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A convergent total synthesis of epolactaene: an application of the bridgehead oxiranyl anion strategy

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Abstract—The generation and reaction of a lactone-derived oxiranyl anion is described. The aldol-type reaction of the epoxylactone and aldehydes was accomplished by a two-step procedure via the trimethylsilyl epoxylactone. The application of this methodology to the total synthesis of (+)-epolactaene and its analogs is described.

1. Introduction

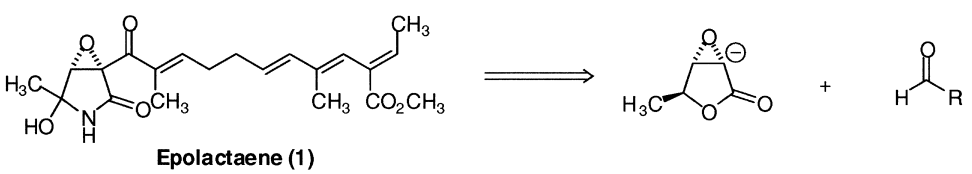
Epolactaene (**1**), which was isolated from fungal strain *Penicillium* sp. BM1689-P by Osada et al., possesses a potent neurite outgrowth activity in a human neuroblastoma cell line SH-SY5Y.[1] The characteristic features of epolactaene include the highly functionalized α,β-epoxy-γ-lactam and the conjugated triene moiety in the side chain. The significant biological activity as well as the structural complexity of epolactaene has stimulated intensive synthetic interests, culminating in the total syntheses and determination of its absolute stereochemistry by two groups.[2]

During the course of our investigation towards the synthesis of epolactaene, we became interested in the strategy involving the reaction of the oxiranyl anion derived from epoxylactone with aldehydes (Scheme 1).[3] Although the oxiranyl anion stabilized by an ethoxycarbonyl group is known,[4] the oxiranyl anion derived from α,β-epoxy-γ-butyrolactone has not been reported. According to Bredt's rule,[5] an oxiranyl anion derived from epoxylactone should be localized at the bridgehead. Therefore the reactivity of this anion as well as the method of generation is of immense interest.[6] This paper describes the generation and reaction of the oxiranyl anion to the synthesis of epolactaene and its anologs.

2. Results and discussion

2.1. The generation and reaction of the oxiranyl anion derived from α,β-epoxy-γ-butyrolactone

We first attempted the direct condensation of propionaldehyde with the oxiranyl anion generated from the racemic β-angelica lactone epoxide ((±)-**2**)[7a] (Table 1). After (±)-**2** was treated with LDA in THF at −78°C, propionaldehyde was added to the reaction mixture. We isolated the dimer **3** in 16% yield but did not obtain the desired product **4** (entry 1). Use of a different solvent, such as ether (0.02 M) at −110°C or the Trapp mixture[8] (THF/Et_2O/hexane=3:1:1)



Scheme 1.

Keywords: epolactaene; epoxylactone; TBAF; aldol reaction.
* Corresponding author. Address: Frontier Research Center for Genomic Drug Discovery, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan. Tel.: +81-4-7121-3671; fax: +81-4-7126-6550; e-mail: kobayash@rs.noda.tus.ac.jp
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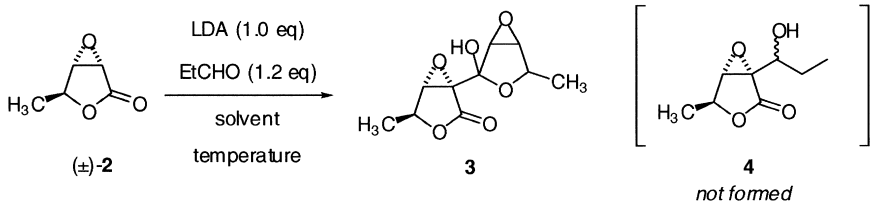
Table 1. Direct condensation of propionaldehyde with β-angelica lactone epoxide



Entry	Solvent	Concentration (M)	Temperature (°C)	Yield (%)
1	THF	0.1	−80	16
2	Et_2O	0.02	−110	43
3	Trapp mixture	0.02	−110	65

at −110°C were also unsuccessful, resulting in the undesirable formation of dimer **3** in moderate yield (entries 2 and 3). Although the desired aldol-type product was not obtained, these results clearly indicated that the oxiranyl anion can be generated and that the anion is so reactive that it attacks another epoxylactone during the lithiation step even at −110°C.

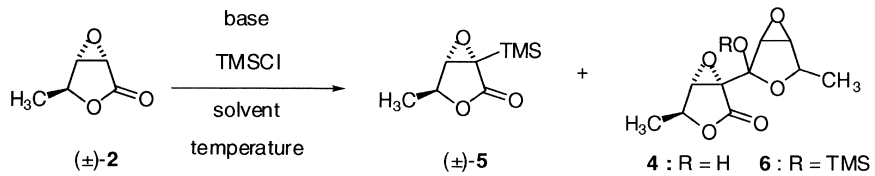
We then examined an alternative stepwise approach via the α-trimethylsilyl epoxylactone. We reasoned that the reactive oxiranyl anion could be trapped as the trimethylsilyl derivative **5** when the deprotonation was carried out in the presence of excess trimethylsilyl chloride (TMSCl). We also expected that the desired aldol-type reaction might occur when a mixture of trimethylsilyl derivative **5** and an aldehyde was treated with a catalytic amount of a fluoride anion. By this method, the generation of the reactive oxiranyl anion becomes possible in the presence of an aldehyde, and the formation of dimer **3** might be prevented.

Following Eisch's method,[4] a solution of LDA was added to a mixture of the epoxylactone (±)-**2** and TMSCl at −110°C. But the silylated product (±)-**5** was not produced and the dimers **3** and **6** were isolated (Table 2; entries 1 and 2). However, when a solution of epoxylactone in Trapp mixture was added to a solution of LDA and TMSCl in Trapp mixture at −110°C, the desired silylated product (±)-**5** was isolated in 70% yield (entry 3).

When ether was used as a solvent instead of Trapp mixture, dimer **3** was the main product and the yield of (−)-**5** was only 5% (entry 4). The reaction did not proceed when MHMDS (M=Li, Na and K) was used as a base, and the epoxylactone (−)-**2** was recovered (entry 5).

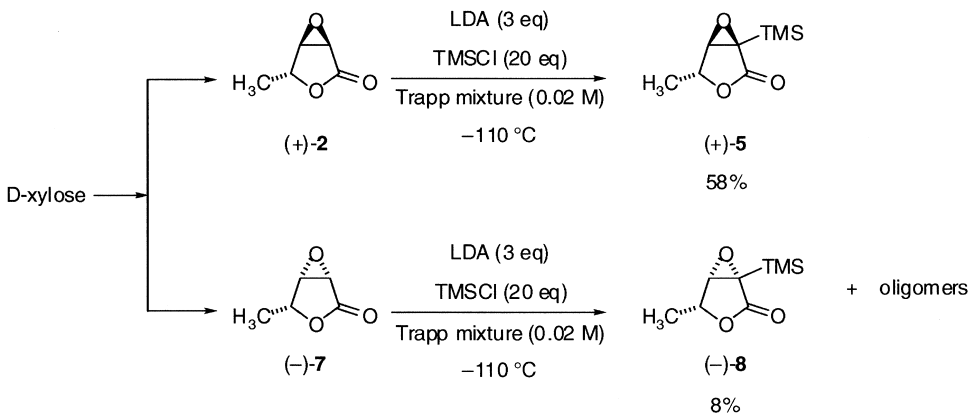
We next carried out the silylation of the chiral *anti*-epoxylactone (+)-**2** and *syn*-epoxylactone (−)-**7** in order to obtain the enantiomerically pure materials and to investigate the structure–reactivity relationships of the bridgehead oxiranyl anion. According to the method reported by Ogawa,[7b] (+)-**2** and (−)-**7** were prepared from D-xylose in a stereoselective manner. Contrary to the *anti*-isomer (+)-**2**, *syn*-isomer (−)-**7** afforded the corresponding silylated product (−)-**8** in only 8% yield under the same reaction conditions. The low yield was due to the formation of undesirable oligomers (Scheme 2). The results might be rationalized by considering the difference in the steric environment around the lactone carbonyl. Both faces of the lactone carbonyl are blocked by either an epoxide oxygen or methyl group in the *anti*-isomer **2**, whereas a nucleophile can readily approach from the *re*-face (upper face) of the lactone carbonyl in the case of the *syn*-isomer **7**.

Table 2. Trimethylsilylation of β-angelica lactone epoxide



Entry[a]	Base (equiv.)	TMSCl (equiv.)	Solvent	Concentration (M)	Yield (%)	
					5	Dimers
1	LDA (1.2)	5	Ether	0.1	-	**3** 65
2[b]	LDA (1.2)	5	Trapp mixture	0.1	-	**3** 13 **6** 58
3	LDA (3.0)	11	Trapp mixture	0.02	70	**3** 6
4	LDA (3.0)	10	Ether	0.02	5	**3** 55 **6** 3
5	MHMDS (3.0)	10	Trapp mixture	0.02	No reaction	

[a] Unless otherwise noted, reactions were carried out as follows: a solution of epoxylactone was added to a mixture of a base and TMSCI in a solvent indicated.
[b] A solution of LDA was added to a mixture of epoxylactone and TMSCl in a solvent indicated.



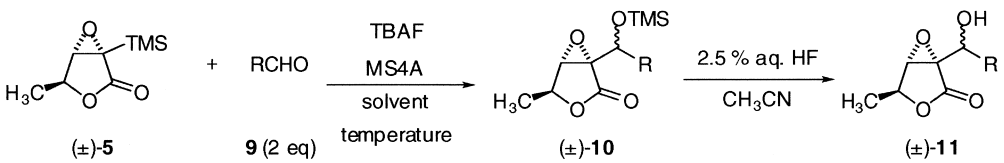
Scheme 2.

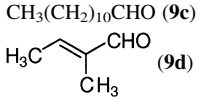
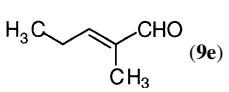
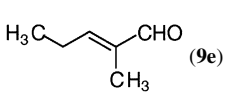
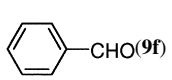
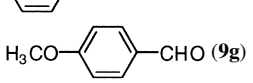
Having prepared the silylated epoxylactone **5**, the coupling of **5** with an aldehyde was attempted. As expected, the aldol-type reaction of **5** and propionaldehyde took place in the presence of 0.1 equiv. of tetrabutylammonium fluoride[9] (TBAF) and MS4A[10] in THF to obtain **11a** in 61% yield after the desilylation (aq. HF in CH_3CN) of the initially formed TMS ether **10a** (Table 3; entry 1). Prolonged reaction time was necessary for long chain aliphatic aldehyde and α-methylated-α,β-unsaturated aldehydes. For example, **11e** was obtained in 23% yield by the treatment of **5** and **9e** with TBAF for three times.[11] The use of an equimolar amount of TBAF resulted in the formation of a complex mixture of products. A catalytic amount of the fluoride anion source appeared to be essential for the reaction. Other fluoride anion sources or the presence of a co-additive such as trimethylsilyl fluoride[12] were not effective. We found that the condensation proceeded moderately in THF/hexane=1:1 (entry 5 vs. entry 6). Condensation of **5** with aromatic aldehydes was also examined to obtain the corresponding condensation products. In this case, an interesting diastereoselectivity was observed (entries 7 and 8).

2.2. Synthetic plan for epolactaene

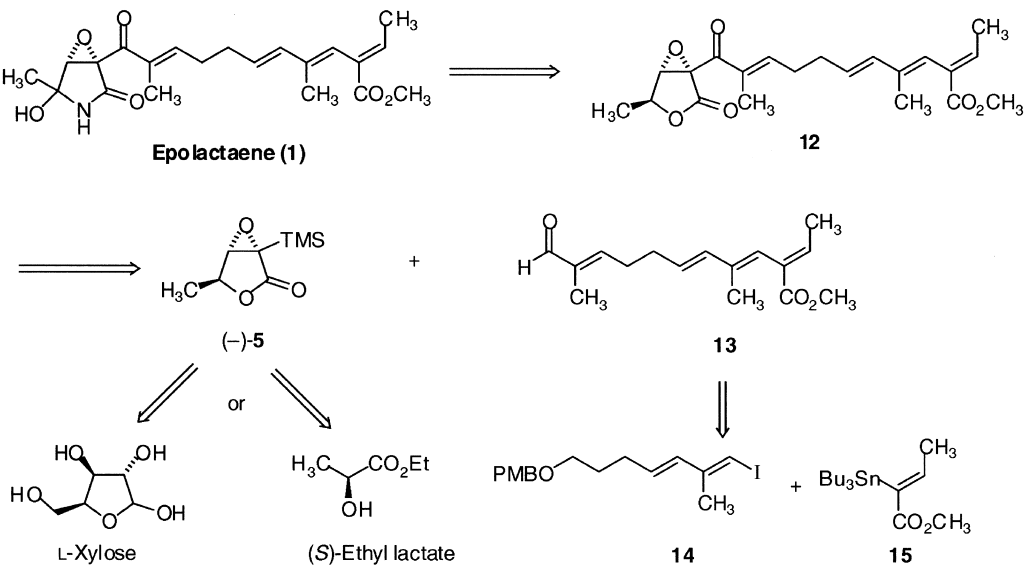
Scheme 3 outlines a strategy for epolactaene based on the oxiranyl anion approach. Epolactaene might be synthesized from the key intermediate **12**, which can be obtained from the condensation of epoxylactone (−)-**5** and aldehyde **13**. The chiral epoxylactone (−)-**5** is derived from L-xylose or from (*S*)-ethyl lactate according to the reported procedure with some modification.[7,13] The side-chain aldehyde **13** can

Table 3. TBAF-catalyzed aldol reaction

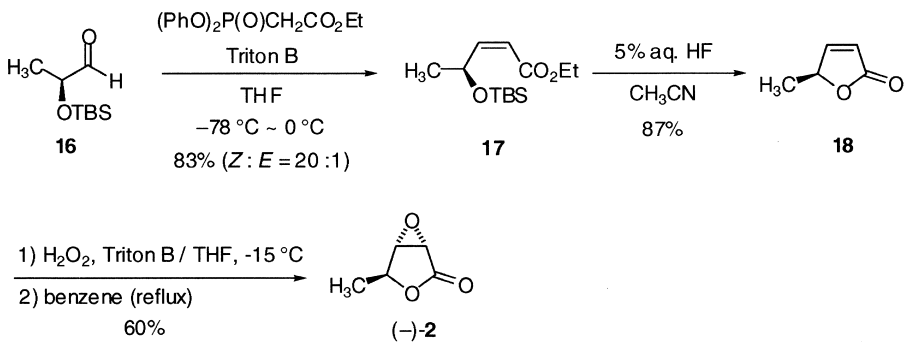


Entry	RCHO (**9**)	Solvent	Temperature (°C)	Time (h)	Yield (**11**) % (ds[a])
1	CH_3CH_2CHO (**9a**)	THF	0−rt	6	61 (ca. 1:1)
2	$CH_3(CH_2)_4CHO$ (**9b**)	THF	rt	11	50 (ca. 1:1)
3	$CH_3(CH_2)_{10}CHO$ (**9c**)	THF/hexane=1:1	rt	24	48 (ca. 1:1)
4	 (**9d**)	THF	rt	24	57 (ca. 1:1)
5	 (**9e**)	THF	rt	24 h×3[b]	23 (ca. 1:1)
6	 (**9e**)	THF/hexane=1: 1	rt	24	57 (ca. 1:1)
7	 (**9f**)	THF/hexane=1:1	rt	25	44 (ca. 1:1)
8	 (**9g**)	THF/hexane=1:1	rt	25	62 (single isomer)

[a] Diastereoselectivity was determined by ^1H NMR.
[b] Reaction was carried out three times.



Scheme 3.



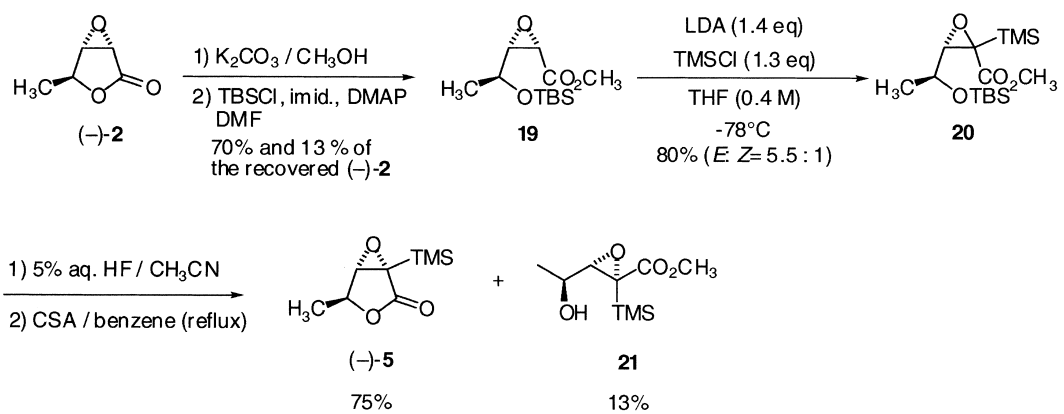
Scheme 4.

be prepared from the dienyl iodide **14** and the vinylstannane **15** using Stille coupling as a key reaction.

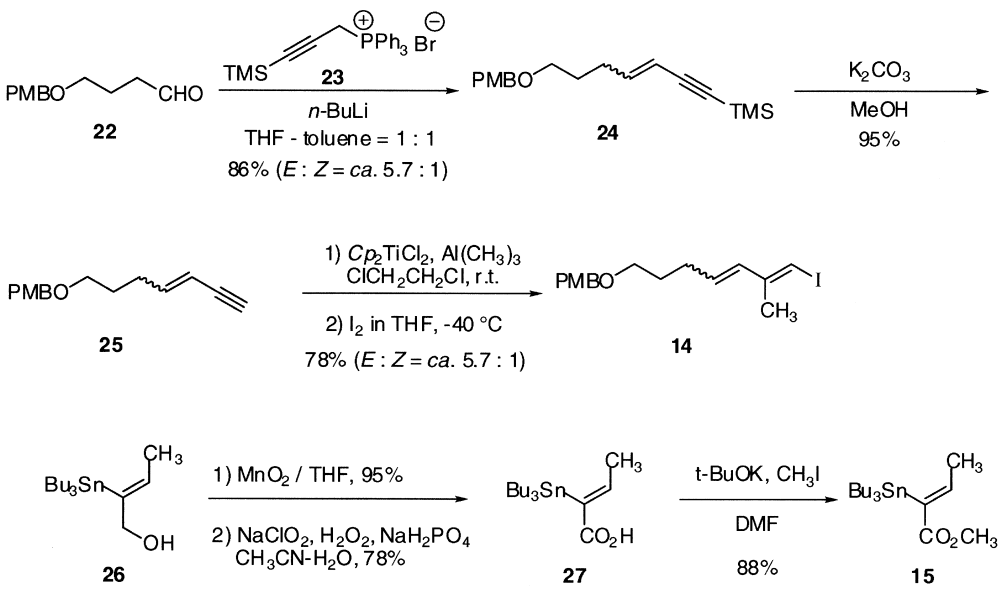
2.3. Synthesis of the enantiomerically pure (−)-β-angelica lactone epoxide (−)-2 and its α-trimethylsilyl derivative

In the preceding paper,[3b] we prepared the enantiomerically pure (−)-β-angelica lactone epoxide (−)-**2** from L-xylose according to the procedure reported by Ogawa.[7b] However, the employment of expensive L-xylose as a starting material is unsuitable for large-scale synthesis. This led us to improve the method for the preparation of the enantiomerically pure epoxylactone (Scheme 4).

The *Z*-selective Horner–Emmons reaction of ethyl diphenylphosphonoacetate[14] with (*S*)-2-(*t*-butyldimethylsilyloxy)-propanal (**16**)[13b] afforded a 20:1 mixture of *Z*- and *E*- α,β-unsaturated esters **17**. The treatment of **17** with aqueous HF in acetonitrile led to desilylation and cyclization to form



Scheme 5.



Scheme 6.

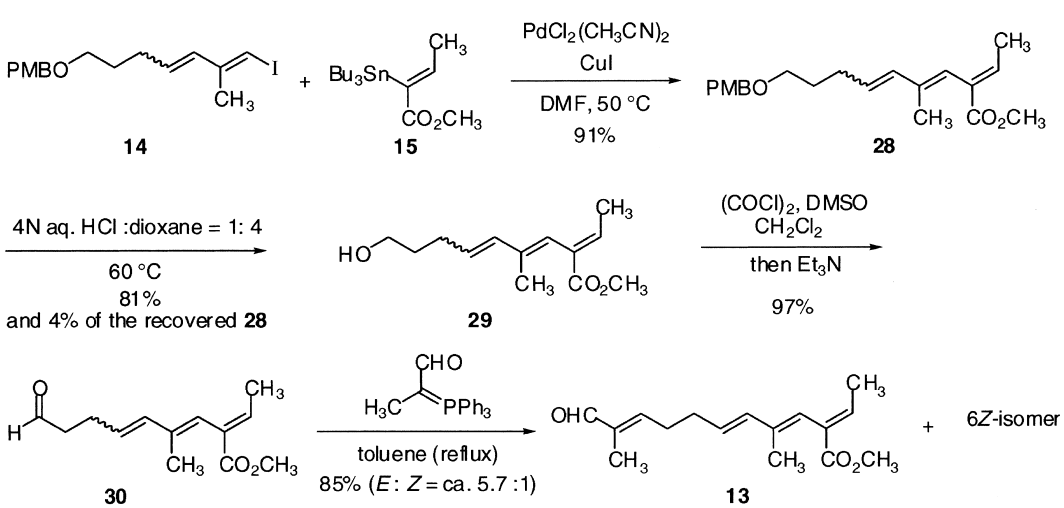
β-angelica lactone **18**. Epoxidation of **18** according to the modified Font's procedure[7a] gave the enantiomerically pure β-angelica lactone epoxide (−)-**2** in 60% yield and 98% ee (by HPLC).

In order to obtain the silylated epoxylactone **5** in large quantities, we also had to improve the trimethylsilylation of the epoxylactone because severe conditions (a high dilution condition, a very low temperature and excess amount of reagents) are necessary to reduce the dimerization of epoxylactone. Although various additives ($MgBr_2{\cdot}Et_2O$, $ZnCl_2$, $CeCl_3$, $Sn(OTf)_2$ etc.) at the silylation step were investigated, no significant improvements were achieved. We reasoned that the dimerization was caused by nucleophilic attack at the carbonyl carbon of the epoxylactone, in addition to the high reactivity of the localized oxiranyl anion.[4] We therefore transformed the lactone into the corresponding acyclic ester (Scheme 5).

After the treatment of (−)-**2** with K_2CO_3 in MeOH, the resulting alcohol was protected as the TBS ether **19**. A solution of the epoxyester **19** in THF was added to a solution of LDA (1.4 equiv.) and TMSCl (1.3 equiv.) in THF, affording a 5.5:1 mixture of the silylated epoxyesters **20** in 80% yield. Selective desilylation with aqueous HF in CH_3CN and recyclization with a catalytic amount of CSA in refluxing benzene gave the desired silyllactone (−)-**5** in 75% yield with 13% of the alcohol **21** derived from the isomerized silyl ester. Despite the requirement for five steps to obtain the silyllactone (−)-**5** from epoxylactone (−)-**2** and the loss in yield due to isomerization during the silylation step, this route can give enantiomerically pure silylated epoxylactone (−)-**5** in large quantities.

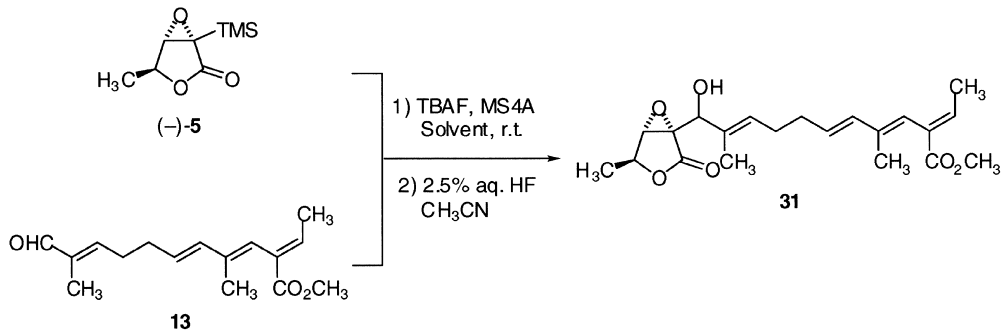
2.4. Synthesis of the side-chain moiety of epolactaene

The preparation of the dienyl iodide **14** and the vinylstannane **15** is shown in Scheme 6. Wittig reaction of **22**,[15] prepared from 1,4-butanediol by 2 steps, with the known phosphonium salt **23**,[16] gave a ca. 5.7:1 mixture of *E* and *Z*-enyne **24**. Without separation of isomers, the enyne **24** was converted into **25** with K_2CO_3 in MeOH.[17] **25** was



Scheme 7.

Table 4. TBAF-catalyzed reaction of (−)-**5** and **13**



Entry	(−)-**5**	**13** (equiv.)	TBAF (equiv.)	Solvent	Time	Yield (%)
1[a]	2.0	1.0	0.2	THF	1 day×7	53 (71)[b]
2	2.0	1.0	0.3	THF/hexane=1:1	3 days×2	35 (63)[b]
3	1.5	1.0	0.1[c]	THF/hexane=1:1	1 day	39 (78)[b]

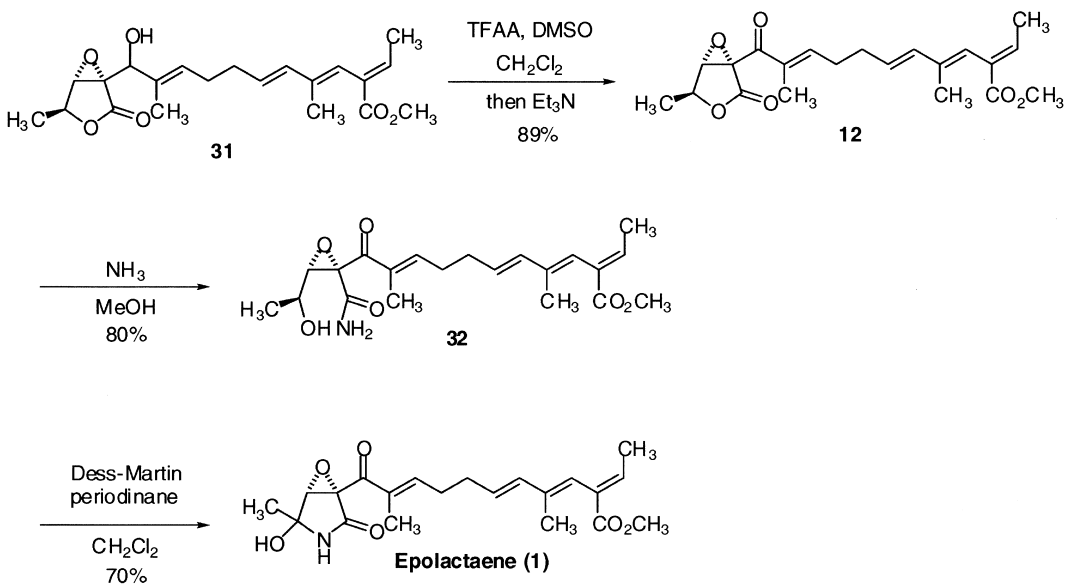
[a] Not treated with aq. HF in CH_3CN.
[b] Yield based on the recovered **13**.
[c] 1 M solution of TBAF in THF was treated with MS4A for 3 h before use.

subjected to a stereoselective carbometallation[18] with Cp_2TiCl_2–Me_3Al followed by treatment with iodine, affording the dienyl iodide **14**. The vinylstannane **15** was prepared from the known stannyl alcohol **26**.[19] A two step oxidation [(i) MnO_2, 95%; (ii) $NaClO_2$–H_2O_2,[20] 71%] of the alcohol **26** gave the carboxylic acid **27**. **27** was transformed to the ester **15** in 88% yield by treatment with CH_3I and *t*-BuOK.

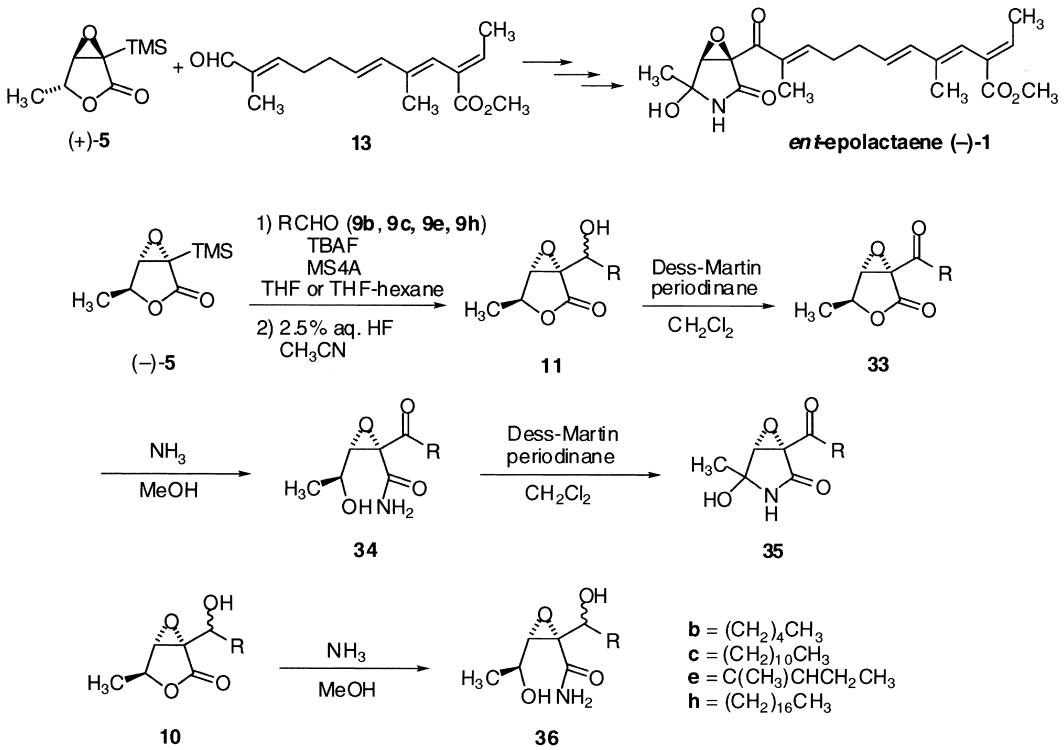
Construction of the conjugated triene moiety was achieved by Stille coupling. The treatment of **14** and **15** with a catalytic amount of $PdCl_2(CH_3CN)_2$ in the presence of CuI in DMF gave **28** in 91% yield.[21] The PMB group in **28** was cleanly cleaved by heating at 60°C in 4N aq. HCl/dioxane (1:4) affording **29** in 81% yield. The conventional method using DDQ or CAN[22] was unsuccessful, resulting in the formation of a complex mixture of products. After Swern oxidation,[23] the resulting aldehyde **30** was subjected to the Wittig reaction[24] to obtain the side-chain aldehyde **13** (Scheme 7). The separation of stereoisomers was conveniently performed at this stage to yield stereochemically pure **13**.

2.5. Coupling of two segments and the completion of the synthesis of epolactaene

The TBAF-catalyzed reaction of (−)-**5** and **13** was examined (Table 4). When the reaction was conducted in THF, only a catalytic amount of the desired aldol-type product **31** (not its TMS ether) was obtained and a considerable amount of (−)-**5** and **13** was recovered (entry 1).[3b] (−)-**5** and **13** were recovered and treated with TBAF and MS4A in THF for 1 day (six times) to obtain **31** in a total yield of 53% (71% yield based on recovered **13**). Based on



Scheme 8.



Scheme 9.

model studies of this aldol-type reaction, the coupling was conducted in THF/hexane (1:1) (entry 2). However, the yield as well as the catalytic cycle was not improved. We thought that the water contained in the commercially available 1 M solution of TBAF in THF might influence the catalytic cycle.[25] Thus when the reaction was performed using a solution of TBAF in THF, which was treated with activated MS4A (1 g/1 mmol) for 3 h, **31** was obtained in 39% (78% yield based on the recovered **13**) in a one-time reaction (entry 3).

Having obtained the desired aldol-type product **31**, we were in a position to complete the total synthesis of epolactaene (Scheme 8). Swern oxidation[23] of **31** with trifluoroacetic anhydride (TFAA) and DMSO produced the corresponding ketone **12**. After ammonolysis of **12**, the resulting hydroxyamide **32**[2] was oxidized with Dess–Martin periodinane[26] to give (+)-epolactaene which was isolated as a 5.4:1 diastereomixture at C-15. Synthetic epolactaene had a specific rotation $[\alpha]_D^{26}$ of +34 (*c* 0.2, MeOH) [lit.: $[\alpha]_D^{21}$=+32 (*c* 0.1, MeOH)] and exhibited spectral data (^{1}H and ^{13}C NMR and HRMS) identical with those reported for the natural product.[1]

2.6. Synthesis of epolactaene analogs and their biological activities

The most significant feature of the present approach is that the trimethylsilylated epoxylactone **5** serves as a potential intermediate for the synthesis of various substituted epolactaene analogs (Scheme 9). The enantiomer of the natural epolactaene was synthesized by the same route using the silylated product (+)-**5**. Several analogs were also prepared by the coupling of the silylated epoxylactone (−)-**5** with aldehydes **9b**, **9c**, **9e** and **9h**. Biological studies on the α, β-epoxy-γ-lactam derivatives **35** as well as the synthetic intermediates containing **11**, **33**, **34** and **36** were investigated. As a result, we observed that the synthetic (+)-epolactaene and **35c** inhibited the activities of mammalian DNA polymerase α, β and human DNA topoisomerase II.[27] We found that the synthetic (+) and (−)-epolactaene, **35b**, **35c**, **35e** and **35h** induced apotosis in BALL-1 cells.[28] Interestingly, there is no difference on the apotosis-inducing activity between epolactaene and its enantiomer. We also found that the α, β-epoxy-γ-lactam, the straight alkyl side-chain, and the carbonyl group at 3-position are required for these activities.

3. Conclusion

In summary, we have successfully performed an aldol-type condensation of the epoxylactone with a series of aldehydes by a two-step procedure via the trimethylsilyl epoxylactone. Although the catalytic efficiency of the reaction is not fully optimized, the present approach provides the first example of the generation and reaction of the highly reactive bridgehead oxiranyl anion derived from the epoxylactone. Its synthetic utility was demonstrated by the total synthesis of epolactaene. The most significant feature of the present approach is that the silylated epoxylactone serves as a key intermediate for the synthesis of various substituted epolactaene analogs. Several analogs were synthesized and are currently undergoing biological studies. Our synthetic probes will be candidate compounds for detailed studies into the mechanism of action of epolactaene.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR were recorded on a JEOL JNM-EX2, JNM-300, JNM-400, JNM-500, or on BRUKER DRX600. Chemical shifts were reported in δ, parts per million (ppm), relative to TMS as an internal standard. IR spectra were recorded on Horiba FT-210 or Hitachi 215 infrared spectrometer. Mass spectra were obtained on Hitachi M-80 spectrometer or API QSTAR Pulsar i spectrometer. Optical rotations were measured on a JASCO DIP-360 digital polarimeter. Column chromatography was carried out on Fujisilisiachem K.K.BW-127ZH. Analytical thin-layer chromatography (TLC) was performed on precoated Merck silica gel HF254 plates, and compounds were visualized by UV illumination (254 nm) or heating 150°C after spraying phosphomolylbdic acid in ethanol. Ether and THF were distilled from sodium/benzophenone. CH_2Cl_2 were distilled from P_2O_5. Benzene, $(CH_2Cl)_2$, diisopropylamine, DMF, DMSO, hexane, toluene and trimethylsilyl chloride were distilled from CaH_2. Hexanal, oxaly chloride, *trans*-2-methyl-2-butenal, 2-methyl-2-pentenal, propionaldehyde were distilled before use. All other solvent and reagents were obtained from commercial sources and used without further purification. Organic extracts were dried over $MgSO_4$, filtered, concentrated using a rotary evaporator. Nonvolatile oils and solids were vacuum dried.

4.1.1. (1*R,4*S**,5*S**)-4-Methyl-1-trimethylsilyl-3,6-dioxa-bicyclo[3.1.0]hexan-2-one 5.** To a solution of diisopropylamine (0.37 mL, 2.62 mmol) in Trapp mixture (THF/hexane/ether=3:1:l, 23 mL) was added *n*-BuLi (1.7 mL of a 1.53 M solution in hexane, 2.60 mmol) at 0°C for 20 min. Then the mixture was cooled at −110°C. After the addition of trimethylsilyl chloride (1.2 mL, 9.48 mmol), a solution of β-angelica lactone epoxide (100.8 mg, 0.883 mmol) in Trapp mixture (20 mL) in portions for 30 min and the mixture was stirred at −110°C for 10 min. The mixture was quenched by the addition of H_2O and extracted with EtOAc (×3). The combined extract was washed with brine, dried and concentrated. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford **5** (116.9 mg, 70%) as a colorless oil. IR (neat) 2962, 2904, 1767, 1450, 1383, 1333, 1254, 1211, 1072, 976, 914, 847, 785 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.22 (9H, s, $SiMe_3$), 1.35 (3H, d, J=6.6 Hz, 4-Me), 3.72 (1H, s, H-5), 4.69 (1H, q, J=6.6 Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −3.9, 18.0, 51.7, 63.4, 75.1, 173.4; HRMS, calcd for $C_8H_{14}O_3Si$ (M^+) 186.0713, found 186.0713.

4.1.2. (1*R*,4*S*,5*S*)-4-Methyl-1-trimethylsilyl-3,6-dioxabicyclo[3.1.0]hexan-2-one (−)-5. $[\alpha]_D^{21}$=−50.6 (*c* 1.01, $CHCl_3$).

4.1.3. (1*S*,4*R*,5*R*)-4-Methyl-1-trimethylsilyl-3,6-dioxabicyclo[3.1.0]hexan-2-one (+)-5. $[\alpha]_D^{21}$=+51.1 (*c* 0.88, $CHCl_3$).

4.1.4. (1*R*,4*R*,5*S*)-4-Methyl-1-trimethylsilyl-3,6-dioxabicyclo[3.1.0]hexan-2-one (−)-8. To a solution of diisopropylamine (0.40 mL, 2.83 mmol) in Trapp mixture (THF/hexane/ether=3:1:1, 23 mL) was added *n*-BuLi (1.8 mL of a 1.53 M solution in hexane, 2.75 mmol) at rt for 20 min. Then the mixture was cooled at −110°C. After the addition of trimethylsilyl chloride (2.4 mL, 18.96 mmol), a solution of β-angelica lactone epoxide (−)-**7** (106.9 mg, 0.937 mmol) in Trapp mixture (30 mL) in portions for 30 min. The mixture was quenched by the addition of H_2O and extracted with EtOAc (×3). The combined extract was washed with brine, dried and concentrated. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford (−)-**8** (13.2 mg, 8%) as a pale yellow oil. $[\alpha]_D^{21}$=−62.5 (*c* 0.80, $CHCl_3$); IR (neat) 2962, 2902, 1774, 1452, 1381, 1346, 1254, 1220, 1101, 989, 908, 847, 781 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.21 (9H, s, $SiMe_3$), 1.47 (3H, d, J=6.6 Hz, 5-Me), 3.83 (1H, d, J=1.7 Hz, H-5), 4.54 (1H, dq, J=1.7, 6.6 Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −3.8, 15.5, 53.6, 62.1, 74.8, 173.5; HRMS, calcd for $C_8H_{14}O_3Si$ (M^+) 186.0713, found 186.0713.

4.2. General method for the preparation of 11

To a solution of (±)-**5** (55.1 mg, 0.296 mmol), propionaldehyde (40 μL, 0.554 mmol) and MS4A (0.21 g) in THF (5 mL) was added TBAF (30 μL of a 1 M solution in THF, 30 μmol) at 0°C. The mixture was stirred at rt for 6 h and then filtrated through Celite and washed with EtOAc. The organic layer was washed with H_2O, brine, dried and concentrated. A solution of the residue in CH_3CN (2 mL) was added a solution of 5% aqueous HF in CH_3CN (1 mL) at rt for 30 min. The mixture was quenched by the addition of H_2O and extracted with EtOAc (×3). The combined extract was washed with brine, dried and concentrated. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford **11a** (31.2 mg, 61%) as a colorless oil.

4.2.1. (1*S,1′*RS*,4*S**,5*S**)-1-(1-Hydroxypropyl)-4-methyl-3,6-dioxabicyclo-[3.1.0]hexan-2-one 11a.** IR (neat) 3493, 2976, 2937, 2881, 1774, 1460, 1382, 1340, 1230, 1111, 1074, 1003, 922, 881, 850, 783, 696 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.06 (3H, t, J=7.3 Hz, H-3′), 1.07* (3H, t, J=7.6 Hz, H-3′), 1.38 (3H, d, J=6.6 Hz, 4-Me), 1.38* (3H, d, J=6.6 Hz, 4-Me), 1.67–1.88 (2H, m, H-2′), 1.67–1.88* (2H, m, H-2′), 2.10 (1H, brs, OH), 2.10* (1H, brs, OH), 3.97 (1H, s, H-5), 3.97* (1H, s, H-5), 4.18 (1H, m, H-1′), 4.18* (1H, m, H-1′), 4.67 (1H, q, J=6.6 Hz, H-4), 4.67* (1H, q, J=6.6 Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.6, 9.8, 17.7, 25.5, 61.6, 61.7, 62.1, 65.9, 67.7, 75.4, 170.5, 170.9 (diasteromeric mixture); HRMS, calcd for $C_8H_{11}O_4$ (M^+−H) 171.0657, found 171.0640.

4.2.2. (1*S,1′*RS*,4*S**,5*S**)-1-(1-Hydroxyhexyl)-4-methyl-3,6-dioxabicyclo-[3.1.0]hexan-2-one 11b.** The title compound was prepared by the coupling of (±)-**5** with **9b** in 50% yield as a colorless oil. IR (neat) 3504, 2956, 2933, 2862, 1774, 1458, 1381, 1340, 1221, 1115, 1012, 923, 854, 785 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89–0.91 (3H, m, H-6′), 0.89–0.91* (3H, m, H-6′), 1.25–1.39 (6H, m, H-3′, H-4′, H-5′), 1.25–1.39* (6H, m, H-3′, H-4′, H-5′), 1.41 (3H, d, J=6.7 Hz, 4-Me), 1.41* (3H, d, J=6.7 Hz, 4-Me), 1.43–1.80 (2H, m, H-2′), 1.43–1.80* (2H, m, H-2′), 2.05 (1H, brs, OH), 2.12* (1H, brs, OH), 3.97 (1H, s, H-5), 3.97* (1H, s, H-5), 4.13–4.15 (1H, m, H-1′), 4.23–4.25* (1H, m, H-1′), 4.65 (1H, q, J=6.7 Hz, H-4), 4.66* (1H, q, J=6.7 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 13.9, 17.7, 22.4, 22.4, 24.8, 25.0, 31.4, 32.1, 32.3, 49.8, 61.7, 61.7, 62.0,

64.7, 66.3, 75.4, 75.4, 170.6, 171.0 (diasteromeric mixture); HRMS, calcd for $C_{11}H_{18}O_4$ (M^+) 214.1204, found 214.1210.

4.2.3. (1*S1′*RS*,4*S**,5*S**)-1-(1-Hydroxydodecyl)-4-methyl-3,6-dioxabicyclo-[3.1.0]hexan-2-one 11c.** The title compound was prepared by the coupling of (±)-**5** with **9c** in THF/hexane (1:1) in 48% yield as a white solid. Mp=47–49°C. IR ($CHCl_3$) 3689, 3026, 2927, 2856, 1778, 1601, 1458, 1383, 1340, 1228, 1072, 1009, 852, 716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.7 Hz, H-12′), 0.88* (3H, t, *J*=6.7 Hz, H-12′), 1.26 (20H, m, H-2′, H-3′, H-4′, H-5′, H-6′, H-7′, H-9′, H 10′, H-11′), 1.26* (20H, m, H-2′, H-3′, H-4′, H-5′, H-6′, H-7′, H-9′, H-10′, H-11′), 1.41 (3H, d, *J*=6.7 Hz, 4-Me), 1.41* (3H, d, *J*=6.7 Hz, 4-Me), 2.17 (1H, brs, OH), 2.27–2.29* (1H, m, OH), 3.97 (1H, s, H-5), 3.97* (1H, s, H-5), 4.10–4.18 (1H, m, H-1′), 4.22–4.24* (1H, m, H-1′), 4.65 (lH, q, *J*=6.7 Hz, H-4), 4.66* (1H, q, *J*=6.7 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 17.8, 17.8, 22.6, 25.2, 25.4, 29.3, 29.3, 29.4, 29.5, 29.6, 31.9, 32.2, 32.3, 61.6, 61.7, 61.7, 62.1, 64.8, 66.4, 75.4, 75.4, 170.5, 170.9 (diasteromeric mixture); HRMS, calcd for $C_{17}H_{30}O_4$ (M^+) 298.2143, found 298.2149.

4.2.4. (1*S,1′*RS*,4*S**,5*S**)-1-(1-Hydroxy-2-methylbut-2-enyl)-4-methyl-3,6-dioxabicyclo-[3.1.0]hexan-2-one 11d.** The title compound was prepared by the coupling of (±)-**5** with **9d** in 57% yield as a colorless oil. IR (neat) 3481, 2983, 2924, 2862, 1778, 1448, 1383, 1340, 1225, 1072, 1030, 921, 858, 802, 733, 694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.41 (3H, d, *J*=6.9 Hz, 4-Me), 1.41* (3H, d, *J*=6.9 Hz, 4-Me), 1.67 (3H, d, *J*=1.3 Hz, 2′-Me), 1.67* (3H, d, *J*=7.6 Hz, H-4′), 1.68 (3H, d, *J*=7.6 Hz, H-4′), 1.69* (3H, d, *J*=1.3 Hz, 2′-Me), 2.23* (1H, brs, OH), 2.58 (1H, d, *J*=6.3 Hz, OH), 3.89 (1H, s, H-5), 4.04* (1H, s, H-5), 4.56 (1H, d, *J*=6.3 Hz, H-1′), 4.66* (1H, q, *J*=6.7 Hz, H-4), 4.67 (1H, q, *J*=6.7 Hz, H-4), 4.76* (1H, s, H-1′), 5.70 (1H, m, H-3′), 5.78* (1H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ:12.1, 13.1, 13.2, 13.3, 17.7, 17.8, 60.7, 60.9, 61.8, 61.9, 71.1, 75.2, 123.6, 126.6, 131.4, 132.5, 169.7, 170.8 (diasteromeric mixture); HRMS, calcd for $C_{10}H_{14}O_4$ (M^+) 198.0893, found 198.0883.

4.2.5. (1*S,1′*RS*,4*S**,5*S**)-1-(1-Hydroxy-2-methylpent-2-enyl)-4-methyl-3,6-dioxabicyclo-[3.1.0]hexan-2-one 11e.** The title compound was prepared by the coupling of (±)-**5** with **9e** in THF/hexane (1:1) in 57% yield as a colorless oil. IR (neat) 3466, 3020, 2968, 2935, 2875, 1778, 1643, 1454, 1383, 1340, 1217, 1072, 1036, 943, 920, 858, 758, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.98 (3H, t, *J*=7.6 Hz, H-5′), 0.99* (3H, t, *J*=7.6 Hz, H-5′), 1.41 (3H, d, *J*=6.9 Hz, 4-Me), 1.41* (3H, d, *J*=6.9 Hz, 4-Me), 1.69* (3H, d, *J*=1.0 Hz, 2′-Me), 1.70 (3H, d, *J*=1.3 Hz, 2′-Me), 2.03–2.14 (2H, m, H-4′), 2.03–2.14* (2H, m, H-4′), 2.20 (1H, d, *J*=0.7 Hz, OH), 2.57 (1H, d, *J*=1.6 Hz, OH), 3.88* (1H, s, H-5), 4.04 (1H, s, H-5), 4.56* (1H, brs, H-1′), 4.59–4.70 (1H, m, H-4), 4.59–4.70* (1H, m, H-4), 4.75 (1H, s, H-1′), 5.58* (1H, dt, *J*=1.0, 7.3 Hz, H-3), 5.67 (1H, dt, *J*=1.3, 7.3 Hz, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.2, 13.2, 13.5, 13.6, 17.6, 17.6, 20.7, 20.8, 49.7, 58.7, 60.6, 60.9, 61.6, 61.8, 69.3, 70.7, 75.1, 75.2, 130.1, 130.7, 131.0, 133.5, 169.8, 170.8 (diasteromeric mixture); HRMS, calcd for $C_{11}H_{16}O_4$ (M^+-H_2O) 194.0943, found 194.0939.

4.2.6. (1*S,1′*RS*,4*S**,5*S**)-1-(1-Hydroxy-1-phenylmethyl)-4-methyl-3,6-dioxabicyclo-[3.1.0]hexan-2-one 11f.** The title compound was prepared by the coupling of (±)-**5** with **9f** in THF/hexane (1:1) in 44% as a colorless oil. IR (neat) 3583, 3020, 2980, 2935, 1778, 1456, 1338, 1216, 1066, 756, 700, 677 cm^{-1} (diastereomeric mixture); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21 (3H, d, *J*=6.8 Hz, 4-Me), 2.73 (1H, s, OH), 3.96 (1H, s, H-5), 4.62 (1H, q, *J*=6.8 Hz, H-4), 5.42 (1H, s, H-1′), 7.34–7.53 (5H, m, Ar) (the major isomer); ^{13}C NMR (75 MHz $CDCl_3$) δ: 17.8, 61.6, 62.3, 66.8, 75.4, 127.1, 127.9, 128.7, 137.0, 170.0 (the major isomer); HRMS, calcd for $C_{12}H_{12}O_4$ (M^+) 220.0735, found 220.0748.

4.2.7. (1*S,1′*RS*,4*S**,5*S**)-1-[1-Hydroxy-1-(4-metoxylphenyl)methyl]-4-methyl-3,6-dioxabicyclo-[3.1.0]hexan-2-one 11g.** The title compound was prepared by the coupling of (±)-**5** with **9g** in THF/hexane (1:1) in 62% as a colorless oil. IR (neat) 3583, 3020, 2979, 2940, 1778, 1614, 1513, 1463, 1338, 1251, 1215, 1174, 1072, 1036, 758, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (3H, d, *J*=6.6 Hz, 4-Me), 3.03 (1H, brs, OH), 3.78 (3H, s, OMe), 4.00 (1H, s, H-5), 4.59 (1H, q, *J*=6.6 Hz, H-4), 5.32 (1H, s, H-1′), 6.88 (2H, d, *J*=8.5 Hz, Ar), 7.35 (2H, d, *J*=8.5 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.7, 55.1, 61.4, 62.2, 66.2, 75.3, 113.9, 128.4, 129.2, 159.8, 170.0; HRMS, calcd for $C_{13}H_{14}O_5$ (M^+) 250.0840, found 250.0850.

4.2.8. (1*S*,1′*RS*,4*S*,5*S*)-1-(1-Hydroxyoctadecyl)-4-methyl-3,6-dioxabicyclo-[3.1.0]hexan-2-one 11h. The title compound was prepared by the coupling of (−)-**5** with **9h** in THF/hexane (1:1) in 52% as a white solid. Mp=62–65°C. IR ($CHCl_3$) 3583, 3019, 2927, 2854, 1776, 1465, 1381, 1340, 1220, 1071, 1009, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.8 Hz, H-18′), 0.88* (3H, t, *J*=6.8 Hz, H-18′), 1.25 (32H, m, H-2′–H-17′), 1.25* (32H, m, H-2′–H-17′), 1.41 (3H, d, *J*=6.7 Hz, 4-Me), 1.41* (3H, d, *J*=6.7 Hz, 4-Me), 1.44–1.78 (2H, m, H-2′), 1.44–1.78* (2H, m, H-2′), 2.13 (1H, brs, OH), 2.17* (1H, brs, OH), 3.98 (1H, s, H-5), 3.98* (1H, s, H-5), 4.14–4.16 (1H, m, H-1′), 4.24* (1H, dd, *J*=2.9, 8.8 Hz, H-1′), 4.65 (1H, q, *J*=6.7 Hz, H-4), 4.66* (1H, q, *J*=6.7 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 17.9, 17.9, 22.7, 25.3, 25.4, 29.3, 29.4, 29.4, 29.5, 29.6, 29.6, 29.7, 29.7,29.7, 31.9, 32.2, 32.3, 32.4, 61.6, 61.8, 61.8, 62.2, 62.2, 64.8, 66.5, 75.4, 75.4, 170.5, 170.9 (diasteromeric mixture); HRMS, calcd for $C_{23}H_{42}O_4$ (M^+) 382.3083, found 382.3091.

4.2.9. Ethyl (4*S*)-4-(*t*-butylsimethylsilyloxy)-(2*Z*)-pent-2-enoate 17. To a solution of ethyl (diphenylphosphono)acetate (151 g, 0.47 mol) in THF (500 mL) was added Triton B (199 g of a 40% solution in MeOH, 0.48 mol) at −78°C and the mixture was stirred at −78°C for 30 min. A solution of **16** (77 g, 0.41 mol) in THF (200 mL) was added to the mixture at −78°C in portions for 10 min. The mixture was warmed up to 0°C and stirred for 0°C for 2 h. Then the mixture was quenched by the addition of H_2O and extracted with EtOAc. The extract was washed with brine, dried and concentrated. The residue was purified by chromatography (20:1 hexane/EtOAc) to afford a ca. 20:1 mixture of **17** (88 g, 83%) as a colorless oil. IR (neat) 3039, 2929, 2858, 1720, 1649, 1464, 1410, 1363, 1306, 1254, 1192, 1117, 1078, 1003, 939, 835, 777, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.02 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.86 (9H,

s, Si*t*-Bu), 1.24 (3H, d, *J*=6.4 Hz, 4-Me), 1.27 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 4.15 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.43 (1H, ddq, *J*=1.5, 6.4, 7,9 Hz, H-4), 5.63 (1H, dd, *J*=1.5, 11.6 Hz, H-2), 6.19 (1H, dd, *J*=7.9, 11.6 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.9, −4.8, 14.2, 18.1, 23.5, 25.7, 25.8, 60.0, 65.5, 116.8, 154.6, 165.8; HRMS, calcd for $C_{13}H_{26}O_3Si$ (M^+) 258.1649, found 258.1641.

4.2.10. (5*S*)-5-Methyl-5*H*-furan-2-one 18. A solution of a 20:1 mixture of the ester **17** (88 g, 0.34 mmol) in CH_3CN (50 mL) was added a solution of 5% aqueous HF in CH_3CN (560 mL) at rt for 45 min. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (×2). The combined extract was washed with brine, dried and concentrated. The residue was purified by chromatography (4:1 hexane /EtOAc) to afford **18** (29 g, 87%) as a colorless oil. IR (neat) 3091, 2985, 2937, 1846, 1761, 1635, 1603, 1452, 1377, 1323, 1167, 1076, 1028, 960, 891, 762, 712, 671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.47 (3H, d, *J*=7.0 Hz, 5-Me), 5.16 (1H, ddq, *J*=1.5, 1.8, 7.0 Hz, H-5), 6.10 (1H, dd, *J*=1.8, 5.8 Hz, H-3), 7.51 (1H, dd, *J*=1.5, 5.8 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.6, 79.5, 120.9, 157.5, 173.0; HRMS, calcd for $C_5H_6O_2$ (M^+) 98.0304, found 98.0307.

4.2.11. (1*R*,4*S*,5*S*)-4-Methyl-3,6-dioxabicyclo[3.1.0]-hexan-2-one (−)-2. To a solution of **18** (1.07 g, 10.9 mmol) in THF (100 mL) was added H_2O_2 (3.18 mL of a 40% solution in H_2O, 32.7 mmol) and Triton B (4.30 mL of a 40% solution in H_2O, 10.9 mmol) at −15°C in portions for 20 min, and the mixture was stirred at −15°C for 4 h. The mixture was quenched by the addition of H_2O and extracted with EtOAc. The aqueous layer was acidified to pH 1 by the addition of aqueous conc. HCl solution and the mixture was stirred at rt for 2 h. Then aqueous layer was extracted with EtOAc (×6). The combined extract was dried and concentrated. A solution of the residue in benzene (10 mL) was refluxed for 2 h and then concentrated. The residue was purified by chromatography (3:1 hexane/EtOAc) to afford (−)-**2** (740 mg, 60%) as a colorless oil. $[\alpha]_D^{21}$=−34.6 (*c* 2.0, $CHCl_3$); IR (neat) 3089, 2987, 2939, 2879, 1878, 1776, 1452, 1385, 1340, 1284, 1190, 1063, 989, 943, 891, 847, 770, 696, 636 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.43 (3H, d, *J*=6.7 Hz, 4-Me), 3.81 (1H, d, *J*=2.4 Hz, H-5), 3.99 (1H, d, *J*=2.4 Hz, H-1), 4.71 (1H, q, *J*=6.7 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.6, 49.8, 58.8, 76.3, 170.3; HRMS, calcd for $C_5H_6O_3$ (M^+) 114.0317, found 114.0320. The enantiomeric purity of (−)-**2** was determined to be 98% ee by analytical HPLC analysis [Daicel Chiralcel OC, *i*-PrOH/hexane=1:10, Flow rate=1 mL/min, t_R=18.17 min ((1*R*,4*S*,5*S*)-isomer), t_R=21.22 min ((1*S*,4*R*,5*R*)-isomer)] with the racemic and authentic sample.

4.2.12. (2*S*,3*S*,4*S*)-Methyl 2,3-epoxy-4-(*t*-butyldimethylsilyloxy)pentanoate 19. A solution of (−)-**2** (11 g, 96 mmol) and K_2CO_3 (1.3 g, 9.3 mmol) in MeOH (60 mL) was stirred at rt for 35 min. The mixture was quenched by the addition of H_2O and extracted with EtOAc (×3). The combined extract was washed with brine, dried and concentrated. To a solution of the residue in DMF (60 mL) was added imidazole (14 g, 206 mmol), TBSCl (16 g, 106 mmol) and DMAP (1 g, 8.2 mmol) at rt and the mixture was stirred at rt for 1 h. The mixture was quenched by the addition of H_2O and extracted with EtOAc. The extract was washed with brine, dried and concentrated. The residue was purified by chromatography (40:1 hexane/EtOAc) to afford **19** (17.5 g, 70%) as a colorless oil and the recovered (−)-**2** (1.44 g, 13%). $[\alpha]_D^{21}$=+35.6 (*c* 1.6, $CHCl_3$); IR (neat) 2956, 2931, 2889, 2858, 1802, 1756, 1463, 1443, 1385, 1254, 1210, 1171, 1111, 1000, 934, 836, 778 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: −0.03 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$), 0.86 (9H, s, *t*-Bu), 1.34 (3H, d, *J*=6.1 Hz, H-5), 3.07 (1H, dd, *J*=4.3 Hz, 7.9 Hz, H-3), 3.55 (1H, d, *J*=4.3 Hz, H-2), 3.78 (1H, m, H-4), 3.79 (3H, s, CO_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: −5.0, −4.5, 17.9, 22.0, 25.6, 52.2, 52.9, 61.2, 64.9, 168.4; HRMS, calcd for $C_{12}H_{25}O_4Si$ ($M+H^+$) 261.1504, found 261.1516.

4.2.13. (2*R*,3*S*,4*S*)-Methyl 2,3-epoxy-4-(*t*-butyldimethylsilyloxy)-2-trimethylsilyl-pentanoate 20. To a solution of diisopropylamine (13.5 mL, 96.3 mmol) in THF (120 mL) was added *n*-BuLi (60 mL of a 1.56 M solution in hexane, 93.6 mmol) at 0°C for 10 min. Then the mixture was cooled at −110°C. After the addition of trimethylsilyl chloride (11 mL, 86.7 mmol), a solution of **19** (17.5 g, 67.2 mmol) in THF (30 mL) was added to the mixture at −78°C and the mixture was stirred at −78°C for 10 min. The mixture was quenched by the addition of H_2O and extracted with EtOAc. The extract was washed with brine, dried and concentrated. The residue was purified by chromatography (40:1 hexane/EtOAc) to afford a 5.5:1 mixture of **20** (17.8 g, 80%) as a colorless oil. IR (neat) 2956, 2931, 2898, 2858, 1803, 1748, 1720, 1472, 1463, 1436, 1370, 1293, 1252, 1214, 1157, 1105, 994, 914, 839, 777 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: −0.06 (3H, s, $SiCH_3$) −0.05 (3H, s, $SiCH_3$), 0.05* (3H, s, $SiCH_3$), 0.06* (3H, s, $SiCH_3$), 0.11 (9H, s, TMS), 0.18* (9H, s, TMS), 0.85 (9H, s, *t*-Bu), 0.86* (9H, s, *t*-Bu), 1.25* (3H, d, *J*=6.3 Hz, H-5), 1.29 (3H, d, *J*=6.2 Hz, H-5), 2.84 (1H, d, *J*=7.3 Hz, H-3), 2.95* (1H, d, *J*=7.9 Hz, H-3), 3.58 (1H, m, H-4), 3.68* (1H, m, H-4), 3.70* (3H, s, CO_2CH_3), 3.71 (3H, s, CO_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: −5.1, −4.4, −4.1*, −3.6, −3,5*, −1.7*, 17.8, 17.9*, 21.5*, 22.0, 25.6, 25.7*, 51.6, 51.9*, 56.8*, 57.4, 63.7, 66.2, 66.7, 67.4, 168.4, 172.8; HRMS, calcd for $C_{15}H_{32}O_4NaSi_2$ ($M+Na^+$) 355.1700, found 355.1731.

4.2.14. (1*R*,4*S*,5*S*)-4-Methyl-1-trimethylsilyl-3,6-dioxabicyclo[3.1.0]hexan-2-one (−)-5. To a solution of **20** (17.8 g, 53.5 mmol) in CH_3CN (50 mL) was added a solution of 5% aqueous HF in CH_3CN (50 mL) at rt. The mixture was stirred for 4 h and the mixture was quenched by the addition of a solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc. The extract was dried and concentrated. A solution of the residue and camphorsulfonic acid (253 mg, 1.1 mmol) in benzene (150 mL) was refluxed for 1 h and the mixture was quenched by the addition of a solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc (×2). The extract was washed with brine, dried and concentrated. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford (−)-**5** (7.5 g, 75%) and **21** (1.5 g, 13%) as a colorless oil.

(−)-**5**: $[\alpha]_D^{22}$=−47.7 (*c* 1.7, $CHCl_3$).

4.2.15. (2*S*,3*S*,4*S*)-Methyl 2,3-epoxy-4-hydroxy-2-trimethylsilylpentanate 21. $[\alpha]_D^{21}$=+11.2 (*c* 1.2, MeOH); IR

(neat) 3496, 2956, 2903, 1727, 1437, 1371, 1251, 1146, 1076, 1014, 949, 900, 847, 766 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 0.20 (9H, s, TMS), 1.34 (3H, d, J=6.2 Hz, H-5), 1.91 (1H, brs, OH), 2.93 (1H, d, J=7.7 Hz, H-3), 3.61 (1H, m, H-4), 3.70 (3H, s, CO_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: −1.7, 21.1, 51.9, 65.7, 66.6, 172.8; HRMS, calcd for $C_9H_{18}O_4NaSi$ ($M+Na^+$) 241.0866, found 241.0866.

4.2.16. (3*E*)-7-(4-Methoxybenzyloxy)-1-trimethylsilyl-3-hepten-1-yne 24. To a solution of **23** (11 g, 24 mmol) in THF/toluene (1:1, 80 mL) was added *n*-BuLi (12 mL of a 1.65 M solution in hexane, 20 mmol) at −60°C and the mixture was stirred at −60°C for 30 min. Then a solution of **22** (4.0 g, 20 mmol) in THF/toluene (1:1, 10 mL) was added at −60°C and the mixture was stirred at −60°C for 2 h. The mixture was quenched by the addition of H_2O and extracted with hexane (×3). The combined extract was washed with brine, dried, concentrated. The residue was purified by chromatography (9:1 hexane/EtOAc) to afford **24** (5.1 g, 86%, *E*/*Z*=5.7:1) as a yellow oil. *E*-isomer: IR (neat) 2956, 2854, 1614, 1514, 1250, 1086, 1038, 845 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.19 (9H, s, TMS), 1.69 (2H, m, H-6), 2.20 (2H, dq, J=1.7, 7.3 Hz, H-5), 3.44 (2H, t, J=6.6 Hz, H-7), 3.81 (3H, s, OCH_3), 4.42 (2H, S, CH_2Ar), 5.51 (1H, td, J=1.7, 16.2 Hz, H-3), 6.21 (1H, td, J=7.3, 16.2 Hz, H-4), 6.88 (2H, d, J=8.6 Hz, Ar), 7.26 (2H, d, J=8.6 Hz, Ar); HRMS, calcd for $C_{18}H_{26}O_2Si$ (M^+) 302.1702, found 302.1702.

4.2.17. (3*E*)-7-(4-Metoxybenzyloxy)-3-hepten-1-yne 25. A solution of **24** (2.2 g, 7.2 mmol) and K_2CO_3 (1.1 g, 7.2 mmol) in MeOH (70 mL) was stirred at rt for 30 min. Then the mixture was quenched by the addition of H_2O and extracted with hexane (×3). The combined extract was washed with brine, dried, concentrated. The residue was purified by chromatography (9:1 hexane/EtOAc) to afford **25** (1.5 g, 95%, *E*/*Z*=5.7:1) as a yellow oil. *E*-isomer: IR (neat) 3286, 2933, 2856, 1612, 1464, 1314, 1248, 1099, 1036 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.67–1.72 (2H, m, H-6), 2.20 (2H, ddt, J=1.3, 6.9, 7.3 Hz, H-5), 2.78 (1H, d, J=2.6 Hz), 3.44 (2H, t, J=6.3 Hz, H-7), 3.80 (3H, s, OCH_3), 4.42 (2H, s, CH_2Ar), 5.46 (1H, m, H-3), 6.24 (1H, td, J=6.9, 15.8 Hz, H-4), 6.88 (2H, d, J=8.6 Hz, Ar), 7.24 (2H, d, J=8.6 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): 28.6, 29.6, 55.2, 68.9, 72.5, 75.8, 82.4, 108.9, 113.7, 129.1, 130.5, 146.0, 159.1; HRMS, calcd for $C_{15}H_{18}O_2$ (M^+) 230.1302, found 230.1299.

4.2.18. (1*E*,3*E*)-1-Iodo-7-(4-metoxybenzyloxy)-2-methyl-1,3-heptentadiene 14. To a solution of Cp_2TiCl_2 (0.78 g, 3.1 mmol) in 1,2-dichloroethane (20 mL) was added Me_3Al (29 mL of 1.08 M solution in hexane, 31 mmol) and the mixture was stirred at rt for 30 min. Then a solution of **25** in 1,2-dichloroethane (7 mL) was added to the mixture and the mixture was stirred at rt for 90 min. The mixture was cooled to −40°C, a solution of I_2 (3.2 g, 13 mmol) was added via canula. After stirring at −40°C for 1 h, the mixture was quenched by the addition of a solution of saturated aqueous K_2CO_3 and extracted with hexane (×3). The combined extract was washed with brine, dried, concentrated. The residue was purified by chromatography (19:1 hexane/EtOAc) to afford **14** (2.6 g, 78%, *E*/*Z*=5.7:1) as a yellow oil. *E*-isomer: IR (neat) 2933, 2852. 1612, 1512, 1464, 1248, 1099, 1038, 820 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.70 (2H, tt, J=6.3, 7.6 Hz, H-6), 1.92 (3H, d, J=1.0 Hz, 2-Me), 2.15 (2H, dt, J=6.9, 7.6 Hz, H-5), 3.44 (2H, t, J=6.3 Hz, H-7), 3.81 (3H, s, OCH_3), 4.42 (2H, s, CH_2Ar), 5,74 (1H, td, J=6.9, 15.5 Hz, H-4), 6.13 (1H, d, J=15.5 Hz, H-3), 6.17 (1H, S. H-1), 6.88 (2H, d, J=8.6 Hz, Ar), 7.26 (2H, d, J=8.6 Hz, Ar); HRMS, calcd for $C_{16}H_{21}O_2I$ (M^+) 372.0586, found 372.0585.

4.2.19. (*Z*)-2-Tributyltin-2-butenoic acid 27. A solution of **26** (1.12 g, 3.1 mmol) and MnO_2(5.0 g, 58 mmol) in THF (28 mL) was stirred at rt for 24 h. Then the mixture was filtered through Celite and washed with EtOAc. After removing solvent, the residue was purified by chromatography (9:1 hexane/EtOAc) to afford the aldehyde (1.06 g, 95%) as a colorless oil. IR (neat) 2956, 2924, 2854, 1674, 1605, 1169, 1066 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.88 (9H, t, J=7.3 Hz), 1.04 (6H, t, J=7.3 Hz), 1.27–1.35 (6H, m), 1.42–1.50 (6H, m), 2.07 (3H, d, J=6.6 Hz, H-4), 7.43 (1H, q, J=6.6 Hz, H-3), 9.59 (1H, s, CHO).

To a solution of the aldehyde (1.06 g, 3.0 mmol), H_2O_2 (0.3 mL of a 35% aqueous solution, 3.0 mmol) and NaH_2PO_4 (127 mg, 0.81 mmol) in CH_3CN/H_2O (20:1, 5 mL) was added $NaClO_2$ (0.49 g, 79%, 4.3 mmol) at 0°C in portions for 30 min. After stirring at rt for 8 h, the mixture was quenched by the addition of H_2O and extracted with CH_2Cl_2 (×5). The combined extract was washed with brine, dried, concentrated. The residue was purified by chromatography (19:1 hexane/EtOAc) to afford **27** (0.86 g, 78%) as a colorless oil. IR (neat) 2956, 2924, 2854, 2629, 1666, 1605, 1458, 1402, 1273 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.88 (9H, t, J=7.3 Hz), 1.00–1.06 (6H, m), 1.23–1.38 (6H, m), 1.43–1.56 (6H, m), 1.92 (3H, d, J=6.9 Hz, H-4), 7.58 (IH, q, J=6.9 Hz, H-3).

4.2.20. Methyl (*Z*)-2-tributyltin-2-butenoate 15. To a solution of **27** (0.86 g, 2.29 mmol) in DMF (4 mL) was added *t*-BuOK (386 mg, 3.40 mmol) at 0°C. After stirring at 0°C for 10 min, CH_3I (210 μL, 3.37 mmol) was added and the mixture was stirred at rt for 30 min. Then the mixture was quenched by the addition of H_2O and extracted with hexane (×3). The combined extract was washed with brine, dried, concentrated. The residue was purified by chromatography (19:1 hexane/EtOAc) to afford **15** (0.79 g, 88%) as a colorless oil. IR (neat) 2956, 2924, 2854, 1713, 1610, 1458, 1433, 1244, 1211 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.89 (9H, t, J=7.3 Hz), 1.01 (6H, t, J=7.3 Hz), 1.27–1.35 (6H, m), 1.45–1.49 (6H, m), 1.89 (3H, d, J=6.9 Hz, H-4), 3.69 (3H, s, CO_2CH_3), 7.45 (IH, q, J=6.9 Hz, H- 3).

4.2.21. Methyl (2*E*,3*E*,5*E*)-2-ethylidene-9-(4-methoxybenzyloxy)-4-methylnona-3,5-dienoate 28. To a solution of $PdCl_2(CH_3CN)_2$ (34 mg, 0.13 mmol) and CuI (254 mg, 1.34 mmol) in degassed DMF (20 mL) was added a solution of **14** (500 mg, 1.34 mmol) in DMF (3 mL) at rt. After stirring at rt for 10 min, a solution of **15** (781 mg, 2.01 mmol) was added to the mixture. Then the mixture was warmed up to 50°C and stirred at 50°C for 24 h. Then the mixture was quenched by the addition of 30% aqueous NH_3 solution and extracted with Et_2O (×3). The combined extract was washed with brine, dried, concentrated.

The residue was purified by chromatography (9:1 hexane/EtOAc) to afford a 5.7:1 mixture of **28** (421 mg, 91%) as a yellow oil. *E*-isomer: IR (neat) 2949, 2852, 1716, 1612, 1514, 1250, 1099, 1036, 822 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.64 (3H, d, J=13 Hz, 4-Me), 1.65–1.70 (2H, m, H-8), 1.72 (3H, dd, J=1.3, 7.3 Hz, CH–Me), 2.17–2.27 (2H, m, H-7), 3.47 (2H, t, J=6.6 Hz, H-9), 3.73 (3H, s, CO_2Me), 3.80 (3H, s, ArOMe), 4.40 (2H, s, $ArCH_2$), 5.71 (1H, m, H-6), 5.92 (1H, brs, H-3), 6.21 (1H, d, J=15.5 Hz, H-5), 6.88 (2H, d, J=8.6 Hz, Ar), 7.26 (IH, dq, J=1.0, 7.3 Hz, CH–Me), 7.27 (2H, d, J=8.6 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ:14.3, 15.8, 29.4, 51.8, 55.2, 69.4, 72.5, 113.7, 122.1, 129.1, 129.2, 129.8, 130.6, 130.7, 134.3, 139.4, 159.1, 167.9; HRMS, calcd for $C_{21}H_{28}O_4$ (M^+) 344.1988, found 344.1987.

4.2.22. Methyl (2*E*,3*E*,5*E*)-2-ethylidene-9-hydroxy-4-methylnona-3,5-dienoate 29. A solution of **28** (31.5 mg, 91.5 μmol) in dioxane/4N aq. HCl (4:1, 5 mL) was stirred at 60°C for 5 h. Then the mixture was quenched by the addition of 30% aqueous NH_3 solution and extracted with Et_2O (×3). The combined extract was washed with H_2O, brine, dried, concentrated. The residue was purified by preparative TLC (5:1 hexane/EtOAc) to afford **29** (11.5 mg, 56%) and the recovered **28** (9.6 mg, 31%). The recovered **28** was treated with HCl in the same way, affording **29** (5.0 mg, 59%) and the recovered **28** (1.4 mg, 11%). **29** (16.5 mg, 81%) and the recovered **28** (1.4 mg, 4%) are obtained in total. **29**: a yellow oil; IR (neat) 3358, 2949, 2858, 1716, 1633, 1434, 1263, 1059, 1026, 731 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.58 (1H, s, OH), 1.64 (3H, d, J=1.0 Hz, 4-Me), 1.65–1.68 (2H, m, H-8), 1.72 (3H, dd, J=1.3, 7.3 Hz, CH–Me), 2.24 (2H, q, J=7.2 Hz, H-7), 3.68 (2H, t, J=6.6 Hz, H-9), 3.73 (3H, s, CO_2Me), 5.74 (1H, m, H-6), 5.94 (1H, brs, H-3), 6.24 (1H, d, J=15.8 Hz, H-5), 6.94 (1H, dq, J=1.0, 7.3 Hz, CH–Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 15.7, 29.1, 32.3, 51.8, 62.3, 122.2, 129.6, 130.5, 134.4, 137.9, 139.6, 167.9; HRMS, calcd for $C_{13}H_{20}O_3$ (M^+) 224.1411, found 224.1398.

4.2.23. Methyl (2*E*,3*E*,5*E*)-2-ethylidene-4-methyl-9-oxonona-3,5-dienoate 30. To a solution of $(COCl)_2$ (0.40 mL, 4.7 mmol) in CH_2Cl_2 (7.5 mL) was added DMSO (0.50 mL, 7.0 mmol) at −78°C. After 10 min at −78°C, a solution of **29** (286 mg, 1.28 mmol) in CH_2Cl_2 (12.5 mL) was added to the mixture and the mixture was stirred at −78°C for 90 min. Then Et_3N (1.8 mL, 12.9 mmol) was added and the mixture was stirred at rt for 10 min. The mixture was quenched by the addition of H_2O and extracted with CH_2Cl_2 (×3). The combined extract was washed with brine, dried, concentrated. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford a 5.7:1 mixture of **30** (270 mg, 95%) as a yellow oil. IR (neat) 2951, 2852, 2723, 1716, 1679, 1633, 1435, 1257, 1134, 1026, 966, 733 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.61 (3H, d, J=1.0 Hz, 4-Me), 1.70 (3H, dd, J=1.0, 7.3 Hz, CH–Me), 2.47 (2H, q, J=6.6 Hz, H-7), 2.56 (2H, dt, J=1.3, 6.6 Hz, H-8), 3.72 (3H, s, CO_2Me), 5.71 (1H, m, H-6), 5.95 (1H, brs, H-3), 6.24 (1H, d, J=15.8 Hz, H-5), 6.94 (1H, dq, J=1.0, 7.3 Hz, CH–Me), 9.80 (IH, t, J=1.3 Hz, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 15.8, 25.3, 43.4, 51.8, 123.1, 127.7, 130.5, 135.2, 137.6, 139.7, 167.8, 201.9; HRMS, calcd for $C_{13}H_{18}O_3$ (M^+) 222.1255, found 222.1262.

4.2.24. Methyl (2*E*,3*E*,5*E*)-2-ethyl-4,10-methyl-11-oxoundeca-3,5,9-trienoate 13. A solution of **30** (270 mg, 1.21 mmol) and 2-(triphenylphosphoranylidene)propionaldehyde (1.75 g, 5.50 mmol) in toluene (40 mL) was refluxed for 17 h. The solvent was removed under a reduced pressure. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford a 5.7:1 mixture of **13** and its 6*Z*-isomer (272 mg, 85%). Further purification by flash chromatography (8:1 hexane/EtOAc) gave **13** as a yellow oil. IR (neat) 2983, 2849, 2850, 1716, 1687, 1641, 1435, 1379, 1360, 1252, 1211, 1133, 1024, 966, 860, 833, 764, 731 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.63 (3H, d, J=1.0 Hz, 4-Me), 1.73 (3H, dd, J=1.0, 7.3 Hz, CH–Me), 1.76 (3H, d, J=l.3 Hz, 10-Me), 2.36 (2H, m, H-7), 2.50 (2H, m, H-8), 3.74 (3H, s, CO_2Me), 5.72 (1H, m, H-6), 5.97 (IH, brs, H-3), 6.27 (1H, d, J=15.7 Hz, H-5), 6.51 (IH, dt, J=1.3, 7.3 Hz, H-9), 6.95 (IH, dq, J=1.0, 7.3 Hz, CH–Me), 9.42 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.3, 14.4, 15.8, 28.8, 31.5, 51.8, 123.0, 128.2, 130.5, 135.2, 137.6, 139.7, 153.5, 167.8, 195.2; HRMS, calcd for $C_{16}H_{22}O_3$ (M^+) 262.1572, found 262.1568.

4.2.25. (1*R*,4*S*,5*R*)-4-Methyl-1-[(2*E*,6*E*,8*E*,10*E*)]-2,8-dimethyl-1-hydroxy-10-methoxycarbonydodeca-2,6,10-trienyl]-3,6-dioxa-bicyclo[3.1.0]hexan-2-one 31. To a solution of (−)-**5** (87.8 mg, 0.47 mmol), **13** (82.4 mg, 0.31 mmol) and MS4A (0.30 g) in THF/hexane (1:1, 2 mL) at rt was added TBAF (60 μL of a 0.5 M solution in THF, 30 μmol), which had been treated with MS4A for 3 h before use. The mixture was stirred at rt for 24 h and then filtered through Celite and diluted with EtOAc. The organic layer was washed with H_2O, brine, dried and concentrated. A solution of the residue in CH_3CN (2 mL) was added a solution of 5% aqueous HF in CH_3CN (2 mL) at rt for 30 min. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (×3). The combined extract was washed with brine, dried and concentrated. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford **31** (46.6 mg, 39%) and the recovered **13** (41.0 mg, 50%). **31**: a pale yellow oil; IR (neat) 3467, 2981, 2922, 2854, 1782, 1716, 1635, 1437, 1381, 1338, 1263, 1213, 1134, 1024, 968, 858, 758, 733, 692 cm^{-1}; ^1H NMR (270 MHz, $CDCI_3$) δ: 1.39 (3H, d, J=6.6 Hz, 4-Me), 1.62 (3H, d, J=l.3 Hz, 8′-Me), 1.71 (3H, s, 2′-Me), 1.71 (3H, dd, J=1.3, 7.3 Hz, H-12′), 2.20–2.23 (4H, m, H-4′ and H-5′), 3.72 (3H, s, CO_2Me), 4.02 (1H, s, H-5), 4.65 (1H, q, J=6.6 Hz, H-4), 4.77 (1H, s, H-1′), 5.68–5.72 (2H, m, H-3′ and H-6′), 5.94 (1H, brs, H-9′), 6.22 (1H, d, J=15.5 Hz, H-7′), 6.94 (1H, dq, J=1.0, 7.3 Hz, H-11′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.6, 14.4, 15.8, 17.8, 27.7, 32.3, 51.8, 61.0, 61.9, 69.7, 75.2, 122.4, 129.5, 130.5, 131.2, 131.3, 134.6, 138.0, 139.6, 167.9, 169.8; HRMS, calcd for $C_{21}H_{28}O_6$ (M^+) 376.1886, found 376.1868.

4.2.26. (1*R*,4*S*,5*R*)-4-Methyl-1-[(2*E*,6*E*,8*E*,10*E*)-2,8-dimethyl-10-methoxycarbony-1-oxododeca-2,6,10-trienyl]-3,6-dioxa-bicyclo[3.1.0]hexan-2-one 12. To a solution of DMSO (71 μL, 0.46 mmol) in CH_2Cl_2 (1 mL) was added TFAA (65 μL, 0.92 mmol) at −78°C. After 10 mm at −78°C, a solution of **31** (57.3 mg, 0.15 mmol) in CH_2Cl_2 (1.5 mL) was added to the mixture and the mixture was stirred at −78°C for 30 min. Then Et_3N (215 μL,

1.54 mmol) was added and the mixture was stirred at rt for 10 min. The mixture was quenched by the addition of H_2O and extracted with CH_2Cl_2 (×2). The combined extract was washed with brine, dried, concentrated. The residue was purified by chromatography (2:1 hexane/EtOAc) to afford **12** (50.8 mg, 89%) as a pale yellow oil. $[\alpha]_D^{21}=-2.2$ (*c* 0.90, $CHCl_3$). IR (neat) 2981, 2925, 2852, 1782, 1713, 1680, 1637, 1435, 1381, 1335, 1250, 1132, 1072, 1024, 970, 871, 779 cm^{-1}; ^1H NMR (270 MHz, CDC1$_3$) δ: 1.50 (3H, d, *J*=6.9 Hz, 4-Me), 1.63 (3H, d, *J*=1.0 Hz, 8′-Me), 1.72 (3H, dd, *J*=1.3, 7.3 Hz, H-12′), 1.86 (3H, s, 2′-Me), 2.35 (2H, m, H- 5′), 2.48 (2H, m, H-4′), 3.73 (3H, s, CO_2Me), 4.07 (1H, s, H-5), 4.71 (1H, q, *J*=6.9 Hz, H-4), 5.71 (2H, m, H-6′), 5.96 (1H, brs, H-9′), 6.26 (1H, d, *J*=15.5 Hz, 11-7′), 6.89 (1H, qt, *J*=1.3, 7.3 Hz, H-3′), 6.95 (1H, dq, *J*=1.0, 7.3 Hz, H-11′); ^{13}C NMR (75 MHz, CDC1$_3$) δ: 11.2, 14.3, 15.8, 17.8, 29.3, 31.6, 51,8, 63.9, 64.0, 75.5, 123.1, 128.0, 130.4, 135.5, 136.0, 137.6, 139.6, 139.7, 149.5, 167.8, 188.3; HRMS, calcd for $C_{21}H_{28}O_6$ (M^+) 374.1729, found 374.1733.

4.2.27. Methyl (3*E*,5*E*,9*E*,12*R*,13*R*,14*S*)-12-carbamoyl-12,13-epoxy-2-[(*E*)-ethylidene]-4,10-dimethyl-14-hydroxy-11-oxopentadeca-3,5,9-trienoate 32. A solution of **12** (50.8 mg, 0.14 mmol) and NH_3 (~1 mL) in MeOH (2 mL) was stirred at 0°C in a sealed tube for 1 h. The solvent was removed under a reduced pressure. The residue was purified by chromatography (1:1–1:2 hexane/EtOAc) to afford **32** (42.3 mg, 80%) as a colorless oil. $[\alpha]_D^{21}=-54.5$ (*c* 0.55, MeOH); IR (neat) 3460, 3344, 2978, 2951, 2929, 2854, 1689, 1635, 1599, 1435, 1392, 1265, 1213, 1061, 1024, 966, 870, 837, 758, 731 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ: 1.33 (3H, d, *J*=6.9 Hz, H-15), 1.62 (3H, d, *J*=1.0 Hz, 4-Me), 1.71 (3H, dd, *J*=1.3, 7.3 Hz, CH–Me), 1.79 (3H, d, *J*=1.0 Hz, 10-Me), 2.38 (2H, m, H-8), 2.46 (2H, m, H-7), 3.17 (1H, d, *J*=8.3 Hz, H-13), 3.61–3.68 (1H, m, H-14), 3.71 (3H, s, CO_2Me), 5.78 (2H, td, *J*=6.9, 15.5 Hz, H-6), 5.94 (1H, brs, H-3), 6.27 (1H, d, *J*=15.5 Hz, H-5), 6.93 (1H, tq, *J*=1.0, 7.3 Hz, H-9), 7.09 (1H, dt, *J*=1.0, 7.3 Hz, CH–Me); ^{13}C NMR (75 MHz, CD_3OD) δ: 12.1, 15.4, 16.7, 21.8, 31.0, 33.4, 53.1, 63.1, 66.1, 67.4, 67.7, 124.5, 130.7, 132.7, 137.2, 137.2, 136.0, 137.6, 141.6, 150.8, 170.2, 171.0, 195.5; HRMS, calcd for $C_{21}H_{29}NO_6$ (M^+) 391.1995, found 391.1999.

4.2.28. Epolactaene (+)-1. To a solution of Dess-Martin periodinane (8.6 mg, 20 μmol) in CH_2Cl_2 (1 mL) was added a solution of **31** (3.3 mg, 8.4 mmol) in CH_2Cl_2 (1 mL) at rt. After stirring for 3 h, the mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL) and saturated aqueous $NaHSO_3$ (1 mL) and extracted with $CHCl_3$ (×3). The combined extract was washed with H_2O brine, dried and concentrated. The residue was purified by chromatography (2:3 hexane/EtOAc) to afford (+)- epolactaene (2.3 mg, 70%) as a ca. 5.4:1 tautomeric mixture as a colorless foam. $[\alpha]_D^{21}=+34.0$ (*c* 0.25, MeOH); IR ($CHCl_3$) 3425, 3026, 2927, 2854, 1728, 1691, 1631, 1439, 1381, 1179, 1140, 964 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ: 1.52 (3H, s, H-16), 1.62 (311, d, *J*=1.0 Hz, H-21), 1.72 (3H, dd, *J*=1.3, 7.3 Hz, H-1), 1.79 (3H, d, *J*=1.0 Hz, H-21), 1.83 (3H, d, *J*=l.3 Hz, H-22), 2.35 (2H, m, H-8), 2.47 (2H, m, H-9), 3.71 (3H, s, H-20), 3.98 (1H, s, H-14), 5.78 (2H, td, *J*=6.9, 15.5 Hz, H-7), 5.94 (1H, brs, H-4), 6.28 (1H, dd, *J*=0.7, 15.5 Hz, H-6), 6.93 (1H, dq, *J*=1.0, 7.3 Hz, H-2), 7.02 (1H, dt, *J*=1.3, 6.6 Hz, H-l0); ^{13}C NMR (75 MHz, CD_3OD) δ: 11.9, 15.4, 16.7, 23.0, 31.0, 33.3, 53.2, 64.7, 66.9, 85.5, 124.4, 130.7, 132.7, 137.2, 137.4, 138.0, 140.4, 141.6, 150.8, 170.4, 173.0, 192.9; HRMS, calcd for $C_{21}H_{27}NO_6$ (M^+) 389.1839, found 389.1843.

4.2.29. *ent*-Epolactaene (−)-1. $[\alpha]_D^{21}=-34.2$ (*c* 0.05, MeOH).

4.3. The general method for the preparation of 33

To a solution of **11b** (36.0 mg, 0.168 mmol), which was prepared by the coupling of (−)-**5** with 1-hexanal, in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (143 mg, 0.336 mmol) at rt and the mixture was stirred for 1 h. Then the mixture was diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, H_2O and brine. The organic layer was dried and concentrated. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford **33b** (26.5 mg, 74%) as a colorless oil.

4.3.1. (1*S*,4*S*,5*S*)-1-Hexanoyl-4-methyl-3,6-dioxabicylo-[3.1.0] hexan-2-one 33b. $[\alpha]_D^{21}=-96.0$ (*c* 2.5, $CHCl_3$); IR (neat) 3061, 2958, 2933, 2864, 1786, 1716, 1460, 1404, 1335, 1255, 1130, 1072, 1016, 958, 910, 854, 775, 750, 696, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J*=6.8 Hz, H-6′), 1.26–1.35 (4H, m, H-4′, H-5′), 1.45 (3H, d, *J*=6.8 Hz, 4-Me), 1.59–1.66 (2H, m, H-3′), 2.56–2.67 (2H, m, H-2′), 4.21 (1H, s, H-5), 4.70 (1H, q, *J*=6.8 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 17.7, 22.2, 22.2, 30.9, 39.6, 59.0, 65.3, 74.8, 166.7, 198.7; HRMS, calcd for $C_{11}H_{16}O_4$ (M-H^+) 211.0970, found 211.0978.

4.3.2. (1*S*,4*S*,5*S*)-1-Dodecanoyl-4-methyl-3,6-dioxabicylo-[3.1.0]hexan-2-one 33c. The title compound was prepared in 90% yield as a white solid. Mp=32°C. $[\alpha]_D^{21}=+63.0$ (*c* 1.86, $CHCl_3$); IR ($CHCl_3$); 3034, 2929, 2856, 1788, 1720, 1462, 1402, 1335, 1238, 1128, 1076, 1016, 962, 914, 856, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 0.86–0.88 (3H, m, H-12′), 1.00 (18H, m, H-3′–H 11′), 1.45 (3H, d, *J*=6.8 Hz, 4-Me), 2.62 (2H, m, H-2′), 4.19 (1H, s, H-5), 4.69 (1H, q, *J*=6.8 Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 17.7, 22.6, 28.9, 29.2, 29.2, 29.3, 29.5, 29.5, 31.8, 39.7, 59.7, 65.4, 74.8, 166.7, 198.7; HRMS, calcd for $C_{17}H_{28}O_4$ (M−H^+) 295.1907, found 295.1913.

4.3.3. (1*S*,4*S*,5*S*)-4-Methyl-1-(2-methylpent-2-enol)-3,6-dioxabicylo-[3.1.0]hexan-2-one 33e. The title compound was prepared in 83% yield as a colorless oil. $[\alpha]_D^{20}=-12.0$ (*c* 0.31, $CHCl_3$); IR (neat) 3550, 3026, 2974, 2937, 2877, 1782, 1678, 1635, 1456, 1385, 1335, 1244, 1215, 1134, 1072, 1016, 982, 924, 845, 756, 696, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, t, *J*=7.6 Hz, H-5′), 1.51 (3H, d, *J*=6.8 Hz, 4-Me), 1.84 (3H, d, *J*=1.2 Hz, 2′-Me), 2.35 (2H, dq, *J*=7.0, 7.6 Hz, H-4′), 4.12 (1H, s, H-5), 4.73 (1H, q, *J*=6.8 Hz, H-4), 6.87 (1H, dq, *J*=1.2, 7.0 Hz, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.8, 12.5, 17.7, 22.7, 60.2, 63.9, 75.5, 135.1, 151.9, 168.3, 188.3; HRMS, calcd for $C_{11}H_{14}O_4$ (M^+) 210.0891, found 210.0900.

4.3.4. (1*S*,4*S*,5*S*)-1-Dodecanoyl-4-methyl-3,6-dioxabicylo-[3.1.0]hexan-2-one 33h. The title compound was prepared in 88% yield as a white solid. Mp=50–54°C.

$[\alpha]_D^{21}=-57.1$ (*c* 0.45, $CHCl_3$); IR ($CHCl_3$); 2927, 2855, 1787, 1717, 1465, 1383, 1335, 1111, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.8 Hz, H-18′), 1.25 (30H, m, H-4′–H-17′), 1.45 (3H, d, *J*=6.8 Hz, 4-Me), 1.49–1.65 (2H, m, H-3′), 2.62 (2H, m, H-2′), 4.17 (1H, s, H-5), 4.69 (1H, q, *J*=6.8 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 17.8, 22.7, 28.9, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 29.6, 29.6, 31.9, 39.8, 59.1, 60.3, 65.4, 74.8, 166.7, 198.7; HRMS, calcd for $C_{23}H_{40}O_4$ (M^+) 380.2927, found 380.2915.

4.4. The general method for the preparation of 34

A solution of **33b** (15.7 mg, 0.074 mmol) and NH_3 (~0.1 mL) in MeOH (0.5 mL) was stirred at 0°C in a sealed tube for 3 h. The solvent was removed under a reduced pressure. The residue was purified by chromatography (1:1 hexane/EtOAc) to afford **34b** (14.6 mg, 86%) as a white solid.

4.4.1. (2*S*,3*S*)-3-[(*S*)-1-Hydroxyethyl]-2-hexanoyloxirane-2-carboxanilde 34b. Mp=63–65°C. $[\alpha]_D^{22}=+19.0$ (*c* 0.56, MeOH); IR (neat) 3476, 3020, 2960, 2933, 2864, 1713, 1684, 1593, 1458, 1400, 1377, 1288, 1215, 1146, 1099, 1063, 970, 905, 756, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J*=7.0 Hz, H-6′), 1.23–1.33 (4H, m, H-4′, H-5′), 1.38 (3H, d, *J*=6.1 Hz, H-2″), 1.53–1.60 (2H, m, H-3′), 2.46–2.52 (1H, m, H-2′), 2.62–2.69 (IH, m, H-2′), 3.17 (1H, d, *J*=7.9 Hz, H-3), 3.64–3.70 (1H, m, H-1′), 6.76 (1H, s, NH), 7.00 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 20.2, 22.3, 22.6, 31.0, 37.8, 65.1, 65.5, 65.6, 167.2, 203.8; HRMS, calcd for $C_{11}H_{19}NO_4$ ($M+H^+$) 230.1391, found 230.1392.

4.4.2. (2*S*,3*S*)-3-[(*S*)-1-Hydroxyethyl]-2-dodecanoyloxirane-2-carboxamide 34c. The title compound was prepared in 92% yield as a white solid. Mp=94–95°C. $[\alpha]_D^{22}=+13.3$ (*c* 0.56, MeOH); IR ($CHCl_3$) 3512, 3477, 3359, 3018, 2927, 2856, 1708, 1695, 1578, 1458, 1396, 1284,1232,1146,1097, 1051,960,912, 656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.8 (3H, t, *J*=6.6 Hz, H-12′), 1.25 (16H, m, H-4′–H-11′), 1.39 (3H, d, *J*=6.2 Hz, H-2″), 1.56 (2H, m, H-3′), 2.49 (1H, td, *J*=7.3, 18.2 Hz, H-2′), 2.66 (IH, td, *J*=7.3, 18.2 Hz, H-2′), 3.17 (lH, d, *J*=7.7 Hz, H-3), 3.62–3.71 (1H, m, H-1″), 6.35 (1H, s, NH), 6.86 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 20.3, 22.7, 23.0, 29.0, 29.3, 29.3, 29.3, 29.4, 29.6, 31.9, 38.0, 65.4, 65.5, 65.6, 167.0, 203.7; HRMS, calcd for $C_{17}H_{31}NO_4$ (M^+) 313.2252, found 313.2269.

4.4.3. (2*S*,3*S*)-3-[(*S*)-1-Hydroxyethyl]-2(2-methylpent-2-enoyl)oxirane-2-carboxamide 34e. The title compound was prepared in 97% yield as a colorless oil. $[\alpha]_D^{22}=-75.9$ (*c* 0.34, MeOH); IR (neat) 3467, 3329, 3018, 2976, 2877, 1686, 1593, 1458, 1398, 1217, 1149, 1070, 968, 899, 843, 758, 667 cm^{-1} ^1H NMR (270 MHz, $CDCl_3$) δ: 1.10 (3H, t, *J*=7.6 Hz, H-5′), 1.38 (3H, t, *J*=6.3 Hz, H-2′), 1.79 (3H, d, *J*=1.3 Hz, 2′-Me), 2.26–2.37 (2H, m, H-4′), 3.17 (1H, d, *J*=7.9 Hz, H-3), 3.60 (1H, brs, OH), 3.69–3.79 (1H, m, H-1″), 6.51 (1H, s, NH), 6.74 (1H, s, NH), 7.09 (1H, dt, *J*=1.3, 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.7, 17,7, 22.2, 22.2, 30.9, 39.6, 59.0, 65.3, 74.8, 166.7, 198.7; HRMS, calcd for $C_{11}H_{17}NO_4$ (M^+) 227.1157, found 227.1159.

4.4.4. (2*S*,3*S*)-3-[(*S*)-1-Hydroxyethyl]-2-octadecanoyloxirane-2-carboxamide 34h. The title compound was prepared in 91% yield. Mp=98–101°C. $[\alpha]_D^{22}=+10.0$ (*c* 0.30, MeOH); IR ($CHCl_3$) 3710, 3650, 3574, 3154, 2988, 2926, 2852, 1715, 1666, 1560, 1466, 1382, 1296, 1210, 1146, 1097, 902, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.8 Hz, H-18′), 1.25 (30H, m, H-4′–H-17′), 1.41 (3H, d, *J*=6.3 Hz, H-2″), 1.45–1.65 (3H, m, H-3′, OH), 2,46–2.55 (1H, m, H-2′), 2.65–2.73 (IH, m, H-2′), 3.17 (1H, d, *J*=7.8 Hz, H-3), 3.66 (1H, m, H-1″), 5.85 (1H, s, NH), 6.75 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 20.3, 22.7, 23.0, 29.0, 29.3, 29.4, 29.4, 29.6, 29.7, 29.7, 29.7, 29.7, 31.9, 38.0, 65.5, 65.6, 65.7, 166.8, 203.8; HRMS, calcd for $C_{23}H_{43}NO_4$ (M^+) 397.3192, found 397.3188.

4.5. The general method for the preparation of 35

To a solution of **34b** (31.1 mg, 0.136 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (115 mg, 0.272 mmol) at rt and the mixture was stirred for 1 h. Then the mixture was diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, H_2O and brine. The organic layer was dried and concentrated. The residue was purified by chromatography (4:1 hexane/EtOAc) to afford **35b** (27.1 mg, 88%) as a ca. 1.7:1 tautomeric mixture, as a colorless foam.

4.5.1. ((1*R*,5*R*)-1-Hexanoyl-4-hydroxy-4-methyl-6-oxa-3-azabicyclo-[3.1.0]hexan-2-one 35b. $[\alpha]_D^{22}=-130.5$ (*c* 0.20, MeOH); IR ($CHCl_3$) 3340, 3020, 2960, 2933, 2864, 1736, 1697, 1593, 1466, 1400, 1365, 1217, 1155, 1119, 943, 889, 760, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.84–0.95 (3H, m, H-6′), 0.84–0.95* (3H, m, H-6′), 1.21–1.35 (6H, m, H-3′–H-5′), 1.21–1.35* (6H, m, H-3′–H-5′), 1.58 (3H, s, 4-Me), 1.61* (3H, s, 4-Me), 2.24–2.81 (2H, m, H-2′), 2.24–2.81* (2H, m, H-2′), 3.96* (IH, d, *J*=2.4 Hz, H-5), 4.21 (1H, d, *J*=2.4 Hz, H-5), 5.25 (1H, brs, OH), 6.22 (1H, brs OH), 6.98 (1H, d, *J*=9.0 Hz, NH), 7.97 (1H, d, *J*=9.0 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 21.3, 22.2, 22.3, 22.7, 24.2, 27.9, 31.0, 31.0, 31.1, 38.2, 38.6, 39.8, 61.2, 62.2, 62.8, 63.9, 65.8, 82.8, 83.5, 165.0, 166.9, 169.2, 199.8, 199.9, 201.8, 202.1 (diastereomeric mixture); HRMS, calcd for $C_{11}H_{17}NO_4$ ($M+H^+$) 228.1234, found 228.1234.

4.5.2. (1*R*,5*R*)-1-Dodecanoyl-4-hydroxy-4-methyl-6-oxa-3-azabicyclo-[3.1.0]hexan-2-one 35c. The title compound was prepared in 88% yield as a ca. 3.7:1 tautomeric mixture, as a colorless foam. $[\alpha]_D^{22}=-75.9$ (*c* 0.12, MeOH); IR ($CHCl_3$) 3455, 3020, 2927, 2856, 1743, 1693, 1408, 1215, 1161, 1117, 1086, 949, 758, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, d, *J*=6.6 Hz, H-12′), 0.88* (3H, t, *J*=6.6 Hz, H-12′), 1.25–150 (18H, m, H-3′–H-11′), 1.25–1.50* (6H, m, H-3′–H-11′), 1.58 (3H, s, 4-Me), 1.62* (3H, s, 4-Me), 2.19–2.30 (1H, m, H-2′), 2.l9–2.30* (1H, m, H-2′), 2.42–2.61 (1H, m, H-2′), 2.42–2.61* (1H, m, H-2′), 3.18* (1H, brs, OH), 3.96* (1H, d, *J*=1.8 Hz, H-5), 4.24 (1H, d, *J*=1.8 Hz, H-5), 5.25 (1H, brs, OH), 6.79 (1H, brs, NH), 8.13 (1H, brs, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 21.3, 22.5, 22.6, 22.7, 24.1, 29.0, 29.3, 29.3, 29.4, 29.4, 29.4, 29.6, 29.6, 29.6, 31.9, 38.1, 39.9, 61.2, 62.8, 63.9, 65,9, 82.8, 83.7, 166.8, 169.4, 199.7, 202.3

(diastereomeric mixture); HRMS, calcd for $C_{17}H_{29}NO_4$ (M^+) 311.2096, found 311.2108.

4.5.3. (1*R*,5*R*)-4-Hydroxy-4-methyl-1-(methylpent-2-enoyl)-6-oxa-3-azabicyclo-[3.1.0]hexan-2-one 35e. The title compound was prepared in 82% yield as a ca. 2.6:1 tautomeric mixture, as a white solid. Mp=86–88°C; $[\alpha]_D^{21}$=+12.6 (*c* 0.18, MeOH); IR ($CHCl_3$) 3338, 2954, 2927, 2854, 1740, 1637, 1460, 1377, 1309, 1161, 1074, 960, 891, 843, 768, 721 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.08 (3H, t, *J*=7.6 Hz, H-5′), 1.09* (3H, t, *J*=7.6 Hz, H-5′), 1.50 (3H, s, 4-Me), 1.59* (3H, s,4-Me), 1.81 (3H, s, 2′-Me), 2.00* (3H, s, 2′-Me), 2.27–2.38 (2H, m, H-4′), 2.27–2.38* (2H, m, H-4′), 3.99 (1H, s, H-5), 4.07* (1H, s, H-5), 6.76* (1H, dt, *J*=1.2, 7.3 Hz, H-3′), 6.98 (1H, dt, *J*=1.2, 7.3 Hz, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.9, 10.9, 12.9, 13.0, 22.2, 23.5, 23.6, 25.4, 63.9, 64.4, 65.9, 84.0, 84.7, 136.4, 136.5, 151.7, 152.2, 172.4, 192.2 (diastereomeric mixture); HRMS, calcd for $C_{11}H_{15}NO_4$ (M^+) 225.1000, found 225.1000.

4.5.4. (I*R*,5*R*)-4-Hydroxy-4-methyl-1-octadecanoyl-6-oxa-3-azabicyclo-[3.1.0]hexan-2-one 35h. The title compound was prepared in 91% yield as a ca. 8.7:1 tautomeric mixture, as a white solid. Mp=92°C; $[\alpha]_D^{21}$=−81.9 (*c* 0.4, MeOH); IR ($CHCl_3$) 3714, 3638, 3534, 3421, 3154, 2990, 2927, 2854, 1741, 1642, 1561, 1465, 1381, 1293, 1158, 1096, 1016, 909, 837, 713 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 0.88 (3H, d, *J*=6.6 Hz, H-12′), 0.88* (3H, t, *J*=6.6 Hz, H-12′), 1.25–1.50 (18H, m, H-3′–H-17′), 1.25–1.50* (6H, m, H-3′–H-17′), 1.59 (3H, s, 4-Me), 1.63* (3H, s, 4-Me), 2.44–2.62 (1H, m, H-2′), 2.44–2.62* (1H, m, H-2′), 2.73–2.81 (1H, m, H-2′), 2.73–2.81* (1H, m, H-2′), 3.96* (1H, d, *J*=2.4 Hz, H-5), 4.21 (1H, d, *J*=2.4 Hz, H-5), 5.86 (1H, brs, OH), 6.26* (1H, brs, OH), 6.88* (1H, brs, NH), 7.81 (1H, brs, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 21.4, 22,6, 28.9, 29.4, 29.5, 29.5, 29.6, 29.6, 29.6, 29.6, 29.7, 29.7, 29.7, 29.7, 29.7, 31.9, 38.3, 61.2, 63.7, 83.6, 169.2, 202.0 (the major isomer); HRMS, calcd for $C_{23}H_{41}NO_4$ (M^+) 395.3036, found 395.3038.

4.6. The general method for the preparation of 36

A solution of **11b** (9.8 mg, 0.047 mmol) and NH_3 (~0.1 mL) in MeOH (0.5 mL) was stirred at 0°C in a sealed tube for 30 min. The solvent was removed under a reduced pressure. The residue was purified by chromatography (1:2 hexane/EtOAc) to afford **36b** (7.8 mg, 74%) as a ca. 1:1 diastereomeric mixture at C-1′, as a white solid.

4.6.1. (2*S*,3*S*)-3-[(*S*)-1-Hydroxyethyl]-2-[1*RS*]-1-hydroxyhexyl]oxirane-2-carboxamide 36b. Mp=79–81°C; IR ($CHCl_3$) 3471, 3359, 3020, 2958, 2933, 2858, 1676, 1414, 1215, 1082, 1045, 964, 935, 756, 669 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ: 0.80–0.83 (3H, m, H-6′), 0.80–0.83* (3H, m, H-6′), 1.14–1.30 (6H, m, H-3′–H-5′), 1.14–1.30* (6H, m, H-3′–H-5′), 1.23 (3H, d, *J*=6.4 Hz, H-2″), 1.23* (3H, d, *J*=6.4 Hz, H-2″), 1.36–1.49 (2H, m, H-2′), 1.36–1.49* (2H, m, H-2′), 2.84 (1H, d, *J*=7.9 Hz, H-3), 3.04* (1H, d, *J*=8.2 Hz, H-3), 3.41–3.47 (1H, m, H-1″), 3.41–3.47* (1H, m, H-1″), 3.57 (1H, dd, *J*=3.2, 9.0 Hz, H-1′), 3.94* (1H, dd, *J*=3.8, 8.4 Hz, H-1′); ^{13}C NMR (125 MHz, CD_3OD) δ: 14.4, 20.9, 23.6, 23.6, 26.3, 26.6, 32.8, 32.8, 33.2, 33.9, 64.3, 64.3, 65.5, 65.6, 65.9, 67.2, 69.0, 70.3, 173.1, 173.5 (diastereomeric mixture); HRMS, calcd for $C_{11}H_{21}NO_4$ (M+H^+) 232.1547, found 232.1555.

4.6.2. (2*S*,3*S*)-3-[(*S*)-1-Hrdroxyethyl]-2-[(1*RS*)-1-hydroxydodecanoyl]oxirane-2-carboxamide 36c. The title compound was prepared in 91% yield as a ca. 1:1 diastereomeric mixture, as a colorless solid. Mp=89–91°C; IR ($CHCl_3$) 3513, 3467, 3398, 3018, 2927, 2856, 1680, 1574, 1468, 1402, 1379, 1294, 1221, 1088, 966, 889, 669 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ: 0.88–0.91 (3H, m, H-l2′), 0.88–0.91* (3H, m, H-12′), 1.29–1.40 (21H, m, H-3′–H-11′, H-2″), 1.29–1.40* (21H, m, H-3′–H-11′, H-2″), 1.45–1.61 (2H, m, H-2′), 1.45–1.61* (2H, m, H-2′), 2.93 (1H, d, *J*=8.2 Hz, H-3), 3.13* (1H, d, *J*=8.2 Hz, H-3), 3.50–3.56 (1H, m, H-1″), 3.50–3.56* (1H, m, H-1″), 3.67 (1H, dd, *J*=3.8, 9.0 Hz, H-1′), 4.04* (1H, dd, *J*=4.0, 8.5 Hz, H-1′); ^{13}C NMR (125 MHz, CD_3OD) δ: 14.5, 20.9, 23.7, 26.6, 27.0, 30.5, 30.5, 30.6, 30.7, 30.8, 30.8, 33.1, 33.2, 34.0, 64.3, 65.5, 65.6, 65.8, 67,2, 69.0, 70.3, 73.0, 173.2, 173.5 (diastereomeric mixture); HRMS, calcd for $C_{17}H_{33}NO_4$ (M+H^+) 316.2488, found 316.2471.

4.6.3. (2*S*,3*S*)-3-[(*S*)-1-Hydroxyethyl]-2-[(1*RS*)-1-hydroxymethyl-2-methylpent-2-enyl]oxirane-2-carboxamide 36e. The title compound was prepared in 93% yield as a ca. 1.6:1 diastereomeric mixture, as a colorless oil. IR (neat) 3473, 3400, 3344, 3018, 2970, 2933, 2873, 1676, 1593, 1443, 1414, 1375, 1304, 1215, 1151, 1095, 1059, 957, 758, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.96 (3H, t, *J*=7.6 Hz, H-5′), 0.96* (3H, t, *J*=7.6 Hz, H-5′), 1.33 (3H, d, *J*=6.3 Hz, H-2″), 1,35* (3H, d, *J*=5.9 Hz, H-2″), 1.64 (3H, s, 2′-Me), 1.64 (3H, s, 2′-Me), 1.98–2.11 (3H, m, H-4′), l.98–2.11* (2H, m, 11-4′), 2.96 (1H, d, *J*=8.2 Hz, H-3), 3.23* (1H, d, *J*=8.2 Hz, H-3), 3.53–3.65 (1H, m, H-1″), 3.53–3.65* (1H, m, H-1″), 4.24 (1H, s, H-1′), 4.57* (1H, s, H-1′), 5.47–5.56* (1H, m, H-3′), 5.47–5.56* (1H, m, H-3′), 6.62 (2H, s, NH_2), 6.39–6.46 (2H, m, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ:12.6, 12.7, 13.8, 14.2, 20.3, 20.3, 20.8, 60.4, 62.4, 65.1, 65.1, 65.2, 65.7, 67.0, 73.7, 130.8, 131.0, 131.1, 131.6, 171.5, 171.9 (diastereomeric mixture); HRMS, calcd for $C_{11}H_{19}NO_4$ (M^+) 229.1314, found 229.1323.

4.6.4. [(*S*)-1-Hyrdoxyethyl]-2-[(1*RS*)-1-hydroxyoctadecanoyl]oxirane-2-carboxamide 36h. The title compound was prepared in 91% yield as a ca. 1:1 diastereomeric mixture, as a colorless solid. Mp=94–97°C; IR ($CHCl_3$) 3671, 3579, 3156, 3091, 3037, 2927, 2858, 1680, 1479, 1382, 1237, 1187, 1097, 1036, 966, 812, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.8 Hz, H-18′), 0.88* (3H, t, *J*=6.8 Hz, H-18′), 1.25 (32H, m, H-3′–H-17′), 1.25* (32H, m, H-3′–H-17′), 1.37 (2H, d, *J*=6.3 Hz, H-2″), 1.37* (2H, d, *J*=6.3 Hz, H-2″), 1.43–1.85 (2H, m, H-2′), 1.43–1.85 (2H, m, H-2′), 2.05 (1H, brs, 1′-OH), 2.18 (1H, brs, OH), 3.08 (1H, d, *J*=8.0 Hz, H-3), 3.17* (1H, d, *J*=8.0 Hz, H-3), 3.47 (1H, brs, OH), 3.47* (1H, brs, OH), 3.63 (1H, m, H-1″), 3.63* (1H, m, H-1″), 4.12 (1H, m, H-1′), 4.12* (IH, m, H-1′), 5.80 (1H, brs, NH), 5.80* (1H, brs, NH), 6.37 (1H, brs, NH), 6.37* (1H, brs, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ:14.1, 14.1, 14.2, 20.3, 20.4, 22.7, 23.0, 23.7, 25.5, 25.8, 28.9, 29.3, 29.3, 29.4, 29.5, 29.5, 29.5, 29.6, 29.6, 29.7, 29.7, 29.8, 29.9, 30.0, 30.3, 30.4, 32.9, 33.0, 39.8,

39.9, 40.1, 40.3, 40.4, 60.4, 63.8, 65.2, 65.2, 65.7, 65.9, 67.3, 68.1, 71.2, 73.5, 170.8, 171.2 (diastereomeric mixture); HRMS, calcd for $C_{23}H_{45}NO_4$ ($M+H^+$) 399.3349, found 399.3339.

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