOAc (1 mL) was hydrogenated on 10% Pd/C (2.8 mg) with stirring at RT for 24 h. The Pd/C was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in THF (3 mL). NaH (62.6% in oil, 12.5 mg, 0.326 mmol) was added to the mixture with stirring at 0 °C. After 1 h at 40 °C, water was added to the reaction mixture, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (10:1)) yielded **31b** (26.4 mg, 78% in 2 steps) as a colorless oil. $[\alpha]_D^{28} = -2.1$ ($c = 1.17$, $CHCl_3$); ^{1}H NMR: $\delta = 0.06$ (s, 6H), 0.86–0.89 (m, 12H), 1.23–1.38 (m, 22H), 1.60–1.69 (m, 1H), 1.82–1.97 (m, 4H), 3.46 (dd, $J = 11.6$, 6.1 Hz, 1H), 3.62 (dd, $J = 11.6$, 3.1 Hz, 1H), 3.75–3.78 (m, 1H), 3.90 (dt, $J = 10.4$, 3.7 Hz, 1H), 4.05–4.10 (m, 1H) ppm; ^{13}C NMR: $\delta = -4.5$, -4.3, 14.1, 18.2, 22.7, 25.4, 25.9 (3C), 27.6, 29.3, 29.57 (2C), 29.59 (2C), 29.64, 29.7, 29.9, 31.9, 34.7, 65.0, 73.4, 79.5, 82.0 ppm; IR (KBr): $\tilde{\nu} = 3462$, 1051 cm^{-1}; MS (FAB): m/z: 437 $[M+Na]^+$; HRMS (FAB): m/z calcd for $C_{24}H_{50}NaO_3Si$: 437.3426; found: 437.3430 $[M+Na]^+$.

One-pot THF-ring formation of 33: A solution of **33** (151 mg, 0.223 mmol) in THF (3 mL) was hydrogenated on 10% Pd/C (15.1 mg) with stirring at RT for 22 h. THF (1.8 mL) and NaH (62.6% in oil, 34.3 mg, 0.892 mmol) were added to the mixture with stirring at 0 °C. After 2 h at 40 °C, water was

added to the reaction mixture, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc (10:1)) yielded **31b** (92.5 mg, quantitative) as a colorless oil.

(2*R*,5*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,5-epoxyoctadecan-1-ol (31c): Compound **26b** was converted into a triol by the same procedure as that described for the conversion of **26a** into **28**. Colorless oil; $[\alpha]_D^{26} = +5.6$ ($c = 1.74$, $CHCl_3$); ^{1}H NMR: $\delta = 0.07$ (s, 3H), 0.08 (s, 3H), 0.88 (t, $J = 7.3$ Hz, 3H), 0.90 (s, 9H), 1.26 (m, 20H), 1.33–1.65 (m, 6H), 2.87 (br s, 3H), 3.46 (dd, $J = 11.0$, 7.3 Hz, 1H), 3.57–3.61 (m, 2H), 3.62 (dd, $J = 11.0$, 3.1 Hz, 1H), 3.68–3.72 (m, 1H) ppm; ^{13}C NMR: $\delta = -4.5$, -4.4, 14.1, 18.0, 22.6, 25.6, 25.8 (3C), 28.6, 29.3, 29.59 (2C), 29.61 (2C), 29.64 (2C), 29.8, 30.8, 31.9, 66.9, 72.4, 75.1, 75.3 ppm; IR (KBr): $\tilde{\nu} = 3321$, 1084 cm^{-1}; MS (FAB): *m/z*: 433 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{24}H_{53}O_4Si$: 433.3713; found: 433.3719 $[M+H]^+$. The triol was converted into a sulfonate by the same procedure as that described for the conversion of **28** into **29**. Colorless oil; $[\alpha]_D^{24} = +3.8$ ($c = 0.73$, $CHCl_3$); ^{1}H NMR: $\delta = 0.06$ (s, 3H), 0.07 (s, 3H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.89 (s, 9H), 1.26 (m, 39H), 1.36–1.49 (m, 4H), 1.73–1.79 (m, 1H), 2.50–2.54 (m, 1H), 2.91 (sep, $J = 6.7$ Hz, 1H), 3.48–3.50 (m, 1H), 3.56–3.61 (m, 2H), 3.87–3.91 (m, 1H), 3.98–4.00 (m, 2H), 4.14 (sep, $J = 6.7$ Hz, 2H), 7.19 (s, 2H) ppm; ^{13}C NMR: $\delta = -4.5$ (2C), 14.1, 18.0, 22.6 (2C), 23.5 (2C), 24.7 (2C), 25.5, 25.8 (3C), 28.1, 29.3, 29.5 (3C), 29.56 (3C), 29.59, 29.8 (2C), 30.6, 30.7, 31.8, 34.2, 69.6, 72.7, 74.7, 75.2, 123.7 (2C), 129.0, 150.8 (2C), 153.7 ppm; IR (KBr): $\tilde{\nu} = 3446$, 1425, 1074 cm^{-1}; MS (FAB) *m/z*: 699 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{39}H_{75}O_6SSi$: 699.5054; found: 699.5046 $[M+H]^+$. The sulfonate was converted into **31c** by the same procedure as that described for the conversion of **29** into **31a**. Colorless oil; $[\alpha]_D^{24} = -15.5$ ($c = 0.53$, $CHCl_3$); ^{1}H NMR: $\delta = 0.071$ (s, 3H), 0.073 (s, 3H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.90 (s, 9H), 1.26 (m, 20H), 1.39–1.49 (m, 2H), 1.65–1.72 (m, 1H), 1.78–1.94 (m, 3H), 2.05 (t, $J = 6.7$ Hz, 1H), 3.49 (ddd, $J = 11.6$, 5.5, 4.9 Hz, 1H), 3.68–3.72 (m, 1H), 3.78 (td, $J = 5.5$, 4.3 Hz, 1H), 3.85 (ddd, $J = 7.9$, 6.7, 4.3 Hz, 1H), 3.99–4.04 (m, 1H) ppm; ^{13}C NMR: $\delta = -4.4$, -4.2, 14.1, 18.1, 22.7, 25.0, 25.8, 25.9 (3C), 27.2, 29.3, 29.57 (2C), 29.63 (2C), 29.7, 29.9, 31.9, 35.0, 65.7, 73.1, 79.4, 82.2 ppm; IR (KBr): $\tilde{\nu} = 3481$, 1063 cm^{-1}; MS (FAB): *m/z*: 415 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{24}H_{51}O_3Si$: 415.3608; found: 415.3614 $[M+H]^+$.

(2*S*,5*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,5-epoxyoctadecan-1-ol (31d): Compound **26b** was converted into an alcohol by the same procedure as that described for the conversion of **26a** into **32**. Colorless oil; $[\alpha]_D^{28} = +5.7$ ($c = 1.31$, $CHCl_3$); ^{1}H NMR: $\delta = 0.08$–0.09 (m, 6H), 0.88–0.92 (m, 12H), 1.27–1.77 (m, 25H), 1.93–2.00 (m, 1H), 2.27 (s, 0.5H), 2.32 (s, 0.5H), 3.49–3.66 (m, 2.5H), 3.73 (t, $J = 7.3$ Hz, 0.5H), 4.12 (t, $J = 7.3$ Hz, 0.5H), 4.25–4.31 (m, 1.5H), 5.82 (s, 0.5H), 5.95 (s, 0.5H), 7.35–7.40 (m, 3H), 7.47–7.51 (m, 2H) ppm; ^{13}C NMR: $\delta = -4.48$, -4.45, 14.1, 18.0, 22.6, 25.5, 25.8 (3C), 27.5 (0.5C), 27.7 (0.5C), 29.3, 29.5, 29.56, 29.59 (2C), 29.62, 29.79, 29.84 (0.5C), 29.9 (0.5C), 30.91 (0.5C), 30.95 (0.5C), 31.9, 69.9 (0.5C), 70.6 (0.5C), 73.98 (0.5C), 74.02 (0.5C), 75.27 (0.5C), 75.30 (0.5C), 76.1 (0.5C), 76.9 (0.5H), 103.1 (0.5C), 104.0 (0.5C), 126.3, 126.6, 128.3, 129.0, 129.2, 137.7 (0.5C), 138.3 (0.5C) ppm; IR (KBr): $\tilde{\nu} = 3507$, 1068 cm^{-1}; MS (FAB): *m/z*: 543 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{31}H_{56}NaO_4Si$: 543.3846; found: 543.3851 $[M+Na]^+$. The alcohol was converted into a tosylate by the same procedure as that described for the conversion of **32** into **33**. Colorless oil; $[\alpha]_D^{24} = -9.7$ ($c = 1.03$, $CHCl_3$); ^{1}H NMR: $\delta = 0.002$ (s, 1.5H), 0.006 (s, 1.5H), 0.022 (s, 1.5H), 0.023 (s, 1.5H), 0.847 (s, 4.5H), 0.854 (s, 4.5H), 0.88 (t, $J = 7.0$ Hz, 3H), 1.19–1.52 (m, 23H), 1.63–1.72 (m, 2H), 1.90–1.96 (m, 1H), 2.44 (s, 3H), 3.50 (t, $J = 7.3$ Hz, 0.5H), 3.57 (dd, $J = 7.3$, 6.4 Hz, 0.5H), 3.84–3.87 (m, 1H), 4.00 (t, $J = 7.3$ Hz, 0.5H), 4.03–4.09 (m, 1H), 4.11 (dd, $J = 7.3$, 6.4 Hz, 0.5H), 4.45–4.52 (m, 1H), 5.75 (s, 0.5H), 5.85 (s, 0.5H), 7.32 (dd, $J = 8.6$, 1.2 Hz, 2H), 7.36–7.39 (m, 3H), 7.42–7.45 (m, 2H), 7.79 (dd, $J = 7.9$, 3.1 Hz, 2H) ppm; ^{13}C NMR: $\delta = -4.81$ (0.5C), -4.79 (0.5C), -4.78 (0.5C), -4.5 (0.5C), 14.1, 18.1, 21.5, 22.6, 23.7 (0.5C), 24.0 (0.5C), 25.4 (0.5C), 25.5 (0.5C), 25.8 (3C), 28.4 (0.5C), 28.8 (0.5C), 29.3, 29.4, 29.48, 29.51, 29.58 (2C), 29.62, 31.9, 34.3, 69.8 (0.5C), 70.3 (0.5C), 73.9 (0.5C), 74.0 (0.5C), 75.3 (0.5C), 76.0 (0.5C), 85.2 (0.5C), 85.3 (0.5C), 102.9 (0.5C), 103.9 (0.5C), 126.2, 126.5, 127.8 (2C), 128.21, 128.24, 129.0 (0.5C), 129.2 (0.5C), 129.6 (2C), 134.3, 137.6 (0.5C), 138.3 (0.5C), 144.6 ppm; IR (KBr): $\tilde{\nu} = 1097$ cm^{-1}; MS (FAB): *m/z*: 697 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{38}H_{62}NaO_6SiS$: 697.3934; found: 697.3936 $[M+Na]^+$. The tosylate was converted into **31d** by the same procedure as that described for the conversion of **33** into **31b**. Colorless oil; $[\alpha]_D^{28} = -3.3$ ($c = 1.02$, $CHCl_3$); ^{1}H NMR: $\delta = 0.078$ (s, 3H), 0.084 (s, 3H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.90 (s, 9H), 1.26–1.69 (m, 22H), 1.79–1.92 (m, 4H), 2.44 (br s, 1H), 3.47 (dt, $J = 10.4$, 5.5 Hz, 1H), 3.59 (ddd, $J = 6.7$, 6.1, 3.7 Hz, 1H), 3.76 (br d, $J = 11.0$ Hz, 1H), 3.96 (td, $J = 6.7$, 3.7 Hz, 1H), 4.05–4.09 (m, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.4, 14.1, 18.2, 22.6, 25.6, 25.9 (3C), 27.3, 27.7, 29.3, 29.58, 29.61 (3C), 29.7, 29.8, 31.9, 34.0, 65.3, 74.7, 79.3, 81.2 ppm; IR (KBr): $\tilde{\nu} = 3448$, 1052 cm^{-1}; MS (FAB): *m/z*: 415 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{24}H_{51}O_3Si$: 415.3607; found: 415.3613 $[M+H]^+$.

(3*R*,4*R*,7*R*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-4,7-epoxy-1-trimethylsilylheneicos-1-yn-3-ol (36a): Dess–Martin periodinane (1.48 g, 3.50 mmol) was added to a solution of **31a** (363 mg, 0.875 mmol) in CH_2Cl_2 (9 mL) and pyridine (1 mL) with stirring at 0 °C. After stirring at RT for 1 h, the mixture was filtered through silica gel and the filtrate was concentrated under the reduced pressure. Purification by flash column chromatography (hexane/EtOAc (30:1)) yielded **35a** (309 mg, 86 %) as a pale yellow oil. The aldehyde was unstable and was therefore used immediately in the next step. Aldehyde **35a** was converted into **36a** by the same procedure as that described for the formation of (2*RS*,4*S*,3′*R*,4′*R*)-**26a** but with trimethylsilylacetylene instead of **25**. Colorless oil; $[\alpha]_D^{24} = +12.9$ ($c = 1.03$, $CHCl_3$); ^{1}H NMR: $\delta = 0.06$ (s, 3H), 0.08 (s, 3H), 0.17 (s, 9H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.89 (s, 9H), 1.23–1.45 (m, 22H), 1.67 (dq, $J = 11.9$, 8.7 Hz, 1H), 1.75–1.83 (m, 1H), 1.89–1.96 (m, 1H), 2.02–2.08 (m, 1H), 2.47 (d, $J = 4.6$ Hz, 1H), 3.57 (td, $J = 6.6$, 3.7 Hz, 1H), 3.91 (td, $J = 8.2$, 6.6 Hz, 1H), 4.04 (q, $J = 6.7$ Hz, 1H), 4.18 (dd, $J = 6.7$, 4.6 Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.1, -0.2 (3C), 14.1, 18.3, 22.7, 25.5, 26.0 (3C), 27.7, 28.3, 29.3, 29.57, 29.59, 29.63 (2C), 29.7, 29.8, 31.9, 33.0, 65.6, 74.9, 82.0, 82.9, 90.3, 103.7 ppm; IR (KBr): $\tilde{\nu} = 3429$, 2175, 1074 cm^{-1}; MS (FAB): *m/z*: 533 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{29}H_{58}NaO_3Si_2$: 533.3822; found: 533.3846 $[M+Na]^+$; CD ($c = 1.96 \times 10^{-3}$, $CHCl_3$) $[\theta]_{max}^{20}$ (nm): $+1.7 \times 10^4$ (184.4).

(3*S*,4*R*,7*R*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-4,7-epoxy-1-trimethylsilylheneicos-1-yn-3-ol (36b): The procedure was the same as that used for preparation of **36a**. Colorless oil; $[\alpha]_D^{24} = +22.1$ ($c = 1.04$, $CHCl_3$); ^{1}H NMR: $\delta = 0.06$ (s, 3H), 0.07 (s, 3H), 0.17 (s, 9H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.89 (s, 9H), 1.23–1.47 (m, 22H), 1.64–1.73 (m, 1H), 1.93–2.05 (m, 3H), 2.35 (d, $J = 6.7$ Hz, 1H), 3.56 (ddd, $J = 7.3$, 5.5, 4.3 Hz, 1H), 4.04 (ddd, $J = 7.9$, 6.1, 5.5 Hz, 1H), 4.12 (td, $J = 7.0$, 3.7 Hz, 1H), 4.39 (dd, $J = 6.1$, 3.7 Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.2, -0.3 (3C), 14.1, 18.2, 22.7, 25.6, 25.9 (3C), 26.7, 27.6, 29.32, 29.58, 29.61 (3C), 29.64, 29.8, 31.9, 32.9, 65.0, 75.0, 81.4, 83.5, 90.5, 103.7 ppm; IR (KBr): $\tilde{\nu} = 3410$, 2175, 1090 cm^{-1}; MS (FAB): *m/z*: 533 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{29}H_{58}NaO_3Si_2$: 533.3822; found: 533.3823 $[M+Na]^+$; CD ($c = 1.96 \times 10^{-3}$, $CHCl_3$) $[\theta]_{max}^{20}$ (nm): $+3.6 \times 10^4$ (184.0).

(3*R*,4*S*,7*S*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-4,7-epoxy-1-trimethylsilylheneicos-1-yn-3-ol (37a): The procedure was the same as that used for preparation of **36a**, but with (1*S*,2*R*)-NME instead of (1*R*,2*S*)-NME. Colorless oil; $[\alpha]_D^{23} = -18.6$ ($c = 1.06$, $CHCl_3$); ^{1}H NMR: $\delta = 0.049$ (s, 3H), 0.052 (s, 3H), 0.17 (s, 9H), 0.88 (t, $J = 7.3$ Hz, 3H), 0.89 (s, 9H), 1.23–1.43 (m, 22H), 1.89–2.05 (m, 4H), 2.33 (d, $J = 6.1$ Hz, 1H), 3.78 (ddd, $J = 6.1$, 5.5, 3.7 Hz, 1H), 4.03 (ddd, $J = 7.3$, 6.7, 3.7 Hz, 1H), 4.10 (td, $J = 6.7$, 3.7 Hz, 1H), 4.36 (dd, $J = 6.1$, 3.7 Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.2, -0.2 (3C), 14.1, 18.1, 22.7, 25.4, 25.5, 25.9 (3C), 26.9, 29.3, 29.55, 29.57, 29.62 (2C), 29.64, 29.8, 31.9, 34.7, 65.2, 73.0, 81.5, 83.6, 90.5, 103.9 ppm; IR (KBr): $\tilde{\nu} = 3417$, 2175, 1105 cm^{-1}; MS (FAB): *m/z*: 533 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{29}H_{58}NaO_3Si_2$: 533.3822; found: 533.3855 $[M+Na]^+$; CD ($c = 1.96 \times 10^{-3}$, $CHCl_3$) $[\theta]_{max}^{20}$ (nm): -3.9×10^4 (184.6).

(3*S*,4*S*,7*S*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-4,7-epoxy-1-trimethylsilylheneicos-1-yn-3-ol (37b): The procedure was the same as that used for preparation of **36b**. Colorless oil; $[\alpha]_D^{24} = -10.3$ ($c = 1.01$, $CHCl_3$); ^{1}H NMR: $\delta = 0.056$ (s, 3H), 0.062 (s, 3H), 0.17 (s, 9H), 0.88 (t, $J = 7.3$ Hz, 3H), 0.89 (s, 9H), 1.23–1.40 (m, 22H), 1.76–1.87 (m, 2H), 1.95 (dq, $J = 11.6$, 8.5 Hz, 1H), 2.01–2.07 (m, 1H), 2.43 (d, $J = 4.3$ Hz, 1H), 3.78–3.81 (m, 1H), 3.92 (ddd, $J = 7.9$, 6.1, 3.1 Hz, 1H), 4.03 (q, $J = 6.7$ Hz, 1H), 4.18 (dd, $J = 6.7$, 4.6 Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.2, -0.2 (3C), 14.1, 18.1, 22.7, 25.2, 25.5, 26.0 (3C), 28.1, 29.3, 29.5, 29.56, 29.61 (2C), 29.64, 29.8, 31.9, 34.7, 65.4, 72.9, 82.0, 82.6, 90.2, 103.9 ppm; IR (KBr): $\tilde{\nu} = 3410$, 2175, 1055 cm^{-1}; MS (FAB): *m/z*: 533 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{29}H_{58}NaO_3Si_2$: 533.3822; found: 533.3821 $[M+Na]^+$; CD ($c = 1.96 \times 10^{-3}$, $CHCl_3$) $[\theta]_{max}^{20}$ (nm): -1.9×10^4 (184.8).

(3*R*,4*R*,7*S*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-4,7-epoxy-1-trimethylsilylheneicos1-yn-3-ol (38a): The procedure was the same as that used for

preparation of **36a**. Colorless oil; $[\alpha]_D^{23} = -5.3$ ($c = 0.90$, $CHCl_3$); ^{1}H NMR: $\delta = 0.08$ (s, 3H), 0.09 (s, 3H), 0.17 (s, 9H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.90 (s, 9H), 1.23–1.33 (m, 20H), 1.38–1.44 (m, 1H), 1.47–1.51 (m, 1H), 1.78–1.84 (m, 2H), 1.85–1.92 (m, 1H), 1.97–2.05 (m, 1H), 2.67 (d, $J = 5.5$ Hz, 1H), 3.79 (ddd, $J = 6.1$, 4.9, 4.3 Hz, 1H), 3.90 (ddd, $J = 7.9$, 6.1, 4.3 Hz, 1H), 3.99 (ddd, $J = 7.9$, 6.1, 4.9 Hz, 1H), 4.17 (dd, $J = 6.1$, 5.5 Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.4$, -4.0, -0.2 (3C), 14.1, 18.1, 22.7, 24.9, 25.5, 25.9 (3C), 28.1, 29.3, 29.55, 29.61 (3C), 29.64, 29.9, 31.9, 35.0, 66.5, 73.0, 81.9, 82.8, 90.0, 103.9 ppm; IR (KBr): $\tilde{\nu} = 3440$, 2175, 1070 cm^{-1}; MS (FAB): *m/z*: 511 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{29}H_{59}O_3Si_2$: 511.4003; found: 511.4003 $[M+H]^+$; CD ($c = 1.96 \times 10^{-3}$, $CHCl_3$) $[\theta]_{max}^{20}$ (nm): -1.5×10^4 (183.4).

(3*S*,4*R*,7*S*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-4,7-epoxy-1-trimethylsilylheneicos-1-yn-3-ol (38b): The procedure was the same as that used for preparation of **36b**. Colorless oil; $[\alpha]_D^{22} = +12.5$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR: $\delta = 0.08$ (s, 3H), 0.09 (s, 3H), 0.17 (s, 9H), 0.88 (t, $J = 7.3$ Hz, 3H), 0.89 (s, 9H), 1.26–1.32 (m, 20H), 1.40–1.46 (m, 1H), 1.51–1.58 (m, 1H), 1.76–1.83 (m, 1H), 1.87–1.99 (m, 2H), 2.11–2.17 (m, 1H), 2.87 (d, $J = 3.1$ Hz, 1H), 3.85 (dt, $J = 6.7$, 4.9 Hz, 1H), 3.92 (ddd, $J = 8.5$, 5.5, 4.9 Hz, 1H), 4.09 (dt, $J = 7.9$, 3.1 Hz, 1H), 4.48 (t, $J = 5.8$ Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.5$, -4.2, -0.2 (3C), 14.1, 18.1, 22.6, 24.8, 25.93, 25.96 (3C), 26.02, 29.3, 29.5, 29.59 (3C), 29.63, 29.9, 31.9, 34.9, 65.4, 73.0, 81.3, 82.4, 90.5, 103.4 ppm; IR (KBr): $\tilde{\nu} = 3442$, 2177, 1051 cm^{-1}; MS (FAB): *m/z*: 511 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{29}H_{59}O_3Si_2$: 511.4003; found: 511.3981 $[M+H]^+$; CD ($c = 1.96 \times 10^{-3}$, $CHCl_3$) $[\theta]_{max}^{20}$ (nm): $+0.27 \times 10^4$ (183.4).

(3*R*,4*S*,7*R*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-4,7-epoxy-1-trimethylsilylheneicos-1-yn-3-ol (39a): The procedure was the same as that used for preparation of **36b**. Colorless oil; $[\alpha]_D^{21} = -37.5$ ($c = 1.13$, $CHCl_3$); ^{1}H NMR: $\delta = 0.08$ (s, 3H), 0.10 (s, 3H), 0.16 (s, 9H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.91 (s, 9H), 1.26–1.33 (m, 20H), 1.41–1.48 (m, 1H), 1.63–1.70 (m, 1H), 1.77–1.90 (m, 2H), 1.96 (dq, $J = 12.8$, 8.5 Hz, 1H), 2.11–2.17 (m, 1H), 3.05 (d, $J = 3.1$ Hz, 1H), 3.62 (ddd, $J = 7.3$, 6.1, 3.7 Hz, 1H), 3.97 (ddd, $J = 7.9$, 6.7, 3.7 Hz, 1H), 4.11 (ddd, $J = 7.9$, 4.9, 3.1 Hz, 1H), 4.50 (dd, $J = 3.7$, 3.1 Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.2, -0.2 (3C), 14.1, 18.3, 22.7, 25.4, 26.0 (3C), 26.1, 27.6, 29.3, 29.56, 29.60 (3C), 29.64, 29.8, 31.9, 34.2, 65.3, 74.6, 81.3, 81.9, 90.1, 103.7 ppm; IR (KBr): $\tilde{\nu} = 3439$, 2177, 1057 cm^{-1}; MS (FAB): *m/z*: 511 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{29}H_{59}O_3Si_2$: 511.4003; found: 511.4007 $[M+H]^+$; CD ($c = 1.96 \times 10^{-3}$, $CHCl_3$) $[\theta]_{max}^{20}$ (nm): -0.41×10^4 (183.6).

(3*R*,4*S*,7*R*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-4,7-epoxy-1-trimethylsilylheneicos-1-yn-3-ol (39b): The procedure was the same as that used for preparation of **36a**. Colorless oil; $[\alpha]_D^{22} = -7.9$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR: $\delta = 0.078$ (s, 3H), 0.083 (s, 3H), 0.17 (s, 9H), 0.88 (t, $J = 7.3$ Hz, 3H), 0.90 (s, 9H), 1.23–1.45 (m, 21H), 1.58–1.65 (m, 1H), 1.77 (dq, $J = 12.2$, 7.9 Hz, 1H), 1.81–1.93 (m, 2H), 2.00 (dq, $J = 12.8$, 7.9 Hz, 1H), 2.85 (d, $J = 5.5$ Hz, 1H), 3.58 (td, $J = 6.1$, 4.3 Hz, 1H), 3.98 (ddd, $J = 7.9$, 6.7, 4.3 Hz, 1H), 4.03 (dt, $J = 7.9$, 5.5 Hz, 1H), 4.18 (t, $J = 5.5$ Hz, 1H) ppm; ^{13}C NMR: $\delta = -4.6$, -4.2, -0.2 (3C), 14.1, 18.2, 22.7, 25.4, 26.0 (3C), 27.1, 28.1, 29.3, 29.59, 29.61 (3C), 29.64, 29.8, 31.9, 33.9, 65.8, 74.5, 81.7, 82.4, 89.7, 104.3 ppm; IR (KBr): $\tilde{\nu} = 3405$, 2175, 1078 cm^{-1}; MS (FAB): *m/z*: 511 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{29}H_{59}O_3Si_2$: 511.4003; found: 511.4022 $[M+H]^+$; CD ($c = 1.96 \times 10^{-3}$, $CHCl_3$) $[\theta]_{max}^{20}$ (nm): $+1.5 \times 10^4$ (183.2).

Acknowledgement

We acknowledge financial support by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (Grant no.: 14572006) and grants from the Research Foundation for Pharmaceutical Sciences and the Shorai Foundation for Science and Technology. N.K. is grateful to Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

[1] For reviews on *annonaceous* acetogenins, see: a) F. Q. Alali, X.-X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504–540; b) M. C. Zafra-Polo, B. Figadère, T. Gallardo, J. R. Tormo, D. Cortes, *Phytochemistry* **1998**, *48*, 1087–1117; c) "Acetogenins from Annonaceae": A. Cavé, B. Figadère, A. Laurens, D. Cortes, in *Progress in the Chemistry of Organic Natural Products*, *Vol. 70* (Ed.: W. Hertz), Springer-Verlag, New York, **1997**, pp. 81–288; d) L. Zeng, Q. Ye, N. H. Oberlies, G. Shi, Z.-M. Gu, K. He, J. L. McLaughlin, *Nat. Prod. Rep.* **1996**, *13*, 275–306; e) M. C. Zafra-Polo, M. C. González, E. Estornell, S. Sahpaz, D. Cortes, *Phytochemistry* **1996**, *42*, 253–271; f) "*Annonaceous* Acetogenins": Z.-M. Gu, G.-X. Zhao, N. H. Oberlies, L. Zeng, J. L. McLaughlin, in *Recent Advances in Phytochemistry*, *Vol. 29* (Eds.: J. T. Arnason, R. Mata, J. T. Romeo), Plenum Press, New York, **1995**, pp. 249–310; g) X.-P. Fang, M. J. Rieser, Z.-M. Gu, G.-X. Zhao, J. L. McLaughlin, *Phytochem. Anal.* **1993**, *4*, 27–67; h) J. K. Rupprecht, Y.-H. Hui, J. L. McLaughlin, *J. Nat. Prod.* **1990**, *53*, 237–278.

[2] For reviews of the synthesis of *annonaceous* acetogenins, see: a) G. Casiraghi, F. Zanardi, L. Battistini, G. Rassu, *Chemtracts-Organic Chemistry* **1998**, *11*, 803–827; b) M. C. Elliott, *J. Chem. Soc. Perkin Trans. 1* **1998**, 4175–4200; c) B. Figadère, *Acc. Chem. Res.* **1995**, *28*, 359–365; d) R. Hoppe, H.-D. Scharf, *Synthesis* **1995**, 1447–1464; e) U. Koert, *Synthesis* **1995**, 115–132.

[3] E. Wolvetang, K. L. Johnson, K. Kramer, A. W. Linnane, *FEBS Lett.* **1994**, *339*, 40–44.

[4] N. H. Oberlies, V. L. Croy, M. L. Harrison, J. L. McLaughlin, *Cancer Lett.* **1997**, *15*, 73–79.

[5] a) F. Zanardi, L. Battistini, G. Rassu, L. Pinna, M. Mor, N. Culeddu, G. Casiraghi, *J. Org. Chem.* **1998**, *63*, 1368–1369; b) B. Figadère, J.-F. Peyrat, A. Cavé, *J. Org. Chem.* **1997**, *62*, 3428–3429.

[6] a) U. Koert, M. Stein, H. Wagner, *Liebigs Ann.* **1995**, 1415–1426, and references therein; b) U. Koert, H. Wagner, U. Pidun, *Chem. Ber.* **1994**, *127*, 1447–1457.

[7] a) N. Maezaki, N. Kojima, H. Tominaga, M. Yanai, T. Tanaka, *Org. Lett.* **2003**, *5*, 1411–1414; b) N. Maezaki, N. Kojima, A. Sakamoto, H. Tominaga, C. Iwata, T. Tanaka, M. Monden, B. Damdinsuren, S. Nakamori, *Chem. Eur. J.* **2003**, *9*, 390–399; c) N. Maezaki, N. Kojima, M. Asai, H. Tominaga, T. Tanaka, *Org. Lett.* **2002**, *4*, 2977–2980; d) N. Maezaki, N. Kojima, A. Sakamoto, C. Iwata, T. Tanaka, *Org. Lett.* **2001**, *3*, 429–432.

[8] a) E. El-Sayed, N. K. Anand, E. M. Carreira, *Org. Lett.* **2001**, *3*, 3017–3020; b) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688; c) H. Sasaki, D. Boyall, E. M. Carreira, *Helv. Chim. Acta* **2001**, *84*, 964–971; d) D. Boyall, F. López, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233–4236; e) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373–381; f) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.

[9] Application to bis-THF-ring cores has already been communicated, see ref. [7a].

[10] X.-F. Ren, E. Turos, C. H. Lake, M. R. Churchill, *J. Org. Chem.* **1995**, *60*, 6468–6483.

[11] a) G. Cainelli, M. Panunzio, E. Bandini, G. Martelli, G. Spunta, *Tetrahedron* **1996**, *52*, 1685–1698; b) L. Banfi, A. Bernardi, L. Colombo, C. Gennari, C. Scolastico, *J. Org. Chem.* **1984**, *49*, 3784–3790.

[12] The absolute configurations of coupling products were determined by the modified Mosher method. See: a) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096; b) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519; c) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543–2549.

[13] The signals of the C3 methine protons in the ^{1}H NMR spectral data of the *syn* adducts appeared upfield by 0.1–0.2 ppm relative to those in the spectra of the *anti* adducts. On the other hand, the signals of the OH protons in the *syn* adducts appeared downfield by 0.1–0.2 ppm relative to those in the *anti* adducts. The shifts were consistent for each compound in this series.

[14] We found that a combination of the aldehyde (*S*)-**6** with (1*S*,2*R*)-NME provided better selectivity than the corresponding combination of (*S*)-**6** with (1*R*,2*S*)-NME. Carreira and co-workers also reported similar results in the asymmetric alkynylation of (*S*)-**6** with acetyl propargyl alcohol,[8a] but the reaction mechanism was not mentioned.

[15] a) O. W. Gooding, C. C. Beard, D. Y. Jackson, D. L. Wren, G. F. Cooper, *J. Org. Chem.* **1991**, *56*, 1083–1088. Other synthetic procedures for 3-butyne-1,2-diol **13** were reported. See: b) O. Yamada, K. Ogasawara, *Synthesis* **1995**, 1291–1294; c) O. Yamada, K. Ogasawara, *Synlett* **1995**, 427–428; d) S. Takano, M. Setoh, O. Yamada, K. Ogasawara, *Synthesis* **1993**, 1253–1256.

[16] P. Michel, D. Gennet, A. Rassat, *Tetrahedron Lett.* **1999**, *40*, 8575–8578.
[17] During the course of our study, Pietruszka reported another solution employing the Bestmann–Ohira reagent for alkyne **13**. See: J. Pietruszka, A. Witt, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4293–4300.
[18] Koert reported a similar double stereodifferentiation in the substrate-controlled addition of α-tetrahydrofuranic aldehyde with the chiral 3,4-isopropylidenedioxybutyl anion.[6b]
[19] a) S. E. Schaus, J. Brånalt, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 4876–4877; b) P. S. Savle, M. J. Lamoreaux, J. F. Berry, R. D. Gandour, *Tetrahedron:Asymmetry* **1998**, *9*, 1843–1846; c) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938.
[20] Stereochemistries of coupling products were assigned by analogy with the ^{1}H NMR spectra of related compounds. The details are described in ref. [13].
[21] V. A. Engelhardt, J. E. Castle, *J. Am. Chem. Soc.* **1953**, *75*, 1734.
[22] J. Yoshida, M. Nakagawa, H. Seki, T. Hino, *J. Chem. Soc. Perkin Trans. 1* **1992**, 343–350.
[23] Stereochemistry of the benzylidene acetal was assumed by analogy the ^{1}H NMR spectra of related compounds. See: a) T. B. Grindley, S. Kusuma, T. S. Cameron, *Can. J. Chem.* **1986**, *64*, 2388–2396; b) N. Baggett, K. W. Buck, A. B. Foster, M. H. Randall, J. M. Webber, *J. Chem. Soc.* **1965**, 3394–3440.
[24] Recently, Carreira and co-workers reported a modified procedure in which $Zn(OTf)_2$ was dried before use.[8d] We found that this protocol is very effective for obtaining reproducibility of the yield. Therefore, the modified procedure was employed after this entry.
[25] Carreira and co-workers reported a catalytic version of the asymmetric alkynylation.[8b] We examined the asymmetric alkynylation of the aldehyde **20** with the alkyne **25** under the catalytic conditions but the reaction did not proceed.
[26] The diastereomeric ratio based on the benzylidene acetal for **26a** and **26b** was almost the same as the ratio of **25a** and **25b** used.
[27] a) D. L. J. Clive, E.-S. Ardelean, *J. Org. Chem.* **2001**, *66*, 4841–4844; b) M. Hirama, T. Shigemoto, S. Ito, *J. Org. Chem.* **1987**, *52*, 3342–3346.
[28] Recently, a one-pot THF-ring formation from the 1,2,5-triol derivatives was reported by Forsyth and co-workers. See: a) A. B. Dounay, G. J. Florence, A. Saito, C. J. Forsyth, *Tetrahedron* **2002**, *58*, 1865–1874; b) A. B. Dounay, C. J. Forsyth, *Org. Lett.* **2001**, *3*, 975–978.
[29] a) H. Sajiki, K. Hirota, *Tetrahedron* **1998**, *54*, 13981–13996; b) H. Sajiki, *Tetrahedron Lett.* **1995**, *36*, 3465–3468.
[30] U. Koert, M. Stein, H. Wagner, *Chem. Eur. J.* **1997**, *3*, 1170–1180, and references therein.
[31] S. Hoppen, S. Bäurle, U. Koert, *Chem. Eur. J.* **2000**, *6*, 2382–2396.
[32] The moderate yields in some entries were caused by base-promoted deprotection of the TMS group in the coupling product and subsequent coupling of the resulting acetylide with another aldehyde.

Received: May 27, 2003 [F5185]