DOI: 10.1002/asia.200700304

Total Synthesis of 2-Hydroxytetracosanolide and 2-Hydroxy-24-oxooctacosanolide By Using an Effective Lactonization

Isamu Shiina,* Akane Sasaki, Takaaki Kikuchi, and Hiroki Fukui[a]

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: We have developed effective methods for the total synthesis of 2-hydroxytetracosanolide and 2-hydroxy-24-oxooctacosanolide, the defensive salivary secretions of termites. The former natural product isolated from *Armitermes neotenicus*, a species of termite that inhabits Guyana, contains a 25-membered lactone backbone, and the latter, extracted from *Pseudacanthoterme springer*, an African termite, includes a 29-membered lactone moiety. The key cyclization to produce the 25- or 29-membered lactone core is performed by using 2-methyl-6-nitrobenzoic anhydride (MNBA) with a stoichiometric amount of 4-(dimethylamino)pyridine (DMAP) or a catalytic amount of 4-(dimethylamino)pyridine *N*-oxide (DMAPO).

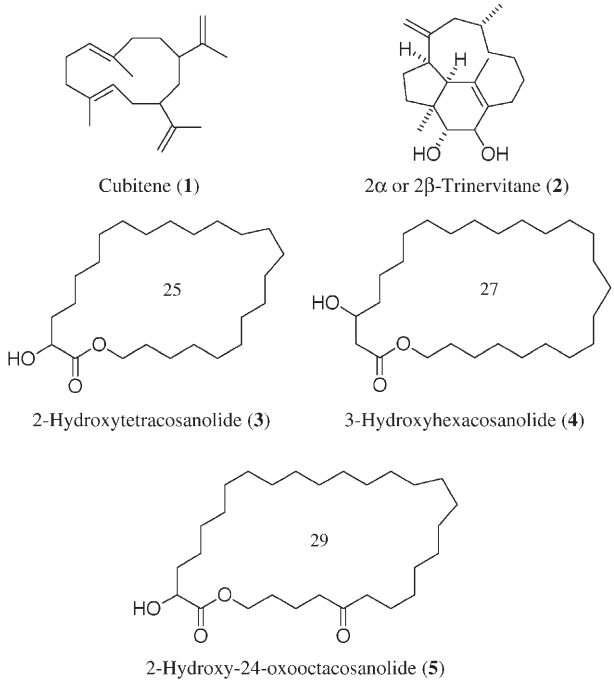
Keywords: lactones · lactonization · macrocycles · natural products · total synthesis

Introduction

Termites have rigidly structured societies that consist of a king, a queen, workers, fertile pairs, and soldiers. Termite soldiers are sterile males or females, and their heads are very different in shape and size from those of the termite workers. The primary role of the soldiers is to protect their colony from intruders and predators. To do this, the soldiers of some termite species produce chemical secretions, such as terpenes, alkanes, alkenes, quinines, nitroalkenes, β-ketoaldehydes, vinyl ketones, and macrocyclic lactones.[1]

Some diterpenes isolated from the frontal gland secretion of a termite soldier, such as cubitene (**1**) and trinervitanes **2**, are reported to be typical defensive substances used by the termites against predators (Scheme 1).[2,3] Related biosynthetic and chemical synthetic studies of cyclic terpenoids have progressed over the last few decades, as reported in excellent articles.[1]

On the other hand, macrocyclic molecules such as **3**, **4**, and **5** were also extracted from the salivary defensive secretion of termites.[4,5] α- and β-Hydroxylactones **3** and **4** were prepared from a crude mixture of the crushed heads of soldier *Armitermes neotenicus*, a species that inhabits the Republic of Guyana,[4] and α-hydroxy-24-oxolactone **5** was iso-



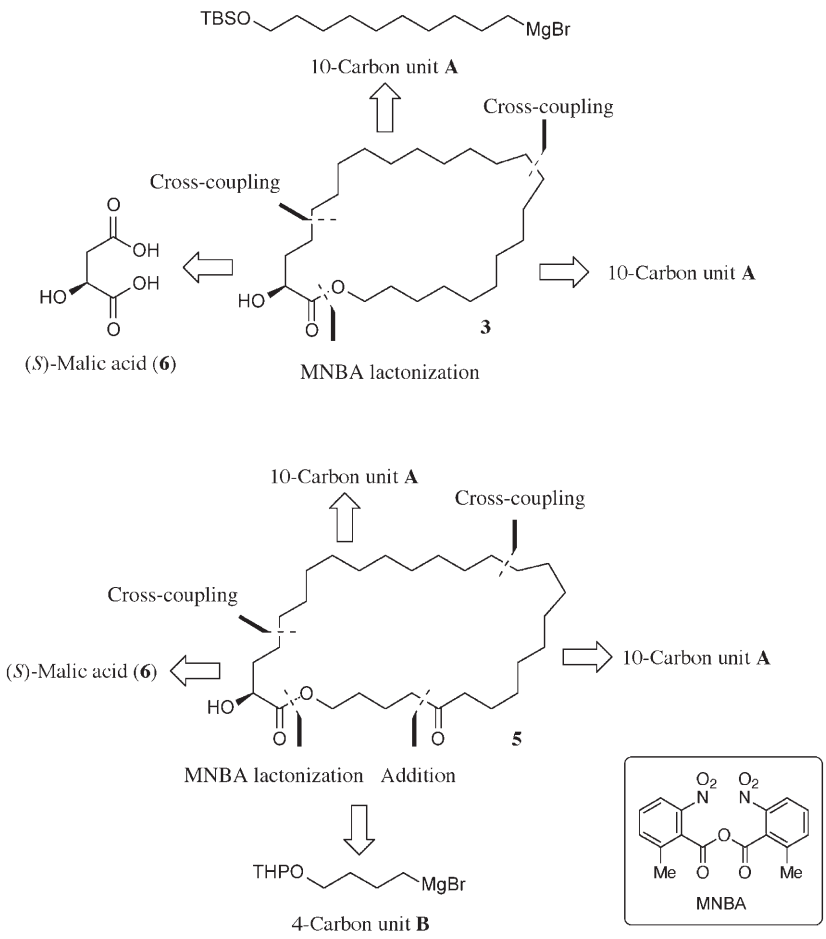
Scheme 1. Some defensive substances produced by termite soldiers.

[a] Prof. Dr. I. Shiina, A. Sasaki, T. Kikuchi, Dr. H. Fukui
Department of Applied Chemistry, Faculty of Science
Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
Fax: (+81) 3-3260-5609
E-mail: shiina@rs.kagu.tus.ac.jp

lated from the salivary defensive secretion of the soldiers of the African termite *Pseudacanthoterme springer*.[5]

These compounds involve very large and peculiar macrocyclic lactone moieties; however, to the best of our knowledge, there are only a few reports that discuss the chemical production of this type of giant lactone. Furthermore, only a very small amount of these lactones have been isolated from the termites; therefore, absolute configurations of these lactones as well as their optical rotations have not yet been determined.

Recently, we developed a new and rapid lactonization of ω-hydroxycarboxylic acids by using symmetrically substituted benzoic anhydrides, such as 2-methyl-6-nitrobenzoic anhydride (MNBA), as a condensation reagent.[6,7] This protocol can be performed by using a very simple procedure, and the desired lactones can be obtained within a very short period of time under mild conditions, as the reaction quickly proceeds in the presence of a nucleophilic promoter such as 4-(dimethylamino)pyridine (DMAP) or its *N*-oxide (DMAPO).



Scheme 2. Synthesis of 25- and 29-membered ring lactones **3** and **5** with benzoic anhydride.

In this paper, we report the effective syntheses of 2-hydroxytetracosanolide (**3**) and 2-hydroxy-24-oxooctacosanolide (**5**)[6h] by using the MNBA lactonization protocol as part of our continuing effort to apply new synthetic methodologies to produce biologically active macrolactones.

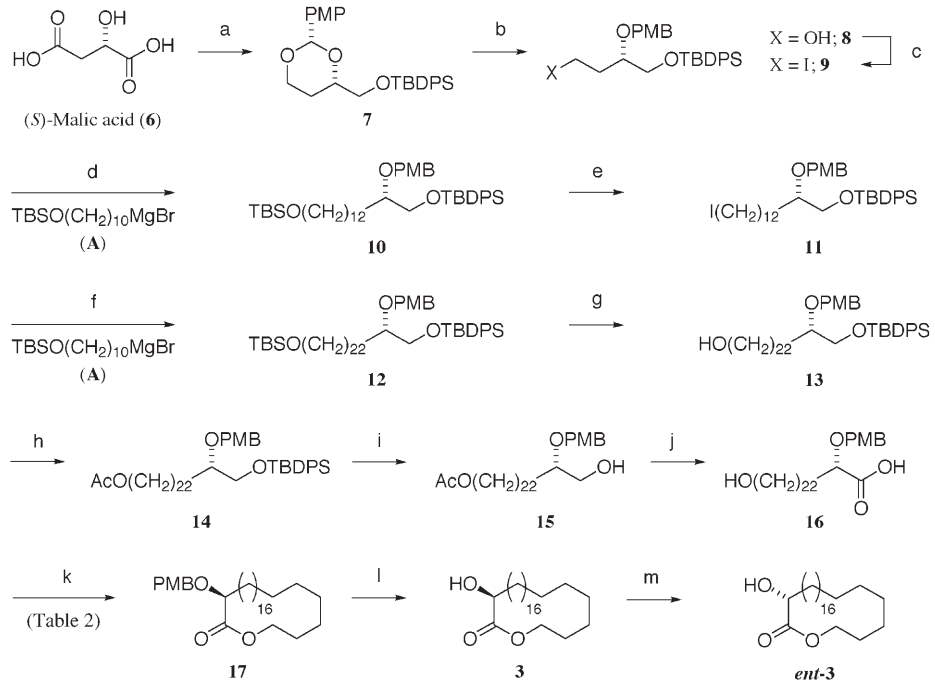
Results and Discussion

The retrosynthetic routes to the desired lactones **3** and **5**, which involve three types of segments, (*S*)-malic acid (**6**), 10-carbon unit **A**, and 4-carbon unit **B**, are depicted in Scheme 2. After assembling these fragments to form the corresponding *seco*-acids, we planned to apply our effective monomer-selective lactone formation with MNBA to the precursors to generate the desired macrocyclic backbones.

First, (*S*)-malic acid (**6**) was converted into the corresponding triol by reduction with $BH_3{\cdot}SMe_2$ in the presence of $B(OMe)_3$ according to the literature method (Scheme 3).[8] The triol was protected as its PMP acetal, and the resulting primary alcohol was transformed into the TBDPS ether **7**. Reductive cleavage of the PMP acetal moiety of **7** with DIBAL regioselectively produced primary alcohol **8**, and the hydroxy group in **8** was then converted into iodine.

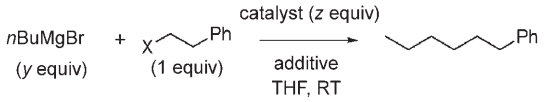
Next, to determine the suitable reaction conditions for the cross-coupling between iodide **9** and Grignard reagent **A**, several copper catalysts were examined for the reaction of β-phenethylhalides with *n*BuMgBr as model cases (Table 1). Although the reactions we attempted by using β-phenethylbromide with *n*BuMgBr did not proceed at all (Table 1, entries 1 and 2), employment of β-phenethyliodide instead of β-phenethylbromide produced a much better result by forming the desired compound in 2% yield in the coupling reaction (Table 1, entry 3). Finally, it was found that the complex generated from CuI with 2,2′-bipyridyl is the best promoter for the coupling reaction of β-phenethyliodide with the Grignard reagent (Table 1, entry 4).[9]

On the basis of the above results, the coupling reaction between **9** and Grignard reagent **A** was attempted in the presence of the complex consisting of CuI and 2,2′-bipyridyl, and the desired 14-carbon segment **10** was successfully obtained in high yield. After the TBS group of **10** was removed, the resulting hydroxy group was replaced with



Scheme 3. Synthesis of **3** and *ent*-**3**. Reagents and conditions: a) i) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, room temperature (97%); ii) $PMPCH(OMe)_2$, CSA, CH_2Cl_2, room temperature (81%); iii) TBDPSCl, imidazole, DMF, room temperature (83%); b) DIBAL, CH_2Cl_2, −78°C (92%); c) I_2, Ph_3P, imidazole, benzene, room temperature (96%); d) **A**, CuI, 2,2′-bipyridyl, THF, room temperature (90%); e) i) 1 M HCl, THF, room temperature (96%); ii) I_2, Ph_3P, imidazole, benzene, room temperature (92%); f) **A**, CuI, 2,2′-bipyridyl, THF, room temperature (96%); g) 1 M HCl, THF, room temperature (99%); h) Ac_2O, DMAP, pyridine, room temperature (97%); i) TBAF, AcOH, THF, room temperature (quant.); j) i) TEMPO, $NaClO_2$, NaOCl, acetnitrile, 35°C (88%); ii) K_2CO_3, MeOH, room temperature (87%); k) MNBA, DMAP, CH_2Cl_2/THF, 50°C (87%); l) DDQ, CH_2Cl_2/H_2O, room temperature (99%); m) i) 3,5-dinitrobenzoic acid, DIAD, Ph_3P, THF, room temperature (71%); ii) Et_3N, MeOH, room temperature (96%). DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, DIAD = diisopropyl azodicarboxylate, DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, PMB = *p*-methoxybenzyl, PMP = *p*-methoxyphenyl, TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butylsilyl, TEMPO = 2,2,6,6-tetramethylpipedinyloxy.

Table 1. Model reactions with copper catalysts for the cross-coupling.



Entry	*y*	RX	Catalyst	*z*	Additive	Yield [%]
1	1.0	$Ph(CH_2)_2Br$	CuI	2.0	none	NR[a]
2	3.0	$Ph(CH_2)_2Br$	$CuBr{\cdot}SMe_2$	3.0	none	NR[a]
3	3.0	$Ph(CH_2)_2I$	$CuBr{\cdot}SMe_2$	3.0	none	2
4	3.5	$Ph(CH_2)_2I$	CuI	0.1	2,2′-bipyridyl	64

[a] No reaction.

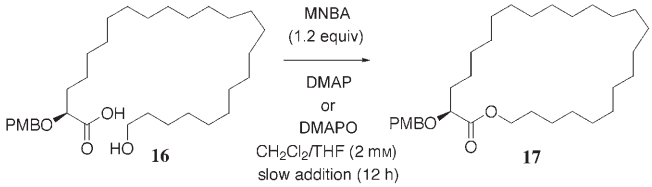
iodine. The successive cross-coupling of **11** with Grignard reagent **A** was carried out again under reaction conditions similar to those of step d to afford the 24-carbon segment **12**.

Further conversion of the linear molecule **12** into the precursor of lactone **3** was then examined. First, the TBS group was deprotected to form the corresponding alcohol **13**, and it was then acetylated to produce the intermediate **14**. After the TBDPS group was removed with TBAF, the generated alcohol **15** was oxidized to the corresponding carboxylic acid with TEMPO. Methanolysis of the acetyl moiety of **15** with K_2CO_3 gave the desired *seco*-acid **16**. Next, optimization of the reaction conditions for the lactonization of **16** was carried out as shown in Table 2.

When a solution of **16** in THF was slowly added to a reaction mixture of 1.2 equivalents of MNBA and a catalytic amount of DMAP (20 mol%) with an excess amount of triethylamine (3.0 equiv) in dichloromethane over a 12 h period at 50°C (bath temperature), the corresponding monomeric lactone **17** was obtained in 69% yield (Table 2, entry 1). Further examination with a stoichiometric amount of DMAP afforded a better yield (87%) of the desired lactone **17** (Table 2, entry 2).

Furthermore, the catalytic use of DMAPO, the *N*-oxide of DMAP, with an excess amount of triethylamine at room temperature or 50°C also produced the cyclized product effectively, with reasonable yields of 63 and 76%, respectively. On the other hand, in the presence of a stoichiometric amount of DMAPO, the MNBA-mediated dehydration at 50°C afforded the desired monomeric lactone **17** in lower yield (53%; Table 2, entry 5). Thus, it was proved that stoichiometric quantities of DMAP or a catalytic amount of DMAPO with the combined use of MNBA at a relatively high temperature are the most effective conditions for the lactonization of *seco*-acid **16** to produce the desired 25-membered lactone **17**

Table 2. Synthesis of the 25-membered macrocyclic lactone **17** from **16** with MNBA.



Entry	Catalyst ([equiv])	Cobase ([equiv])	*T* [°C]	Yield [%]
1	DMAP (0.2)	Et_3N (3.0)	50	69
2	DMAP (3.0)	none	50	87
3	DMAPO (0.2)	Et_3N (3.0)	RT	63
4	DMAPO (0.2)	Et_3N (3.0)	50	76
5	DMAPO (3.0)	none	50	53

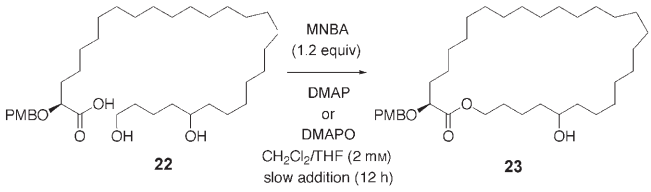
(Table 2, entries 2 and 4). Although the MNBA lactonization provided the desired macrocycle **17** in high yield (87%; Table 2, entry 2), other closure protocols, such as the *S*-pyridyl ester method and the Yamaguchi stepwise cyclization in refluxing toluene gave **17** in medium and good yields (50 and 75%, respectively).

Finally, the PMB group of **17** was removed with DDQ to produce the target molecule, (*S*)-2-hydroxytetracosanolide (**3**), in high yield. All spectral data, including the ^{1}H and ^{13}C NMR chemical shifts and the mass spectra of synthetic (−)-**3**, correspond to those of the natural 25-membered lactone.[4] (*R*)-**2**-Hydroxytetracosanolide ((+)-**3**), an enantiomer of (−)-**3**, was also prepared from the synthetic sample by Mitsunobu inversion followed by debenzoylation. The enantiopurity of each compound was determined by chiral HPLC of its benzoate derivative.

Further conversion of the 24-carbon linear segment **13** into the elongated 28-carbon *seco*-acid **22** was then attempted as follows (Scheme 4): Compound **13** was oxidized with PCC to yield aldehyde **18**. Elongation of the 4-carbon unit was attained by the addition of Grignard reagent **B** to **18**. The resulting secondary alcohol **19** was protected as its THP ether. Removal of the terminal TBDPS group of **20** by treatment with a mixture of TBAF and acetic acid smoothly occurred to give the corresponding primary alcohol **21**, which was directly oxidized to form the carboxylic acid. Finally, removal of the two THP groups of the carboxylic acid was simultaneously achieved with hydrochloric acid to afford the diol **22**, the desired *seco*-acid, in good yield.

Optimization of the reaction conditions for the lactonization of **22** was eventually carried out as shown in Table 3. First, a solution of **22** in THF was slowly added to the reaction mixture containing 1.2 equivalents of MNBA and 0.2 or 3.0 equivalents of DMAP in dichloromethane over a 12 h period at 50°C, and the corresponding monomeric lactone **23** was obtained in 64 or 69% yield, respectively (Table 3, entries 1 and 2).

Table 3. Synthesis of the 29-membered macrocyclic lactone **23** from **22** with MNBA.

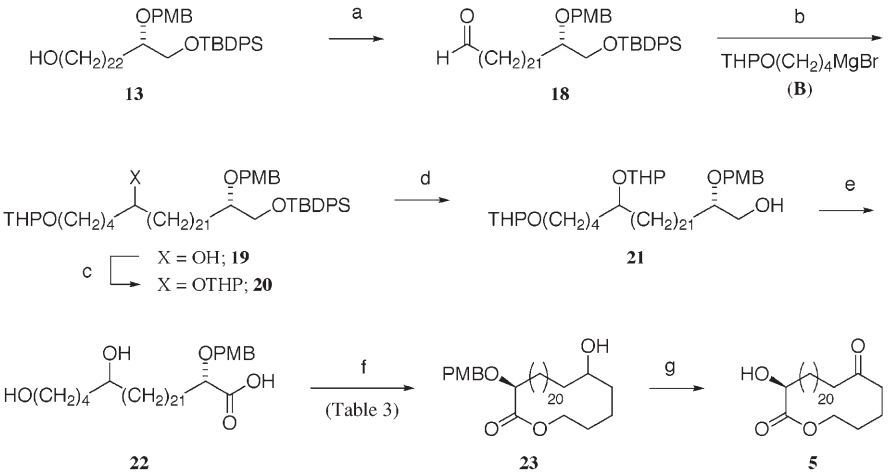


Entry	Catalyst ([equiv])	Cobase ([equiv])	*T* [°C]	Yield [%]
1	DMAP (0.2)	Et_3N (3.0)	50	64
2	DMAP (3.0)	none	50	69
3	DMAPO (0.2)	Et_3N (3.0)	RT	29
4	DMAPO (0.2)	Et_3N (3.0)	50	77
5	DMAPO (3.0)	none	50	38

On the other hand, when DMAPO was employed together with MNBA at room temperature, the yield of the desired monomeric lactone **23** decreased to only 29% (Table 3, entry 3). Although the stoichiometric use of DMAPO without triethylamine at 50°C gave a significantly lower yield (38%; Table 3, entry 5), the yield of the 29-membered lactone **23** increased remarkably to 77% when the same reaction was carried out at 50°C in the presence of a catalytic amount of DMAPO with 3.0 equivalents of triethylamine (Table 3, entry 4).

As a conclusion concerning the lactonization of **22**, it was revealed that the use of MNBA with either a stoichiometric amount of DMAP or a catalytic amount of DMAPO at 50°C is the most effective combination to afford the desired 29-membered lactone **23** (Table 3, entries 2 and 4). These conditions, suitable for the production of the giant lactone **23**, are similar to the best reaction conditions for the synthesis of the 25-membered lactone **17** (see Tables 2 and 3).

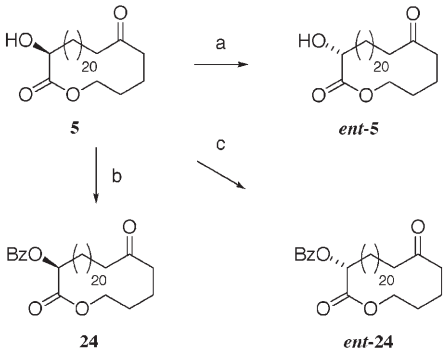
To compare the efficiency of this procedure for the key lactonization to form the 29-membered ring to that of the other generally effective protocols, two additional lactonizations were carried out. When the *S*-pyridyl ester method was applied to the cyclization of the *seco*-acid **22** with $(PyS)_2$ and Ph_3P followed by slow addition to gently refluxing toluene over 12 h under the standard reaction conditions (2.0 mM),[10] the desired lactone **23** was prepared in low yield (35%). Furthermore, Yamagu-



Scheme 4. Synthesis of **5**. Reagents and conditions: a) PCC, CH_2Cl_2, room temperature (85%); b) **B**, THF, 0°C (81%); c) DHP, TsOH, CH_2Cl_2, room temperature (86%); d) TBAF, AcOH, THF, room temperature (96%); e) i) TEMPO, $NaClO_2$, NaOCl, MeCN, CH_2Cl_2, 35°C; ii) 1M HCl, THF, room temperature (56%, 2 steps); f) MNBA, DMAPO, Et_3N, CH_2Cl_2/THF, 50°C (77%); g) i) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2, 0°C (94%); ii) DDQ, CH_2Cl_2/H_2O, room temperature (80%). DHP = 3,4-dihydro-2*H*-pyran, NMO = *N*-methylmorpholine *N*-oxide, PCC = pyridinium chlorochromate, THP = 2-tetrahydropyranyl, TPAP = tetra-*n*-propylammonium perruthenate, Ts = *p*-toluenesulfonyl.

chi lactonization also afforded lactone **23** in 29% yield through the generation of the mixed anhydride by using 2,4,6-trichlorobenzoyl chloride with triethylamine, although favorable conditions were employed for the ring-closing reaction of the mixed anhydride by slow addition to a solution of DMAP (3.0 equivalents) in gently refluxing toluene over 12 h under high dilution (2.0 mM).[11]

The facile oxidation of **23** with TPAP/NMO was then carried out to produce a keto lactone, which was in turn converted into the final target lactone (−)-**5** by removal of the PMB group with DDQ/H_2O. All spectral data, including the ^1H and ^{13}C NMR chemical shifts and IR and mass spectra of synthetic (−)-**5**, correspond to those of the natural 29-membered lactone.[5] The (−)-**5** produced was further converted into its benzoate **24** to determine the optical purity (Scheme 5). Mitsunobu inversion of (−)-**5** with benzoic acid



Scheme 5. Synthesis of *ent*-**5**. Reagents and conditions: a) i) 3,5-dinitrobenzoic acid, DIAD, Ph_3P, THF, room temperature (71%); ii) Et_3N, MeOH, room temperature (96%); b) Bz_2O, DMAP, CH_2Cl_2, room temperature (quant.); c) BzOH, DEAD, Ph_3P, THF, room temperature (quant.). Bz = benzoyl, DEAD = diethyl azodicarboxylate.

in the presence of DEAD and Ph_3P produced the corresponding antipode ester *ent*-**24** in good yield. HPLC analysis of the pair of enantiomers (**24** and *ent*-**24**) showed that these esters have very high enantiopurity (>99% *ee*). This result reveals that synthetic **5** and all of the other intermediates described in Scheme 3 have very high optical purities. Furthermore, (+)-**5**, an enantiomer of (−)-**5**, was also produced by Mitsunobu inversion at the C2 position, followed by selective cleavage of the 3,5-dinitrobenzoate group (Scheme 5).

Conclusions

The substituted benzoic anhydride method was successfully applied to the formation of the 25- and 29-membered lactones **17** and **23** in good yields under mild reaction conditions. The combination of MNBA, a powerful dehydrating reagent, with DMAP or DMAPO, a novel nucleophilic catalyst, functions as a very effective promoter for the intramolecular dehydration condensation that creates the giant cyclic cores of **3** and **5**. On the basis of these total syntheses, the structures of the basic skeletons of **3** and **5** proposed by Prestwich et al.[4] and Braekman and co-workers[5] were unambiguously confirmed. Further investigations into the absolute stereochemistry of the natural macrocyclic molecules are now in progress in this laboratory.

Experimental Section

General Methods

All reactions were carried out under argon atmosphere in dried glassware, unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide then calcium hydride and dried over 4-Å molecular sieves, benzene, toluene, and DMF were distilled from diphosphorus pentoxide and dried over 4-Å molecular sieves, and THF was distilled from sodium/benzophenone immediately prior to use.

Column chromatography was performed on silica gel 60 (Merck) or Wakogel B5F. Thin-layer chromatography was performed on Wakogel B5F. ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS), chloroform (in [D]chloroform), or benzene (in [D_6]benzene) as internal standard.

Starting materials

All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc., or Aldrich Chemical Co., Inc. and used without further purification, unless otherwise noted. MNBA was purchased from Tokyo Kasei Kogyo Co., Ltd. (TCI, M1439).

Syntheses

(*S*)-(−)-1,2,4-Butanetriol:[8] Trimethylborate (12.5 mL, 110 mmol) and THF (25 mL) were added to a solution of borane–dimethylsulfide complex (11.4 mL, 120 mmol) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, and then (*S*)-malic acid (**6**; 5.00 g, 37.3 mmol) was added. After the reaction mixture had been stirred for 23 h at room temperature, methanol was added at 0 °C. The solvent was removed by evaporation, and then the residue was filtered through a short pad of silica gel (dichloromethane/methanol = 4:1). The filtrate was concentrated, and the residue was filtered again through a short pad of absorbent cotton (dichloromethane/methanol = 9:1). Evaporation of the solvent gave (*S*)-(−)-1,2,4-butanetriol (3.84 g, 97%) as a colorless oil. The crude product was instantly used in the following reaction without further purification.

(2*S*)-2,4-[(*S*)-*p*-Methoxybenzylidenedioxy]butanol:[8] Camphorsulfonic acid (CSA; 799 mg, 3.44 mmol) was added to a solution of (*S*)-(−)-1,2,4-butanetriol (3.64 g, 34.3 mmol) and *p*-methoxybenzaldehyde dimethylacetal (11.6 mL, 68.1 mmol) in dichloromethane (36.4 mL) at room temperature. After the reaction mixture had been stirred for 19 h at room temperature, triethylamine was added. The mixture was concentrated by evaporation of the solvent, and then the crude product was purified by column chromatography (hexane/ethyl acetate = 1:1) to afford (2*S*)-2,4-[(*S*)-*p*-methoxybenzylidenedioxy]butanol (6.25 g, 81%) as a colorless oil: ^1H NMR (C_6D_6): δ = 7.56 (ddd, J = 9.0, 3.0, 2.5 Hz, 2H, PMP), 6.82 (ddd, J = 9.0, 3.0, 2.5 Hz, 2H, PMP), 5.32 (s, 1H, CHPMP), 3.94 (ddd, J = 12.0, 5.0, 1.0 Hz, 1H, 4-H), 3.58 (dddd, J = 12.5, 6.0, 4.0, 2.5 Hz, 1H, 2-H), 3.49 (ddd, J = 12.0, 11.5, 3.0 Hz, 1H, 4-H), 3.48 (dd, J = 11.5, 6.0 Hz, 1H, 1-H), 3.44 (dd, J = 11.5, 4.0 Hz, 1H, 1-H), 3.29 (s, 3H, OMe), 2.21 (br s, 1H, OH), 1.62 (dddd, J = 13.0, 12.5, 11.5, 5.0 Hz, 1H, 3-H), 0.85 ppm (dddd, J = 13.0, 3.0, 2.5, 1.0 Hz, 1H, 3-H); HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{16}O_4Na$: 247.0941 [M+Na]$^+$; found: 247.0941.

7:[8] A solution of (2*S*)-2,4-[(*S*)-*p*-methoxybenzylidenedioxy]butanol (754.6 mg, 3.36 mmol) in DMF (6.68 mL) was added to a solution of imidazole (555 mg, 8.15 mmol) and *tert*-butylchlorodiphenylsilane (1.03 mL, 4.01 mmol) in DMF (6.68 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature, and then water was added at 0 °C. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was

purified by column chromatography on silica gel 60N (spherical, neutral, Kanto Chem. Co., Inc.) (hexane/ethyl acetate = 10:1) to afford (2*S*)-1-(*tert*-butyldiphenylsiloxy)-2,4-[(*S*)-*p*-methoxybenzylidenedioxy]butane (**7**; 1.29 g, 83%) as a colorless oil. ^{1}H NMR (C_6D_6): δ = 7.84–7.80 (m, 4H, TBDPS), 7.68 (ddd, *J* = 9.0, 3.2, 2.1 Hz, 2H, PMP), 7.24–7.19 (m, 6H, TBDPS), 6.82 (ddd, *J* = 9.0, 3.2, 2.1 Hz, 2H, PMP), 5.39 (s, 1H, CHPMP), 3.98 (ddd, *J* = 11.4, 5.4, 1.2 Hz, 1H, 4-H), 3.86 (dd, *J* = 9.9, 5.4 Hz, 1H, 1-H), 3.78 (dddd, *J* = 12.0, 5.4, 4.8, 2.1 Hz, 1H, 2-H), 3.68 (dd, *J* = 9.9, 4.8 Hz, 1H, 1-H), 3.52 (ddd, *J* = 11.4, 11.1, 2.7 Hz, 1H, 4-H), 3.26 (s, 3H, OMe), 1.70 (dddd, *J* = 12.3, 12.0, 11.1, 5.4 Hz, 1H, 3-H), 1.18 (s, 9H, TBDPS), 1.13 ppm (dddd, *J* = 12.3, 2.7, 2.1, 1.2 Hz, 1H, 3-H); HRMS (ESI-TOF): *m*/*z* calcd for $C_{28}H_{34}O_4SiNa$: 485.2119 $[M+Na]^+$; found: 485.2124.

8:[8] A solution of DIBAL in dichloromethane (1.0 M, 75.7 mL, 75.7 mmol) was added to a solution of **7** (7.05 g, 15.2 mmol) in dichloromethane (75.7 mL) at −78 °C. After the reaction mixture had been stirred for 4.5 h at −78 °C, methanol was added. The mixture was allowed to warm to room temperature, and then saturated aqueous potassium sodium tartrate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 2:1) to afford (3*S*)-4-(*tert*-butyldiphenylsiloxy)-3-(*p*-methoxybenzyloxy)butanol (**8**; 6.46 g, 92%) as a colorless oil. $[\alpha]_D^{23}$ = −30.4 (*c* 1.03, benzene); IR (neat): $\tilde{\nu}$ = 3436 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.71–7.66 (m, 4H, TBDPS), 7.48–7.36 (m, 6H, TBDPS), 7.23 (d, *J* = 8.4 Hz, 2H, PMP), 6.88 = (d, *J* = 8.6 Hz, 2H, PMP), 4.66 (d, *J* = 11.3 Hz, 1H, PMB), 4.44 (d, *J* = 11.3 Hz, 1H, PMB), 3.80 (s, 3H, OMe), 3.78–3.65 (m, 5H, 1-H, 3-H, 4-H), 2.41 (br s, 1H, OH), 1.92–1.71 (m, 2H, 2-H), 1.08 ppm (s, 9H, TBDPS); ^{13}C NMR ($CDCl_3$): δ = 159.2 (PMP), 135.6 (Ar), 135.6 (Ar), 133.3 (Ar), 133.2 (Ar), 130.4 (Ar), 129.8 (Ar), 129.5 (Ar), 129.4 (Ar), 127.7 (Ar), 127.7 (Ar), 113.8 (PMP), 78.4 (C3), 71.8 (PMB), 65.9 (C4), 60.5 (C1), 55.3 (OMe), 34.1 (C2), 26.8 (TBDPS), 19.2 ppm (TBDPS); HRMS (ESI TOF): *m*/*z* calcd for $C_{28}H_{36}O_4SiNa$: 487.2275 $[M+Na]^+$; found: 487.2293.

9: Iodine (6.07 g, 24.0 mmol) was added to a solution of **8** (5.56 g, 12.0 mmol), imidazole (2.05 g, 30.1 mmol), and triphenylphosphine (7.88 g, 30.1 mmol) in benzene (60 mL) at 0 °C. The reaction mixture was stirred for 5 h at room temperature, and then saturated aqueous sodium thiosulfate was added. The mixture was extracted with diethyl ether, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to afford (2*S*)-1-(*tert*-butyldiphenylsiloxy)-4-iodo-2-(*p*-methoxybenzyloxy)butane (**9**; 6.66 g, 96%) as a colorless oil. $[\alpha]_D^{21}$ = −10.0 (*c* 0.313, benzene); IR (neat): $\tilde{\nu}$ = 3071, 2928, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.68–7.63 (m, 4H, TBDPS), 7.46–7.34 (m, 6H, TBDPS), 7.25–7.23 (m, 2H, PMP), 6.87–6.84 (m, 2H, PMP), 4.57 (d, *J* = 9.7 Hz, 1H, PMB), 4.39 (d, *J* = 9.7 Hz, 1H, PMB), 3.86–3.75 (m, 1H, 1-H), 3.81 (s, 3H, OMe), 3.79–3.54 (m, 1H, 2-H), 3.72 (dd, *J* = 9.3, 4.6 Hz, 1H, 1-H), 3.35 (dd, *J* = 9.5, 4.9 Hz, 1H, 4-H), 3.31 (dd, *J* = 7.7, 3.9 Hz, 1H, 4-H), 1.96–1.71 (m, 2H, 3-H), 1.05 ppm (s, 9H, TBDPS); ^{13}C NMR ($CDCl_3$): δ = 159.2 (PMP), 135.6 (Ar), 135.6 (Ar), 133.3 (Ar), 133.3 (Ar), 130.6 (Ar), 129.7 (Ar), 129.5 (Ar), 129.4 (Ar), 127.7 (Ar), 127.7 (Ar), 113.8 (PMP), 78.4 (C2), 71.8 (PMB), 65.9 (C1), 55.3 (OMe), 34.1 (C3), 26.8 (TBDPS), 19.2 (TBDPS), 3.34 ppm (C4); HRMS (FAB): *m*/*z* calcd for $C_{28}H_{35}O_3ISi$: 574.1400 $[M+H]^+$; found: 574.1298.

10: A solution of **9** (100 mg, 0.179 mmol) in THF (5 mL) was added to a solution of copper(I) iodide (3.42 mg, 18.0 μmol) and 2,2′-bipyridyl (2.81 mg, 18.0 μmol) in THF (1 mL) at room temperature. After the reaction mixture had been stirred for 5 min at room temperature, a solution of Grignard reagent **A** (0.90 M, 0.70 mL, 0.63 mmol) was added at −20 °C. The reaction mixture was stirred for 1 h at room temperature, and then saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 20:1) to afford (2*S*)-14-(*tert*-butyldimethylsiloxy)-1-(*tert*-butyldiphenylsiloxy)-2-(*p*-methoxybenzyloxy)tetradecane (**10**; 116.1 mg, 90%) as a colorless oil. $[\alpha]_D^{23}$ = −14.5 (*c* 0.800, benzene); IR (neat): $\tilde{\nu}$ = 3071, 2928, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.70–7.67 (m, 4H, TBDPS), 7.45–7.34 (m, 6H, TBDPS), 7.23 (d, *J* = 8.9 Hz, 2H, PMP), 6.85 (d, *J* = 8.9 Hz, 2H, PMP), 4.60 (d, *J* = 11.3 Hz, 1H, PMB), 4.44 (d, *J* = 11.1 Hz, 1H, PMB), 3.80 (s, 3H, OMe), 3.73 (dd, *J* = 10.5, 5.7 Hz, 1H, 1-H), 3.65–3.53 (m, 1H, 1-H), 3.60 (t, *J* = 4.1 Hz, 2H, 14-H), 3.50–3.42 (m, 1H, 2-H), 1.56–1.48 (m, 5H), 1.39–1.12 (m, 17H), 1.06 (s, 9H, TBDPS), 0.90 (s, 9H, TBS), 0.05 ppm (s, 6H, TBS); ^{13}C NMR ($CDCl_3$): δ = 160.9 (PMP), 135.6 (Ar), 133.7 (Ar), 131.0 (Ar), 129.6 (Ar), 129.3 (Ar), 127.6 (Ar), 113.7 (PMP), 79.5 (C2), 71.8 (PMB), 66.0 (C1), 63.4 (C14), 55.3 (OMe), 32.9 (C13), 31.7 (C3), 29.6 and 29.5 (C5–C11), 26.8 (TBDPS), 26.0 (TBS), 25.8 (C12), 25.3 (C4), 19.5 (TBDPS), 18.4 (TBS), −5.3 ppm (TBS); HRMS (FAB): *m*/*z* calcd for $C_{44}H_{70}O_4Si_2$: 718.4813 $[M+H]^+$; found: 718.4709.

(13*S*)-14-(*tert*-Butyldiphenylsiloxy)-13-(*p*-methoxybenzyloxy)tetradecanol: Hydrochloric acid (1 M, 60 mL) was added to a solution of **10** (868 mg, 1.21 mmol) in THF (120 mL) at 0 °C. The reaction mixture was stirred for 6 h at room temperature, and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 3:1) to afford (13*S*)-14-(*tert*-butyldiphenylsiloxy)-13-(*p*-methoxybenzyloxy)tetradecanol (710 mg, 96%) as a colorless oil. $[\alpha]_D^{23}$ = −16.5 (*c* 1.00, benzene); IR (neat): $\tilde{\nu}$ = 3374 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.72–7.64 (m, 4H, TBDPS), 7.40–7.32 (m, 6H, TBDPS), 7.26–7.17 (m, 2H, PMP), 6.87–6.81 (m, 2H, PMP), 4.60 (d, *J* = 11.3 Hz, 1H, PMB), 4.44 (d, *J* = 11.1 Hz, 1H, PMB), 3.80 (s, 3H, OMe), 3.73 (dd, *J* = 10.5, 5.9 Hz, 1H, 1-H), 3.68–3.60 (m, 3H, 1-H, 14-H), 3.53–3.43 (m, 1H, 2-H), 1.66–1.18 (m, 23H), 1.11 ppm (s, 9H, TBDPS); ^{13}C NMR ($CDCl_3$): δ = 160.9 (PMP), 135.6 (Ar), 133.7 (Ar), 131.0 (Ar), 129.6 (Ar), 129.3 (Ar), 127.6 (Ar), 113.7 (PMP), 79.5 (C2), 71.8 (PMB), 66.0 (C1), 63.1 (C14), 55.3 (OMe), 32.8 (C13), 31.7 (C3), [29.7, 29.6, and 29.4] (C5–C11), 26.8 (TBDPS), 25.7 (C12), 25.4 (C4), 19.4 ppm (TBDPS); HRMS (FAB): *m*/*z* calcd for $C_{38}H_{56}O_4Si$: 604.3948 $[M+H]^+$; found: 604.3848.

11: Iodine (595 mg, 2.35 mmol) was added to a solution of (13*S*)-14-(*tert*-butyldiphenylsiloxy)-13-(*p*-methoxybenzyloxy)tetradecanol (710 mg, 1.17 mmol), imidazole (200 mg, 2.93 mmol), and triphenylphosphine (770 mg, 2.93 mmol) in benzene (9.4 mL) at 0 °C. The reaction mixture was stirred for 30 min at room temperature, and then saturated aqueous sodium thiosulfate was added. The mixture was extracted with diethyl ether, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 30:1) to afford (2*S*)-1-(*tert*-butyldiphenylsiloxy)-14-iodo-2-(*p*-methoxybenzyloxy)tetradecane (**11**; 770 mg, 92%) as a colorless oil. $[\alpha]_D^{21}$ = −6.61 (*c* 0.947, benzene); IR (neat): $\tilde{\nu}$ = 3070, 3048, 2998, 2927, 2854 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.71–7.63 (m, 4H, TBDPS), 7.46–7.33 (m, 6H, TBDPS), 7.26–7.23 (m, 2H, PMP), 6.88–6.84 (m, 2H, PMP), 4.61 (d, *J* = 11.3 Hz, 1H, PMB), 4.44 (d, *J* = 11.1 Hz, 1H, PMB), 3.80 (s, 3H, OMe), 3.73 (dd, *J* = 10.5, 5.9 Hz, 1H, 1-H), 3.63 (dd, *J* = 10.5, 4.6 Hz, 1H, 1-H), 3.53–3.43 (m, 1H, 2-H), 3.19 (t, *J* = 7.0 Hz, 2H, 14-H), 1.82 (dt, *J* = 7.0, 5.9 Hz, 2H, 3-H), 1.60–1.18 (m, 20H), 1.07 ppm (s, 9H, TBS); ^{13}C NMR ($CDCl_3$): δ = 160.9 (PMP), 135.6 (Ar), 133.6 (Ar), 131.2 (Ar), 129.6 (Ar), 129.3 (Ar), 127.6 (Ar), 113.6 (PMP), 79.4 (C2), 71.8 (PMB), 66.4 (C1), 55.3 (OMe), 33.6 (C13), 31.6 (C3), 30.5 (C12), [29.7, 29.6, and 29.4] (C5–C10), 28.5 (C11), 26.8 (TBDPS), 25.4 (C4), 19.2 (TBDPS), 7.4 ppm (C14); HRMS (FAB): *m*/*z* calcd for $C_{38}H_{55}O_3Si$: 714.2965 $[M+H]^+$; found: 714.2864.

12: A solution of **11** (3.57 g, 5.00 mmol) in THF (10 mL) was added to a solution of copper(I) iodide (285 mg, 1.50 mmol) and 2,2′-bipyridyl (235 mg, 1.50 mmol) in THF (1.1 mL) at room temperature. After the reaction mixture had been stirred for 5 min at room temperature, a solution of Grignard reagent **A** (0.555 M, 18.4 mL, 10.2 mmol) was added at −17 °C. The reaction mixture was stirred for 1 h at room temperature, and then saturated aqueous ammonium chloride was added. The mixture was filtered through a short pad of celite, and the filtrate was extracted

with diethyl ether. The organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 10:1) to afford (2*S*)-24-(*tert*-butyldimethylsiloxy)-1-(*tert*-butyldiphenylsiloxy)-2-(*p*-methoxybenzyloxy)tetracosane (**12**; 4.10 g, 96%) as a colorless oil. $[\alpha]_D^{21} = -12.1$ (*c* 1.01, benzene); IR (neat): $\tilde{\nu} = 3071$, 3049, 2999, 2926, 2854 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.72$–7.65 (m, 4H, TBDPS), 7.46–7.35 (m, 6H, TBDPS), 7.26–7.23 (m, 2H, PMP), 6.88–6.84 (m, 2H, PMP), 4.61 (d, $J = 11.3$ Hz, 1H, PMB), 4.45 (d, $J = 11.3$ Hz, 1H, PMB), 3.81 (s, 3H, OMe), 3.74 (dd, $J = 10.5$, 5.9 Hz, 1H, 1-H), 3.63 (dd, $J = 10.5$, 4.6 Hz, 1H, 1-H), 3.61 (t, $J = 6.8$ Hz, 2H, 24-H), 3.54–3.43 (m, 1H, 2-H), 1.63–1.49 (m, 4H), 1.37–1.19 (m, 38H), 1.08 (s, 9H, TBDPS), 0.91 (s, 9H, TBS), 0.06 ppm (s, 6H, TBS); ^{13}C NMR ($CDCl_3$): $\delta = 159.0$ (PMP), 135.6 (Ar), 133.6 (Ar), 131.2 (Ar), 129.6 (Ar), 129.3 (Ar), 127.6 (Ar), 113.6 (PMP), 79.4 (C2), 71.8 (PMB), 66.3 (C1), 63.3 (C24), 55.2 (OMe), 32.8 (C23), 31.6 (C3), [29.7, 29.6, and 29.4] (C5–C21), 26.8 (TBDPS), 26.0 (TBS), 25.8 (C22), 25.4 (C4), 19.2 (TBDPS), 18.4 (TBS), −5.3 ppm (TBS); HRMS (ESI-TOF): *m*/*z* calcd for $C_{54}H_{90}O_4Si_2Na$: 881.6270 $[M+Na]^+$; found: 881.6249.

13: Hydrochloric acid (1 M, 14.8 mL) was added to a solution of **12** (254 mg, 0.296 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred for 6 h at room temperature, and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 5:1) to afford (23*S*)-24-(*tert*-butyldiphenylsiloxy)-23-(*p*-methoxybenzyloxy)tetradecanol (**13**; 216 mg, 99%) as a colorless oil. $[\alpha]_D^{27} = -9.90$ (*c* 1.03, benzene); IR (neat): $\tilde{\nu} = 3357$ cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.75$–7.72 (m, 4H, TBDPS), 7.51–7.35 (m, 6H, TBDPS), 7.29–7.26 (m, 2H, PMP), 6.90–6.87 (m, 2H, PMP), 4.64 (d, $J = 11.3$ Hz, 1H, PMB), 4.48 (d, $J = 11.3$ Hz, 1H, PMB), 3.82 (s, 3H, OMe), 3.81–3.61 (m, 2H, 1-H), 3.65 (t, $J = 6.6$ Hz, 2H, 24-H), 3.56–3.46 (m, 1H, 2-H), 1.65–1.18 (m, 42H), 1.11 ppm (s, 9H, TBDPS); ^{13}C NMR ($CDCl_3$): $\delta =$ 159.0 (PMP), 135.6 (Ar), 133.6 (Ar), 131.1 (Ar), 129.6 (Ar), 129.3 (Ar), 127.6 (Ar), 113.6 (PMP), 79.4 (C2), 71.7 (PMB), 66.3 (C1), 63.0 (C24), 55.2 (OMe), 32.7 (C23), 31.6 (C3), [29.7, 29.6, and 29.4] (C5–C21), 26.8 (TBDPS), 25.7 (C22), 25.3 (C4), 19.2 ppm (TBDPS); HRMS (ESI-TOF): *m*/*z* calcd for $C_{48}H_{76}O_4SiNa$: 767.5405 $[M+Na]^+$; found: 767.5406.

14: Acetic anhydride (0.300 mL, 3.22 mmol) was added to a solution of **13** (1.20 g, 1.61 mmol) and DMAP (39.9 mg, 0.327 mmol) in pyridine (16 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous copper sulfate, water, saturated aqueous sodium hydrogencarbonate, and brine. The organic layer was dried over sodium sulfate and then filtered. After evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to afford (23*S*)-24-(*tert*-butyldiphenylsiloxy)-23-(*p*-methoxybenzyloxy)tetracosyl acetate (**14**; 1.23 g, 97%) as a colorless oil. $[\alpha]_D^{22} = -14.0$ (*c* 1.04, benzene); IR (neat): $\tilde{\nu} = 2925$, 2853, 1741, 1614, 1514, 1465, 1363, 1246, 1112, 1037 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.71$–7.67 (m, 4H), 7.44–7.25 (m, 6H), 7.23 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 4.61 (d, $J = 11.4$ Hz, 1H), 4.45 (d, $J = 11.4$ Hz, 1H), 4.06 (t, $J =$ 6.8 Hz, 2H, 24-H), 3.79 (s, 3H), 3.74 (dd, $J = 10.4$, 5.8 Hz, 1H, 1-H), 3.64 (dd, $J = 10.4$, 4.8 Hz, 1H, 1-H), 3.51–3.45 (m, 1H, 2-H), 2.04 (s, 3H), 1.66–1.44 (m, 3H), 1.36–1.24 (m, 39H), 1.06 ppm (s, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 171.1$ (Ac), 159.0 (PMB), 135.6 (Ar), 135.5 (Ar), 133.6 (Ar), 133.6 (Ar), 131.2 (Ar), 129.5 (Ar), 129.3 (Ar), 127.6 (Ar), 113.6 (PMB), 79.4 (C2), 71.7 (PMB), 66.3 (C1), 64.6 (C24), 55.2 (OMe), 31.6 (C3), [29.7, 29.6, 29.5, and 29.2] (C5–C21), 26.8 (TBDPS), 25.9 (C22), 25.3 (C4), 20.9 (C23), 19.2 ppm (TBDPS); HRMS (ESI-TOF): *m*/*z* calcd for $C_{50}H_{78}O_5SiNa$: 809.5516 $[M+Na]^+$; found: 809.5511.

15: Acetic acid (0.270 mL, 4.65 mmol) and a solution of TBAF in THF (1.0 M, 4.70 mL, 4.70 mmol) were added to a solution of **14** (1.22 g, 1.55 mmol) in THF (15.5 mL) at 0 °C. After the reaction mixture had been stirred for 41 h at room temperature, saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 4:1) to afford (23*S*)-24-hydroxy-23-(*p*-methoxybenzyloxy)tetracosyl acetate (**15**; 851 mg, quant.) as a white solid. M.p.: 66–67 °C (hexane); $[\alpha]_D^{23} = +6.92$ (*c* 1.00, benzene); IR (KBr): $\tilde{\nu} = 3444$, 2917, 2850, 1730, 1615, 1517, 1472, 1250, 1180, 1104, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.27$ (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 4.56 (d, $J =$ 11.2 Hz, 1H), 4.48 (d, $J = 11.2$ Hz, 1H), 4.06 (t, $J = 6.8$ Hz, 2H, 24-H), 3.80 (s, 3H), 3.67 (br d, $J = 10.0$ Hz, 1H, 1-H), 3.54–3.45 (m, 2H, 1-H, 2-H), 2.04 (s, 3H), 1.66–1.57 (m, 3H), 1.36–1.22 ppm (m, 39H); ^{13}C NMR ($CDCl_3$): $\delta = 171.1$ (Ac), 159.2 (PMB), 130.6 (PMB), 129.3 (PMB), 113.6 (PMB), 79.5 (C2), 71.1 (PMB), 64.6 (C1), 64.2 (C24), 55.2 (OMe), 30.8 (C3), [29.6, 29.5, 29.4, 29.2, and 28.5] (C5–C21), 25.8 (C22), 25.3 (C4), 20.9 ppm (C23); HRMS (ESI-TOF): *m*/*z* calcd for $C_{34}H_{60}O_5Na$: 571.4338 $[M+Na]^+$; found: 571.4333.

(2*S*)-24-Acetoxy-2-(*p*-methoxybenzyloxy)tetradecanoic acid: TEMPO (2.8 mg, 18 μmol) and phosphate buffer (pH 7, 0.49 mL) were added to a solution of **15** (71.2 mg, 0.130 mmol) in acetonitrile (1.30 mL) at room temperature. After the reaction mixture had been warmed to 35 °C, a solution of sodium chlorite in water (2.0 M, 0.260 mL, 0.520 mmol) and a solution of sodium hypochlorite in water (available chlorine > 0.25%, 68.0 μL, 5.19 μmol) and THF (0.500 mL) were added. The mixture was stirred for 2.5 h at 35 °C, and then water (0.97 mL) was added at room temperature. A solution of 6% sodium sulfite in water was added to the reaction mixture at 0 °C, and the solution was acidified to pH 6 by addition of 1 M hydrochloric acid. The mixture was extracted with diethyl ether, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (chloroform/methanol = 10:1) to give (2*S*)-24-acetoxy-2-(*p*-methoxybenzyloxy)tetradecanoic acid (64.5 mg, 88%) as a colorless solid. M.p.: 70–72 °C (hexane); $[\alpha]_D^{23} = -23.7$ (*c* 0.99, benzene); IR (KBr): $\tilde{\nu} = 2919$, 2849, 1747, 1731, 1613, 1516, 1472, 1250, 1174, 1093, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.25$ (d, $J = 7.6$ Hz, 2H), 6.89 (d, $J = 7.6$ Hz, 2H), 4.62 (br s, 1H), 4.40 (br s, 1H), 4.05 (t, $J = 6.8$ Hz, 2H, 24-H), 3.91 (br s, 1H), 3.78 (s, 3H), 2.04 (s, 3H), 1.73 (br s, 1H), 1.61 (dt, $J = 6.8$, 6.8 Hz, 2H), 1.35–1.22 ppm (m, 39H); ^{13}C NMR ($CDCl_3$): $\delta = 177.6$ (C1), 171.3 (Ac), 159.4 (PMB), 129.7 (PMB), 129.3 (PMB), 113.8 (PMB), 79.5 (C2), 71.1 (PMB), 64.7 (C24), 55.2 (OMe), 32.6 (C3), [29.7, 29.6, 29.5, 29.3, 29.2, and 28.6] (C5–C21), 25.9 (C22), 25.1 (C4), 20.9 ppm (C23); HRMS (ESI-TOF): *m*/*z* calcd for $C_{34}H_{58}O_6Na$: 585.4131 $[M+Na]^+$; found: 585.4127.

16: Potassium carbonate (32.7 mg, 0.237 mmol) was added to a solution of (2*S*)-24-acetoxy-2-(*p*-methoxybenzyloxy)tetradecanoic acid (64.5 mg, 0.115 mmol) in MeOH (1.6 mL) at 0 °C. The reaction mixture was stirred for 20 h at room temperature and then stirred for 22 h at 40 °C. The solution was acidified to pH 6 by addition of 1 M hydrochloric acid, the mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (chloroform/methanol = 9:1) to afford (2*S*)-24-hydroxy-2-(*p*-methoxybenzyloxy)tetradecanoic acid (**16**; 51.9 mg, 87%) as a white solid. M.p.: 81–82 °C (hexane/benzene); $[\alpha]_D^{24} = -36.0$ (*c* 0.99, EtOH); IR (KBr): $\tilde{\nu} = 3370$, 2915, 2849, 1731, 1612, 1585, 1514, 1468, 1303, 1249, 1176, 1097, 1033 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.25$ (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 4.62 (d, $J = 11.6$ Hz, 1H), 4.37 (d, $J = 11.6$ Hz, 1H), 3.91 (t, $J = 6.4$ Hz, 1H, 2-H), 3.77 (s, 3H), 3.61 (t, $J = 6.8$ Hz, 2H, 24-H), 2.04 (s, 3H), 1.74 (dt, $J = 7.2$, 6.4 Hz, 2H, 3-H), 1.54 (dt, $J = 6.8$, 6.8 Hz, 2H), 1.42–1.23 ppm (m, 38H); ^{13}C NMR ($CDCl_3$): $\delta = 176.9$ (C1), 159.5 (PMB), 129.7 (PMB), 129.3 (PMB), 113.8 (PMB), 77.3 (C2), 72.0 (PMB), 63.0 (C24), 55.2 (OMe), 32.6 (C3), 32.6 (C23), [29.6, 29.5, 29.4, and 29.2] (C5–C21), 25.6 (C22), 25.1 ppm (C4); HRMS (ESI-TOF): *m*/*z* calcd for $C_{32}H_{56}O_5Na$: 543.4025 $[M+Na]^+$; found: 543.4031.

17: A solution of **16** (86.7 mg, 1.67 mmol) in THF (48 mL) was slowly added to a solution of MNBA (74.6 mg, 0.217 mmol) and DMAP (60.9 mg, 0.499 mmol) in dichloromethane (33 mL) at 50 °C with a mechanically driven syringe over a 12-h period. After the reaction mixture

had been stirred for 1 h at 50 °C, saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to afford (2*S*)-2-(*p*-methoxybenzyloxy)tetracosanolide (**17**; 72.5 mg, 87 %) as a colorless solid. M.p.: 56–57 °C (methanol); $[\alpha]_D^{23} = -41.5$ (*c* 0.99, benzene); IR (KBr): $\tilde{\nu} = 2922$, 2851, 1736, 1614, 1514, 1475, 1249, 1233, 1146, 1110, 1033 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.28$ (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 4.63 (d, $J = 11.6$ Hz, 1H), 4.34 (d, $J = 11.6$ Hz, 1H), 4.23 (dt, $J = 10.8$, 6.4 Hz, 1H, 24-H), 4.10 (dt, $J = 10.8$, 6.0 Hz, 1H, 24-H), 3.91 (t, $J = 6.4$ Hz, 1H, 2-H), 3.80 (s, 3H), 1.78–1.72 (m, 2H), 1.68–1.61 (m, 2H), 1.39–1.26 ppm (m, 38H); ^{13}C NMR ($CDCl_3$): $\delta = 173.0$ (C1), 159.3 (PMB), 129.8 (PMB), 129.6 (PMB), 113.8 (PMB), 77.8 (C2), 71.7 (PMB), 64.7 (C24), 55.2 (OMe), 33.0 (C3), [29.2, 29.1, 29.0, 29.8, 28.7, 28.6, 28.5, 28.2, 28.1, 28.0, and 27.8] (C5–C22), 26.0 (C23), 24.9 ppm (C4); HRMS (ESI-TOF): *m*/*z* calcd for $C_{32}H_{54}O_4Na$: 525.3920 $[M+Na]^+$; found: 525.3914.

(−)-**3**: DDQ (8.30 mg, 36.6 μmol) was added to a suspension of **17** (16.3 mg, 32.4 μmol) in dichloromethane (0.6 mL) and water (0.06 mL) at 0 °C. The reaction mixture was stirred for 8 h at room temperature, and then phosphate buffer (pH 7) was added. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 5:1) to afford (2*S*)-2-hydroxytetracosanolide ((−)-**3**; 12.3 mg, 99 %) as a white solid. M.p.: 67–68 °C (acetonitrile); $[\alpha]_D^{19} = -11.2$ (*c* 0.93, benzene); IR (KBr): $\tilde{\nu} = 3448$, 3405, 2921, 2852, 1739, 1722, 1463, 1406, 1224, 1141, 1095 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 4.34$ (dt, $J = 10.6$, 7.2 Hz, 1H, 24-H), 4.18 (dd, $J = 5.2$, 5.6 Hz, 1H, 2-H), 4.05 (dt, $J = 10.6$, 5.6 Hz, 1H, 24-H), 2.80 (d, $J = 5.2$ Hz, 1H, OH), 1.82–1.59 (m, 4H), 1.48–1.13 ppm (m, 40H); ^{13}C NMR ($CDCl_3$): $\delta = 175.6$ (C1), 70.4 (C2), 65.7 (C24), 34.3 (C3), [29.3, 29.2, 29.1, 29.0, 28.8, 28.6, 28.5, 28.4, 28.1, 28.0, and 27.8] (C5–C22), 26.0 (C23), 24.3 (C4) ppm; HRMS (ESI-TOF): *m*/*z* calcd for $C_{24}H_{46}O_3Na$: 405.3339 $[M+Na]^+$; found: 405.3337.

3:[4] ^1H NMR ($CDCl_3$): $\delta = 4.31$ (ddd, $J = 5$–6 Hz each, 1H, 24-H), 4.17 (ddd, $J = 4.7$, 5.2, 6.0 Hz, 1H, 2-H), 4.06 (ddd, $J = 5$–6 Hz each, 1H, 24-H), 2.70 (d, $J = 6.0$ Hz, 1H, OH), 1.6–0.9 ppm (m, 46H); ^{13}C NMR ($CDCl_3$): $\delta = 175.7$ (C1), 70.5 (C2), 65.9 (C24), 34.5 (C3), [29.3, 29.1, 28.9, 28.7, 28.6, 28.5, 28.2, and 27.9] (internal methylenes), 26.1 (C4 or C23), 24.5 ppm (C23 or C4).

(2*R*)-2-(3,5-Dinitrobenzoyloxy)tetracosanolide: Diisopropyl azodicarboxylate (15.0 μL, 28.8 μmol) was added to a solution of **3** (5.5 mg, 14 μmol), triphenylphosphine (8.5 mg, 32 μmol), and 3,5-dinitrobenzoic acid (15.1 mg, 71.2 μmol) in THF (0.29 mL) at 0 °C. The reaction mixture was stirred for 22 h at room temperature, and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with hexane, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography twice (benzene/diethyl ether = 20:1 then hexane/ethyl acetate = 5:1) to afford (2*R*)-2-(3,5-dinitrobenzoyloxy)tetracosanolide (5.9 mg, 71 %) as a colorless solid.

(+)-**3**: Triethylamine (7.40 μL, 52.9 μmol) was added to a solution of (2*R*)-2-(3,5-dinitrobenzoyloxy)tetracosanolide (6.10 mg, 10.6 μmol) in methanol (0.1 mL) at room temperature. The reaction mixture was stirred for 30 min at room temperature, and then saturated aqueous sodium hydrogencarbonate was added at room temperature. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 5:1) to afford (2*R*)-2-hydroxytetracosanolide ((+)-**3**; 4.3 mg, 96 %) as a colorless solid. $[\alpha]_D^{21} = +11.3$ (*c* 0.86, benzene).

18: PCC (43.3 mg, 0.201 mmol) was added to a solution of **13** (100 mg, 0.134 mmol) in dichloromethane (1.5 mL). The reaction mixture was stirred for 22 h at room temperature and then diluted with diethyl ether. After filtration of the mixture through a short pad of celite and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 3:1) to afford (23*S*)-24-(*tert*-butyldiphenylsiloxy)-23-(*p*-methoxybenzyloxy)tetradecanal (**18**; 85.0 mg, 85 %) as a colorless oil. $[\alpha]_D^{22} = -14.3$ (*c* 1.03, benzene); IR (neat): $\tilde{\nu} = 1727$ cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 9.76$ (s, 1H, CHO), 7.70–7.67 (m, 4H, TBDPS), 7.45–7.34 (m, 6H, TBDPS), 7.23 (d, $J = 8.7$ Hz, 2H, PMP), 6.85 (d, $J = 9.0$ Hz, 2H, PMP), 4.60 (d, $J = 11.4$ Hz, 1H, PMB), 4.44 (d, $J = 11.4$ Hz, 1H), 3.80 (s, 3H, PMB), 3.73 (dd, $J = 11.9$, 5.9 Hz, 1H, 1-H), 3.62 (dd, $J = 10.8$, 4.8 Hz, 1H, 1-H), 3.50–3.44 (m, 1H, 2-H), 2.42 (dt, $J = 7.4$, 1.8 Hz, 2H, 23-H), 1.65–1.44 (m, 4H, 3-H, 22-H), 1.35–1.18 (m, 38H, 4-H to 21-H), 1.06 ppm (s, 9H, TBDPS); ^{13}C NMR ($CDCl_3$): $\delta = 203.0$ (C24), 159.0 (PMP), 135.6 (Ar), 133.6 (Ar), 131.2 (Ar), 129.6 (Ar), 129.3 (Ar), 127.6 (Ar), 113.6 (PMP), 79.4 (C2), 71.7 (PMB), 66.4 (C1), 55.2 (OMe), 43.9 (C23), 31.6 (C3), [29.70, 29.63, 29.59, 29.41, 29.34, and 29.14] (C5–C21), 26.8 (TBDPS), 25.4 (C4), 22.1 (C22), 19.2 ppm (TBDPS); HRMS (ESI-TOF): *m*/*z* calcd for $C_{48}H_{74}O_4SiNa$: 765.5249 $[M+Na]^+$; found: 765.5270.

19: A solution of Grignard reagent **B** (0.556 M, 3.0 mL, 1.67 mmol) was added to a solution of **18** (565 mg, 0.760 mmol) in THF (2.5 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C, and then saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 10:1) to afford (2*S*)-1-(*tert*-butyldiphenylsiloxy)-2-(*p*-methoxybenzyloxy)-28-(tetrahydro-2*H*-pyran-2-yloxy)octacosan-24-ol (**19**; 557 mg, 81 %) as a colorless oil. IR (neat): $\tilde{\nu} = 3448$ cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.78$–7.64 (m, 4H, TBDPS), 7.47–7.33 (m, 6H, TBDPS), 7.28–7.20 (m, 2H, PMP), 6.89–6.81 (m, 2H, PMP), 4.61 (d, $J = 11.1$ Hz, 1H, PMB), 4.59 (s, 1H, THP), 4.45 (d, $J = 11.1$ Hz, 1H, PMB), 3.93–3.36 (m, 8H, 1-H, 2-H, 24-H, 28-H, THP), 3.80 (s, 3H, OMe), 1.89–1.15 ppm (m, 54H); ^{13}C NMR ($CDCl_3$): $\delta = 159.0$ (PMP), 135.6 (Ar), 133.6 (Ar), 131.2 (Ar), 129.6 (Ar), 129.3 (Ar), 127.6 (Ar), 113.6 (PMP), 98.9 (THP), 79.4 (C2), 71.7 (PMB), 67.5 (C24), 66.4 (C1), 64.3 (C28), 62.3 (THP), 55.2 (OMe), 37.5 (C23), 37.1 (C25), 31.6 (C3), 30.7 (C27), [29.7 and 29.6] (C5–C21), 26.8 (TBDPS), [25.6 and 25.3] (C4 or C26), 22.3 (C22), 19.6 (TBDPS), 19.2 ppm (THP); HRMS (ESI-TOF): *m*/*z* calcd for $C_{57}H_{92}O_6SiNa$: 923.6555 $[M+Na]^+$; found: 923.6554.

20: *p*-Toluenesulfonic acid monohydrate (32.7 mg, 0.190 mmol) was added to a solution of **19** (1.38 g, 1.53 mmol) and 3,4-dihydro-2*H*-pyran (0.200 mL, 2.19 mmol) in dichloromethane (6 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 15:1) to afford (2*S*)-1-(*tert*-butyldiphenylsiloxy)-2-(*p*-methoxybenzyloxy)-24,28-di(tetrahydro-2*H*-pyran-2-yloxy)octacosane (**20**; 1.30 g, 86 %) as a colorless oil. IR (neat): $\tilde{\nu} = 3070$, 3044, 2924, 2853 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.71$–7.67 (m, 4H, TBDPS), 7.47–7.35 (m, 6H, TBDPS), 7.26–7.17 (m, 2H, PMP), 6.88–6.80 (m, 2H, PMP), 4.60 (d, $J = 11.1$ Hz, 1H, PMB), 4.58 (s, 1H, THP), 4.44 (d, $J = 11.3$ Hz, 1H, PMB), 3.92–3.32 (m, 8H, 1-H, 2-H, 24-H, 28-H, THP), 3.80 (s, 3H, OMe), 1.88–1.11 (m, 54H), 1.07 ppm (s, 9H, TBDPS); ^{13}C NMR ($CDCl_3$): $\delta = 158.9$ (PMP), 135.6 (Ar), 133.6 (Ar), 131.1 (Ar), 129.6 (Ar), 129.3 (Ar), 127.6 (Ar), 113.6 (PMP), 100.5 (THP), 95.4 (THP), 79.4 (C2), 71.8 (PMB), 67.5 (C24), 66.4 (C1), 62.7 (C28), 62.2 (THP), 62.1 (THP), 55.3 (OMe), 35.0 (C23), 34.8 (C25), 30.8 (C3), 30.7 (C27), [29.9 and 29.5] (C5–C21), 26.8 (TBDPS), [25.5 and 25.0] (C4 or C26), 22.3 (C22), 20.0 (TBDPS), 19.7 (THP), 19.6 ppm (THP); HRMS (ESI-TOF): *m*/*z* calcd for $C_{62}H_{100}O_7SiNa$: 1007.7131 $[M+Na]^+$; found: 1007.7123.

21: Acetic acid (0.12 mL, 2.10 mmol) and a solution of TBAF in THF (1.0 M, 2.00 mL, 2.00 mmol) were added to a solution of **20** (655 mg, 0.664 mmol) in THF (7.2 mL) at 0 °C. After the reaction mixture had been stirred for 22.5 h at room temperature, saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine and dried

over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/ethyl acetate = 3:1) to afford (2*S*)-2-(*p*-methoxybenzyloxy)-24,28-di(tetrahydro-2*H*-pyran-2-yloxy)octacosanol (**21**; 474 mg, 96%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3466 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.27 (d, J = 8.4 Hz, 2H, PMP), 6.91–6.86 (m, 2H, PMP), 4.67–4.62 (m, 1H, THP), 4.60–4.55 (m, 1H, THP), 4.56 (d, J = 11.3 Hz, 1H, PMB), 4.46 (d, J = 11.1 Hz, 1H, PMB), 3.95–3.34 (m, 10H, 1-H, 2-H, 24-H, 28-H, THP), 3.81 (s, 3H, OMe), 1.86–1.38 (m, 20H, 3-H, 23-H, 25-H, 27-H, THP), 1.38–1.16 ppm (m, 40H); ^{13}C NMR ($CDCl_3$): δ = 159.2 (PMP), 130.6 (PMP), 129.3 (PMP), 113.8 (PMP), 98.8 (THP), 97.6 (THP), 79.4 (C2), 71.1 (PMB), 67.5 (C24), 64.3 (C1), 62.7 (C28), 62.3 (THP), 62.2 (THP), 55.3 (OMe), 35.0 (C23), 34.8 (C25), 30.8 (C3), 30.7 (C27), [29.9 and 29.5] (C5–C21), [25.5 and 25.0] (C4 or C26), 22.3 (C22), 20.0 (THP), 19.6 ppm (THP); HRMS (ESI-TOF): m/z calcd for $C_{46}H_{82}O_7Na$: 769.5953 $[M+Na]^+$; found: 769.5953.

(2*S*)-2-(*p*-Methoxybenzyloxy)-24,28-di(tetrahydro-2*H*-pyran-2-yloxy)octacosanoic acid: TEMPO (18.0 mg, 0.110 mmol) and phosphate buffer (pH 7, 2.95 mL) were added to a solution of **21** (588.1 mg, 0.787 mmol) in acetonitrile (3.9 mL) at room temperature. After the reaction mixture had been warmed to 35 °C, a solution of sodium chlorite in water (2.0 M, 1.58 mL, 3.15 mmol) and a solution of sodium hypochlorite in water (available chlorine > 0.25%, 0.414 mL, 31.5 μmol) were added. The mixture was stirred for 8.5 h at 35 °C, and then water (5.9 mL) was added at room temperature. A solution of 6% sodium sulfite in water was added to the reaction mixture at 0 °C, and the solution was acidified to pH 6 by addition of 1 M hydrochloric acid. The mixture was extracted with diethyl ether, and the organic layer was filtered through a short pad of silica (chloroform/methanol = 10:1). Evaporation of the solvent gave (2*S*)-2-(*p*-methoxybenzyloxy)-24,28-di(tetrahydro-2*H*-pyran-2-yloxy)octacosanoic acid (604 mg, quant.) as a colorless oil. The crude product was instantly used in the following reaction without further purification. For the analysis, the carboxylic acid was purified by column chromatography ($CH_2Cl_2 \rightarrow$ 5% MeOH in CH_2Cl_2) on silica gel 60N (spherical, neutral, Kanto Chem. Co., Inc.) to give pure (2*S*)-2-(*p*-methoxybenzyloxy)-24,28-di(tetrahydro-2*H*-pyran-2-yloxy)octacosanoic acid as a colorless oil. IR (neat): $\tilde{\nu}$ = 3446, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.27 (d, J = 8.7 Hz, 2H, PMP), 6.89 (d, J = 8.7 Hz, 2H, PMP), 4.58 (s, 2H, THP), 4.55 (d, J = 11.3 Hz, 1H, PMB), 4.47 (d, J = 11.1 Hz, 1H, PMB), 3.93–3.34 (m, 8H, 2-H, 24-H, 28-H, THP), 3.80 (s, 3H, OMe), 1.95–1.16 ppm (m, 60H); HRMS (ESI-TOF): m/z calcd for $C_{46}H_{80}O_8Na$: 783.5745 $[M+Na]^+$; found: 783.5739.

22: Hydrochloric acid (1 M, 4 mL) was added to a solution of crude (2*S*)-2-(*p*-methoxybenzyloxy)-24,28-di(tetrahydro-2*H*-pyran-2-yloxy)octacosanoic acid (604 mg, 0.793 mmol) in THF (40 mL) at 0 °C. The reaction mixture was stirred for 71 h at room temperature. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (dichloromethane/methanol = 10:1) to afford (2*S*)-24,28-dihydroxy-2-(*p*-methoxybenzyloxy)octacosanoic acid (**22**; 262.3 mg, 56% over 2 steps) as a white solid. M.p.: 62–63 °C; IR (KBr): $\tilde{\nu}$ = 3416, 1716 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.29–7.26 (m, 2H, PMP), 6.92–6.87 (m, 2H, PMP), 4.60 (d, J = 11.4 Hz, 1H, PMB), 4.46 (d, J = 11.4 Hz, 1H, PMB), 3.98 (t, J = 5.9 Hz, 1H, 2-H), 3.81 (s, 3H, OMe), 3.67 (t, J = 6.3 Hz, 2H, 28-H), 3.61 (m, 1H, 24-H), 1.82–1.72 (m, 2H), 1.61–1.25 ppm (m, 48H); ^{13}C NMR ($CDCl_3$): δ = 174.7 (C1), 159.3 (PMP), 129.8 (PMP), 129.0 (PMP), 113.9 (PMP), 72.3 (C2), 72.0 (PMB), 70.0 (C24), 62.8 (C28), 55.3 (OMe), 37.5 (C23), 36.9 (C25), 32.3 (C3), [29.6 and 29.4] (C5–C21), 29.2 (C27), [25.6 and 24.8] (C4 or C26), 21.8 ppm (C22); HRMS (ESI-TOF): m/z calcd for $C_{36}H_{64}O_6Na$: 615.4595 $[M+Na]^+$; found: 615.4597.

23: A solution of **22** (31.8 mg, 53.6 μmol) in THF (16.3 mL) was slowly added to a solution of MNBA (24.8 mg, 72.0 μmol), DMAPO (1.7 mg, 12.3 μmol), and triethylamine (0.02 mL, 0.161 mmol) in dichloromethane (9.6 mL) at 50 °C with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 3:1) to afford (2*S*)-24-hydroxy-2-(*p*-methoxybenzyloxy)octacosanolide (**23**; 23.6 mg, 77%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3446, 1636 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.28 (d, J = 8.5 Hz, 2H, PMP), 6.88 (d, J = 8.5 Hz, 2H, PMP), 4.63 (d, J = 11.0 Hz, 1H, PMB), 4.34 (d, J = 11.0 Hz, 1H, PMB), 4.22–4.18 (m, 1H, 28-H), 4.16–4.09 (m, 1H, 28-H), 3.90 (t, J = 6.5 Hz, 1H, 2-H), 3.80 (s, 3H, OMe), 3.66–3.55 (m, 1H, 24-H), 1.76–1.26 ppm (m, 48H); ^{13}C NMR ($CDCl_3$): δ = 174.0 (C1), 159.3 (PMP), 131.9 (PMP), 129.7 (PMP), 113.7 (PMP), 77.4 (C2), 71.8 (C24), 71.6 (PMB), 64.7 (C28), 55.3 (OMe), 37.3 (C23), 36.8 (C25), 33.0 (C3), [29.4, 29.43, 29.2, 29.1, 29.0, 28.9, 28.9, 28.8, 28.7, 28.6, and 28.6] (C5–C21), 25.4 (C26), 25.3 (C4), 25.0 (C22), 22.1 ppm (C27); HRMS (ESI-TOF): m/z calcd for $C_{36}H_{62}O_5Na$: 597.4489 $[M+Na]^+$; found: 597.4489.

(2*S*)-2-(*p*-Methoxybenzyloxy)-24-oxooctacosanolide: NMO (1.84 mg, 15.7 μmol) was added to a mixture of 4-Å molecular sieves (3.1 mg) and **23** (3.20 mg, 5.57 μmol) in dichloromethane (0.5 mL) at room temperature. After the reaction mixture had been stirred for 5 min at room temperature, TPAP (0.37 mg, 1.05 μmol) was added at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then filtered through a precooled short pad of silica gel (ethyl acetate). After the solvent was evaporated, the crude product was purified by thin-layer chromatography (benzene/diethyl ether = 3:1) to afford (2*S*)-2-(*p*-methoxybenzyloxy)-24-oxooctacosanolide (3.0 mg, 94%) as a colorless oil. $[\alpha]_D^{22} = -34.4$ (*c* 0.753, benzene); IR (neat): $\tilde{\nu}$ = 1737, 1712 cm^{-1}; ^1H NMR ($CDCl_3$): = 7.30–7.26 (m, 2H, PMP), 6.90–6.84 (m, 2H, PMP), 4.62 (d, J = 11.1 Hz, 1H, PMB), 4.33 (d, J = 11.3 Hz, 1H, PMB), 4.20–4.07 (m, 2H, 28-H), 3.89 (t, J = 6.5 Hz, 1H, 2-H), 3.80 (s, 3H, OMe), 2.45 (t, J = 7.0 Hz, 2H, 25-H), 2.38 (t, J = 7.4 Hz, 2H, 23-H), 1.78–1.50 (m, 10H), 1.45–1.18 ppm (m, 34H); ^{13}C NMR ($CDCl_3$): δ = 210.8 (C24), 173.0 (C1), 159.3 (PMP), 132.7 (PMP), 129.7 (PMP), 113.3 (PMP), 71.9 (C2), 64.4 (C28), 55.3 (OMe), 42.8 (C23), 42.0 (C25), 33.0 (C3), [29.3, 29.2, 29.2, 29.1, 29.0, 28.8, 28.7, 28.6, and 28.6] (C5–C21), 28.2 (C26), 25.2 (C4), 23.8 (C22), 20.3 ppm (C27); HRMS (ESI-TOF): m/z calcd for $C_{36}H_{60}O_5Na$: 595.4333 $[M+Na]^+$; found: 595.4333.

(−)-**5**: DDQ (1.43 mg, 6.30 μmol) was added to a suspension of (2*S*)-2-(*p*-methoxybenzyloxy)-24-oxooctacosanolide (3.00 mg, 5.20 μmol) in dichloromethane (0.47 mL) and water (0.05 mL) at 0 °C. The reaction mixture was stirred for 2.5 h at room temperature, and then phosphate buffer (pH 7) was added. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (benzene/diethyl ether = 3:1) to afford (2*S*)-2-hydroxy-24-oxooctacosanolide ((−)-**5**; 1.9 mg, 80%) as a white solid. M.p.: 67–68 °C; $[\alpha]_D^{21} = -9.6$ (*c* 0.96, benzene); IR (KBr): $\tilde{\nu}$ = 3445, 1739, 1713 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.28–4.24 (m, 1H, 28-H), 4.18–4.16 (m, 1H, 2-H), 4.13–4.09 (m, 1H, 28-H), 2.45 (t, J = 7.0 Hz, 2H, 25-H), 2.40 (t, J = 7.5 Hz, 2H, 23-H), 1.81–1.75 (m, 2H, 3-H), 1.69–1.63 (m, 2H, 27-H), 1.67–1.61 (m, 2H, 26-H), 1.61–1.56 (m, 2H, 22-H), 1.56–1.45 (m, 2H, 4-H), 1.45–1.17 ppm (m, 34H, 5-H to 21-H); ^{13}C NMR ($CDCl_3$): δ = 210.7 (C24), 175.6 (C1), 70.4 (C2), 65.4 (C28), 42.8 (C23), 42.0 (C25), 34.4 (C3), [29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 28.9, 28.9, 28.8, 28.7, 28.7, 28.7, 28.6, 28.6, and 28.5] (C5–C21), 28.1 (C26), 24.7 (C4), 23.7 (C22), 20.2 ppm (C27); HRMS (ESI-TOF): m/z calcd for $C_{28}H_{52}O_4Na$: 475.3758 $[M+Na]^+$; found: 475.3758.

5:[5] Amorphous solid. ^1H NMR ($CDCl_3$): δ = 4.24 and 4.10 (m, 2H, 28-H), 4.15 (m, 1H, 2-H), 2.73 (d, J = 5 Hz, 1H, OH), 2.44 (t, J = 6.5 Hz, 2H, 25-H), 2.38 (t, J = 7 Hz, 2H, 23-H), 1.76 and 1.63 (m, 2H, 3-H), 1.65 (m, 2H, 27-H), 1.63 (m, 2H, 26-H), 1.58 (m, 2H, 22-H), 1.45–1.30 (m, 2H, 4-H), 1.25 ppm (m, 34H, 5-H–21-H); ^{13}C NMR ($CDCl_3$): δ = 211.4 (C24), 176.2 (C1), 71.1 (C2), 66.0 (C28), 43.5 (C23), 42.7 (C25), 35.1 (C3), 29.0 (C5–C21), 28.8 (C26), 25.3 (C4), 24.4 (C22), 20.8 ppm (C27); MS: m/z calcd for $C_{28}H_5O_4$: 452.3865 $[M]^+$; found: 452.3867.

24: DMAP (0.60 mg, 4.9 μmol) and benzoic anhydride (1.43 mg, 6.30 μmol) were added to a solution of (−)-**5** (1.00 mg, 2.21 μmol) in dichloromethane (0.2 mL) at 0 °C. The reaction mixture was stirred for 21 h at room temperature, and then saturated aqueous sodium hydrogencarbon-

ate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 5:1) to afford (2*S*)-2-benzoyloxy-24-oxooctacosanolide (**24**; 1.2 mg, quant.) as a colorless oil. IR (neat): $\tilde{\nu}$ = 1757, 1726 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.10–8.07 (m, 2H, Bz), 7.65–7.55 (m, 1H, Bz), 7.48–7.31 (m, 2H, Bz), 5.21 (t, J = 6.8 Hz, 1H, 2-H), 4.23–4.16 (m, 2H, 28-H), 2.43 (t, J = 6.8 Hz, 2H, 25-H), 2.38 (t, J = 7.3 Hz, 2H, 23-H), 1.82–1.48 (m, 2H, 3-H), 1.70–1.62 (m, 2H, 26-H), 1.70–1.62 (m, 2H, 27-H), 1.62–1.48 (m, 2H, 22-H), 1.62–1.48 (m, 2H, 4-H), 1.27–1.25 ppm (m, 34H, 5-H to 21-H); HRMS (ESI-TOF): m/z calcd for $C_{35}H_{56}O_5Na$: 579.4020 $[M+Na]^+$; found: 579.4020; HPLC (CHIRALCEL OD-H*2, *i*PrOH/hexane = 1:20, flow rate = 0.3 mL min^{-1}): t_R = 46.6 (< 1%), 47.6 min (> 99%).

ent-**24**: DEAD (5.00 mg, 28.3 μmol) was added to a solution of (−)-**5** (1.40 mg, 1.89 μmol), benzoic acid (1.40 mg, 11.4 μmol), and triphenylphosphine (2.30 mg, 8.70 μmol) in THF (0.1 mL) at 0 °C. The reaction mixture was stirred for 9 h at room temperature, and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with diethyl ether, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 5:1) to afford (2*R*)-2-benzoyloxy-24-oxooctacosanolide (*ent*-**24**; 1.7 mg, quant.) as a colorless oil. IR (neat): $\tilde{\nu}$ = 1752, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.10–8.07 (m, 2H, Bz), 7.65–7.55 (m, 1H, Bz), 7.48–7.31 (m, 2H, Bz), 5.21 (t, J = 6.8 Hz, 1H, 2-H), 4.23–4.16 (m, 2H, 28-H), 2.43 (t, J = 6.8 Hz, 2H, 25-H), 2.38 (t, J = 7.3 Hz, 2H, 23-H), 1.82–1.48 (m, 2H, 3-H), 1.70–1.62 (m, 2H, 26-H), 1.70–1.62 (m, 2H, 27-H), 1.62–1.48 (m, 2H, 22-H), 1.62–1.48 (m, 2H, 4-H), 1.27–1.25 ppm (m, 34H, 5-H–21-H); HRMS (ESI-TOF): m/z calcd for $C_{35}H_{56}O_5Na$: 579.4020 $[M+Na]^+$; found: 579.4020; HPLC (CHIRALCEL OD-H*2, *i*PrOH/hexane = 1:20, flow rate = 0.3 mL min^{-1}): t_R = 46.6 (> 99%), 47.6 min (< 1%).

(2*R*)-2-(3,5-Dinitrobenzoyloxy)-24-oxooctacosanolide: to a solution of (−)-**5** (5.40 mg, 11.9 μmol), triphenylphosphine (6.50 mg, 24.8 μmol), and 3,5-dinitrobenzoic acid (6.50 mg, 30.6 μmol) in THF (0.12 mL) at room temperature was added diisopropyl azodicarboxylate (4.80 mg, 23.9 μmol). The reaction mixture was stirred for 2 h at room temperature, and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with hexane, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 3:1) to afford (2*R*)-2-(3,5-dinitrobenzoyloxy)-24-oxooctacosanolide (6.0 mg, 78%) and recovered (−)-**5** (1.2 mg, 22%) as colorless oils.

(2*R*)-2-(3,5-Dinitrobenzoyloxy)-24-oxooctacosanolide: IR (neat): $\tilde{\nu}$ = 1736, 1714, 1547 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.26 (t, J = 2.0 Hz, 1H, Ar), 9.19 (t, J = 2.0 Hz, 2H, Ar), 5.32 (dd, J = 12.5, 5.0 Hz, 1H, 2-H), 4.24–4.21 (m, 1H, 28-H), 4.18–4.15 (m, 1H, 28-H), 2.45 (t, J = 6.0 Hz, 2H, 25-H), 2.40 (t, J = 7.0 Hz, 2H, 23-H), 2.08–2.03 (m, 2H, 3-H), 1.67–1.66 (m, 2H, 27-H), 1.67–1.66 (m, 2H, 26-H), 1.55–1.49 (m, 2H, 4-H), 1.48–1.39 (m, 2H, 22-H), 1.35–1.25 ppm (m, 34H, 5-H–21-H); HRMS (ESI-TOF): m/z calcd for $C_{35}H_{54}N_2O_9Na$: 669.3722 $[M+Na]^+$; found: 669.3722.

(+)-**5**: Triethylamine (6.5 μL) was added to a solution of (2*R*)-2-(3,5-dinitrobenzoyloxy)-24-oxooctacosanolide (6.00 mg, 9.28 μmol) in methanol (0.1 mL) at room temperature. The reaction mixture was stirred for 30 min at room temperature, and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography (hexane/ethyl acetate = 3:1) to afford (2*R*)-2-hydroxy-24-oxooctacosanolide ((+)-**5**; 3.5 mg, 83%) as a colorless solid. M.p.: 69–70 °C; $[\alpha]_D^{22}$ = +9.54 (*c* 0.44, benzene); HRMS (ESI-TOF): m/z calcd for $C_{28}H_{52}O_4Na$: 475.3758 $[M+Na]^+$; found: 475.3758.

Acknowledgements

This study was partially supported by a Research Grant from the Center for Green Photo-Science and Technology and Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

[1] Reviews for defensive compounds of insects: a) G. D. Prestwich, *Sci. Am.* **1983**, *249*, 68–75; b) P. Laurent, J.-C. Braekman, D. Daloze, J. Pasteels, *Eur. J. Org. Chem.* **2003**, 2733–2743.

[2] Cubitene and related compounds: isolation: a) G. D. Prestwich, D. F. Wiemer, J. Meinwald, J. Clardy, *J. Am. Chem. Soc.* **1978**, *100*, 2560–2561; b) D. F. Wiemer, J. Meinwald, G. D. Prestwich, I. Miura, *J. Org. Chem.* **1979**, *44*, 3950–3952; c) D. F. Wiemer, J. Meinwald, G. D. Prestwich, B. A. Solheim, J. Clardy, *J. Org. Chem.* **1980**, *45*, 191–192; d) M. S. Tempesta, J. K. Pawlak, T. Iwashita, Y. Naya, K. Nakanishi, *J. Org. Chem.* **1984**, *49*, 2077–2079; synthesis: e) K. Shimada, M. Kodama, S. Ito, *Tetrahedron Lett.* **1981**, *22*, 4275–4276; f) M. Kodama, T. Takahashi, T. Kojima, S. Ito, *Tetrahedron Lett.* **1982**, *23*, 3397–3400; g) K. Mori, M. Waku, *Tetrahedron* **1984**, *40*, 305–309; h) K. A. Parker, J. G. Farmar, *J. Org. Chem.* **1986**, *51*, 4023–4028; i) S. K. Paknikar, A. E. Greene, *J. Nat. Prod.* **1988**, *51*, 326–327.

[3] Trinervitane and related compounds: isolation: a) G. D. Prestwich, S. P. Tanis, J. P. Springer, J. Clardy, *J. Am. Chem. Soc.* **1976**, *98*, 6061–6062; b) G. D. Prestwich, S. P. Tanis, F. G. Pilkiewicz, I. Miura, K. Nakanishi, *J. Am. Chem. Soc.* **1976**, *98*, 6062–6064; c) J. Vrkoc, M. Budesinsky, P. Sedmera, *Collect. Czech. Chem. Commun.* **1978**, *43*, 2478–2485; synthesis: d) T. Kato, M. Tanaka, M. Hoshikawa, M. Yagi, *Tetrahedron Lett.* **1998**, *39*, 7553–7556; e) T. Kato, S. Ebihara, T. Furukawa, H. Tanahashi, M. Hoshikawa, *Tetrahedron: Asymmetry* **1999**, *10*, 3691–3700; f) M. Hoshikawa, K. Hayashi, M. Yagi, T. Kato, *Chem. Commun.* **2001**, 623–624; g) M. Kodama, M. Matsushita, S. Yoshio, K. Tanimoto, E. Noda, H. Hioki, Y. Fukuyama, *The 39th Symposium on Natural Products*, **1997**, *39*, 289.

[4] a) G. D. Prestwich, M. S. Collins, *Tetrahedron Lett.* **1981**, *22*, 4587–4590; b) G. D. Prestwich, *Tetrahedron* **1982**, *38*, 1911–1919.

[5] V. Plasman, D. Daloze, J.-C. Braekman, S. Connétable, A. Robert, C. Bordereau, *Tetrahedron Lett.* **1999**, *40*, 9229–9232.

[6] a) I. Shiina, R. Ibuka, M. Kubota, *Chem. Lett.* **2002**, 286–287; b) I. Shiina, M. Kubota, R. Ibuka, *Tetrahedron Lett.* **2002**, *43*, 7535–7539; c) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822–1830; d) I. Shiina, H. Oshiumi, M. Hashizume, Y. Yamai, R. Ibuka, *Tetrahedron Lett.* **2004**, *45*, 543–547; e) I. Shiina, M. Hashizume, Y. Yamai, H. Oshiumi, T. Shimazaki, Y. Takasuna, R. Ibuka, *Chem. Eur. J.* **2005**, *11*, 6601–6608; f) I. Shiina, M. Hashizume, *Tetrahedron* **2006**, *62*, 7934–7939; g) I. Shiina, Y. Takasuna, R. Suzuki, H. Oshiumi, Y. Komiyama, S. Hitomi, H. Fukui, *Org. Lett.* **2006**, *8*, 5279–5282; preliminarily communication for the total synthesis of 2-hydroxy-24-oxooctacosanolide: h) I. Shiina, T. Kikuchi, A. Sasaki, *Org. Lett.* **2006**, *8*, 4955–4958.

[7] a) I. Shiina, *Chem. Rev.* **2007**, *107*, 239–273; for applications of MNBA condensation by other authors, see: b) J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2003**, *5*, 3021–3024; c) M. Inoue, T. Sasaki, S. Hatano, M. Hirama, *Angew. Chem.* **2004**, *116*, 6662–6667; *Angew. Chem. Int. Ed.* **2004**, *43*, 6500–6505; d) M. Inoue, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 501–510; e) M. Morita, N. Mase, H. Yoda, K. Takabe, *Tetrahedron: Asymmetry* **2005**, *16*, 3176–3182; f) M.-T. Dinh, S. BouzBouz, J.-L. Peglion, J. Cossy, *Synlett* **2005**, 2851–2853; g) T. Doi, Y. Iijima, K. Shin-ya, A. Ganesan, T. Takahashi, *Tetrahedron Lett.* **2006**, *47*, 1177–1180; h) S. Hosokawa, M. Seki, H. Fukuda, K. Tatsuta, *Tetrahedron Lett.* **2006**, *47*, 2439–2442; i) K. C. Nicolaou, H. Xu, *Chem. Commun.* **2006**, 600–602; j) H. Tsuchikawa, N. Matsushita, N. Matsumori, M. Murata, T. Oishi, *Tetrahedron Lett.* **2006**, *47*, 6187–6191; k) Y. Wu, Y.-Q. Yang, *J. Org. Chem.* **2006**, *71*, 4296–4301; l) Y. Matsuya, T. Kawaguchi, K. Ishihara, K. Ahmed, Q.-L. Zhao, T. Kondo, H. Nemoto, *Org. Lett.* **2006**, *8*, 4609–4612; m) K. Yamashita, S. Kobayashi, S. Tsukamoto,

M. Numazawa, *Steroids* **2007**, *72*, 50–59; n) T. Saito, T. Takeuchi, M. Matsuhashi, T. Nakata, *Heterocycles* **2007**, *72*, 151–156; o) B. M. Trost, H. Yang, O. R. Thiel, A. J. Frontier, C. S. Brindle, *J. Am. Chem. Soc.* **2007**, *129*, 2206–2207; p) F. Ren, P. C. Hogan, A. J. Anderson, A. G. Myers, *J. Am. Chem. Soc.* **2007**, *129*, 5381–5383; q) J. R. Falck, A. He, H. Fukui, H. Tsutsui, A. Radha, *Angew. Chem.* **2007**, *119*, 4611–4613; *Angew. Chem. Int. Ed.* **2007**, *46*, 4527–4529; r) T. Ito, M. Ito, H. Arimoto, H. Takamura, D. Uemura, *Tetrahedron Lett.* **2007**, *48*, 5465–5469; s) J. R. Scheerer, J. F. Lawrence, G. C. Wang, D. A. Evans, *J. Am. Chem. Soc.* **2007**, *129*, 8968–8969; t) G. R. Pettit, T. H. Smith, S. Feng, J. C. Knight, R. Tan, R. K. Pettit, P. A. Hinrichs, *J. Nat. Prod.* **2007**, *70*, 1073–1083.

[8] H. Toshima, K. Maru, M. Saito, A. Ichikawa, *Tetrahedron* **1999**, *55*, 5793–5808.

[9] M. Ito, C. Kibayashi, *Tetrahedron* **1991**, *47*, 9329–9350.

[10] a) E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616; b) E. J. Corey, P. Ulrich, J. M. Fitzpatrick, *J. Am. Chem. Soc.* **1976**, *98*, 222–224; c) E. J. Corey, D. J. Brunelle, P. J. Stork, *Tetrahedron Lett.* **1976**, *17*, 3405–3408.

[11] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993. See also: b) A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939.

Received: September 15, 2007
Published online: January 18, 2008

