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ORIGINAL ARTICLE

A three-component coupling approach to the ACE-ring substructure of C19-diterpene alkaloids

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C19-diterpene alkaloids are a class of alkaloids with pharmacologically important activities having an intricately fused hexacyclic ABCDEF-ring system. Here we report expeditious assembly of the ACE-ring substructure 4a by applying a three-component coupling strategy. A radical–polar crossover reaction between an AE-ring radical precursor, a C-ring radical acceptor and an aldehyde was realized by the actions of Et_3B and O_2, resulting in the installation of three new stereocenters and extension of the carbon chain corresponding to the B-ring. As the ACE-ring 4a possesses the correct C4,11-quaternary and C10-tertiary carbons, 4a would serve as an advanced intermediate for constructing the entire C19-diterpene alkaloid structures.
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INTRODUCTION

C19-diterpene alkaloids are a class of natural products present in the plants of the genera *Aconitum* and *Delphinium*, and many exhibit pharmacologically important biological activities.[1] The structures of talatisamine and puberuline C are depicted in Scheme 1a as representative examples. The intricately fused hexacyclic ABCDEF-ring system of the C19-diterpene alkaloids has inspired chemists to invent synthetic methods for their assembly,[2–6] culminating in the full chemical construction of several members of this family.[7–11] Recently, we successfully synthesized the ABCDE-ring system[12] of talatisamine and the ABCDEF-ring system[13] of puberuline C based on our development of a new radical-based strategy. In these synthetic studies, a C11-bridgehead radical of the AE-ring moiety undergoes cyclization with the C-ring enone to form a seven-membered B-ring. The success of the intramolecular C11-radical addition led us to explore its intermolecular version, because intermolecular multicomponent reactions generally ensure more convergent, and thus more efficient, approaches to complex molecular architectures.[14–19] Here we report the three-component coupling reaction between the bicyclic AE-ring, the 5-membered C-ring and the C6-8 carbon chain to assemble the ACE-ring substructure **4a** with the correct C4,11-quaternary and C10-tertiary carbons in a single step (Scheme 1b).

RESULTS AND DISCUSSION

We previously realized a three-component reaction between **2a**, **3b** and O,Te-acetal **5** using a reagent combination of Et_3B and O_2 (Scheme 1c).[20,21] Treatment of O,Te-acetal **5** with Et_3B/O_2 generated the highly reactive bridgehead radical species **D**[22–26] that sequentially coupled with α,β-unsaturated ketone **2a** and aldehyde **3b** via a radical–polar crossover mechanism to provide adduct **6**. This method intermolecularly connected the three simple units with stereoselective installation of the three new stereocenters, and thus significantly increased the molecular complexity in a single step.

To explore efficient strategies for synthesizing the C19-diterpene alkaloids, we decided to construct the ACE-ring system **4a** with the C6-8 carbon chain by employing the radical–polar three-component reaction (Scheme 1b). We planned to assemble the structure of **4a** from the azabicyclo[3.3.1]nonane AE-ring **1**, 5-membered C-ring **2a** and the C6-8 carbon chain **3a**. Et_3B/O_2-promoted C-I bond cleavage of **1** would produce the nucleophilic C11-bridgehead radical **A** that would add to the electron-deficient double bond of C-ring **2a**, leading to **Ba**.[27,28] Then, radical **Ba** would be captured by Et_3B to form boron enolate **Ca**[29] that would undergo the aldol reaction with aldehyde **3a**.[30–32] Hence, the one-pot radical and polar additions were expected to afford **4a** possessing the correct C4,11-quaternary and C10-tertiary carbon centers of the C19-diterpene alkaloids, such as talatisamine and puberuline C (highlighted by small circles).

Before investigating the key coupling reactions, we prepared the optically active AE-ring **1** from 2-(methoxycarbonyl)cyclohexanone (**7**) (Scheme 2). Bromination of **7**, followed by exchange of the bromide of **8** with iodide using NaI, led to **9**. The resultant **9** underwent the double Mannich reaction in the presence of formaldehyde and ethyl amine, giving rise to the azabicyclo[3.3.1]nonane structure (±)-**10** as the racemate.[33] The methyl ester and the ketone groups of (±)-**10** were in turn simultaneously reduced with DIBAL-H (diisobutylaluminium hydride) to the primary and secondary hydroxy groups of (±)-**11** (dr at C5 = 1:1). Then, the racemic (±)-**11** was subjected to enzymatic resolution to obtain enantio-enriched (−)-**11**. Although (±)-**11** possesses two potentially reactive hydroxy groups for the enzymatic acylation, screening of enzymes and acylating reagents permitted us to realize the chemo- and enantioselective functionalization of the C18-primary hydroxy group. Namely,

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Dedicated with respect and admiration to Professor KC Nicolaou for his many outstanding contributions to natural product synthesis.
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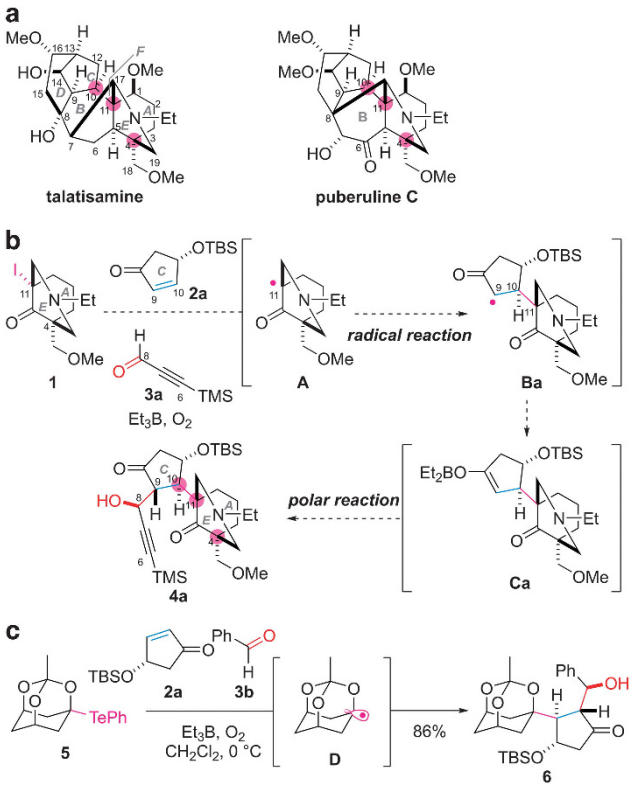
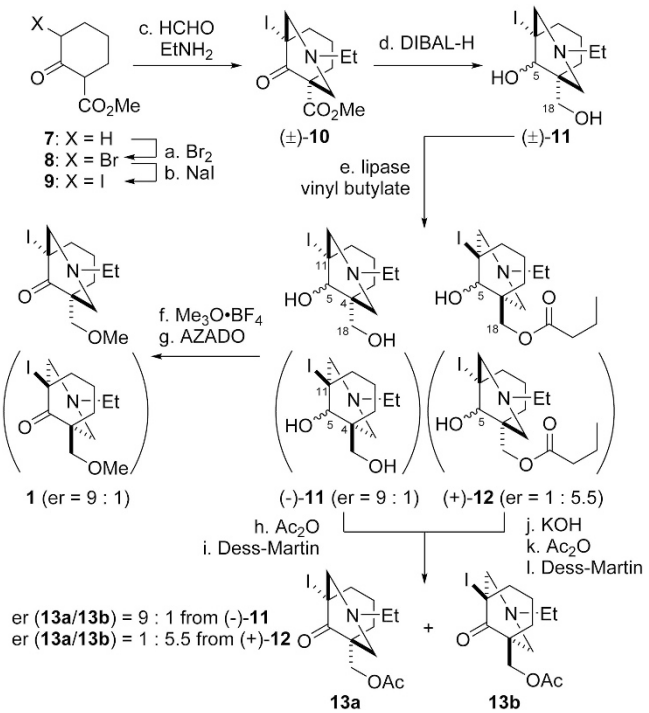


Scheme 1 (**a**) Structures of the C19-diterpene alkaloids, talatisamine and puberuline C. (**b**) Plan for assembly of the AE-ring, C-ring and C6-8 carbon chain of the C19-diterpene alkaloids by the three-component coupling reaction. (**c**) Previously developed radical–polar crossover three-component coupling reaction.

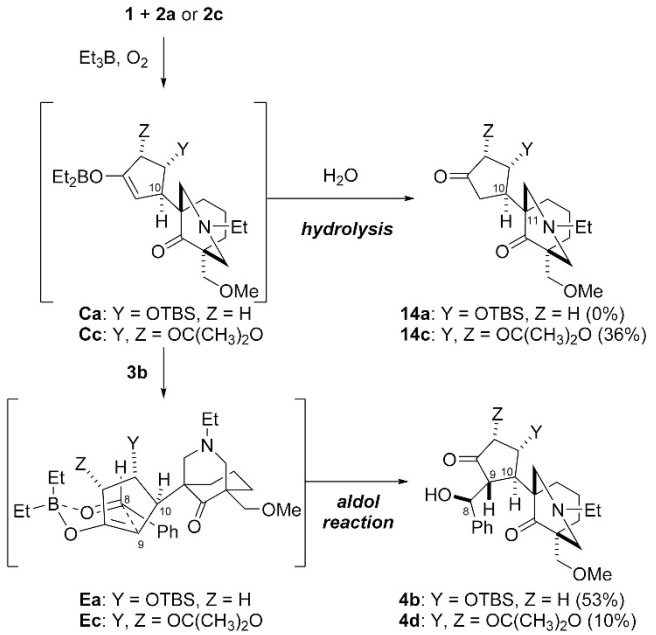


Scheme 2 Synthesis of optically active AE-ring fragment **1**. Reagents and conditions: (a) Br_2, Et_2O; (b) NaI, acetone; (c) aq HCHO, aq $EtNH_2$, MeOH, 45 °C, 83% (3 steps); (d) DIBAL-H, THF, 87%, (dr at C5 = 1:1); (e) lipase from *Candida rugosa*, vinyl butyrate, *i*-Pr_2O, 28 °C, 39% for (−)-**11** (dr at C5 = 1:1), 39% for (+)-**12** (dr at C5 = 1.7:1); (f) $Me_3O•BF_4$, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; (g) AZADO, DMAP, 2,2′-bipyridine, CuCl, air, CH_3CN, 48% (2 steps); (h) Ac_2O, pyridine, 100% from (−)-**11**; (i) Dess–Martin reagent, CH_2Cl_2, 80%, **13a**: **13b** = 9: 1; (j) 1M KOH, MeOH, 73% from (+)-**12**; (k) Ac_2O, pyridine, 100%; (l) Dess–Martin reagent, CH_2Cl_2, 84%, **13a**: **13b** = 1: 5.5.

treatment of diol (±)-**11** (dr at C5 = 1:1) with *Candida rugosa* lipase[34–36] and vinyl butyrate in *i*-Pr_2O at 28 °C provided (−)-**11** (39% yield) along with (+)-**12** having a C18-butyrate group (39% yield). The C4,11-absolute configurations of (−)-**11** were elucidated by NMR experiments of derivatives of **4a** (Table 1, see Supplementary Information for details). To determine the enantiomeric ratio of the C5-diastereomeric mixtures (−)-**11** and (+)-**12**, the corresponding C5-ketone **13a/b** was prepared separately from these compounds, and then analyzed with the chiral HPLC. Acetylation of the C18-hydroxy group of (−)-**11**, and subsequent Dess–Martin oxidation of the C5-hydroxy group provided **13a** and **13b** in a 9:1 enantiomeric ratio. On the other hand, basic hydrolysis of the butyrate of (+)-**12** was followed by acetylation and oxidation to afford **13a** and **13b** in a 1:5.5 ratio. Finally, compound (−)-**11** (er = 9:1) was converted to the requisite AE-ring fragment **1** in two steps; site-selective methyl ether formation by the action of $Me_3O•BF_4$ and 2,6-di-*tert*-butylpyridine, and 2-azaadamantane *N*-oxyl (AZADO)-catalyzed C5-oxidation in the presence of CuCl.[37]

To evaluate the reactivity of AE-ring iodide **1** as a radical precursor, we first examined the formation of the corresponding radical **A** and subsequent addition to the cyclopentenone derivatives (**2a–c**) (Table 1). Upon treatment of **1** and cyclopentenone **2b** with Et_3B and O_2 in CH_2Cl_2 at room temperature, the C-I bond at the congested bridgehead position was homolytically cleaved to generate bridgehead radical **A** that reacted with **2b** to furnish **14b** in 65% yield (dr at C10 = 1:1, entry 1). When the enantiopure cyclopentenone derivatives **2a** and **2c**[38] were used under the same conditions (entries 2 and 3), the radical reaction of **1** occurred from the opposite side of the preexisting *tert*-butyldimethylsilyl (TBS)-oxy and acetonide groups, providing **14a** (51%) and **14c** (52%), respectively, in a C11-stereospecific and C10-stereoselective manner. Thus, the sterically cumbersome bond between the C11-quaternary and C10-tertiary carbon atoms of **14a-c** were intermolecularly connected under mild conditions, corroborating the potent reactivity of radical **A**.

The bridgehead radical reaction was next extended to the radical–polar crossover three-component reactions. Et_3B/O_2 successfully promoted the reaction between iodide **1**, chiral cyclopentenone **2a** and benzaldehyde (**3b**) in CH_2Cl_2 at room temperature to afford adduct **4b** in a C8,9,10-stereoselective manner (53%, entry 4). (Trimethylsilyl)propynal (**3a**) participated in the coupling with **1** and **2a** in the presence of Et_3B and O_2 to selectively yield **4a** (55%, dr at C8 = 4:1, entry 5). No radical reaction to the triple bond of **3a** or **4a** was observed, showing the high chemoselectivity of the present method. Moreover, acid/base-sensitive aldehyde **3c** with the β-silyloxy group functioned as an effective electrophile to provide **4c** (52%, dr at C8 = 2.9:1, entry 6). The newly generated C8,9,10-stereochemistry of coupling products **4a-c** was consistent, and determined by extensive NMR experiments using their derivatives (see Supplementary Information for details). Significantly, the C9-substituted ACE-ring systems **4a–c** with the two quaternary carbons (C4,11) and one tertiary carbon (C10) of the C19-diterpene alkaloids were built in a single operation in neutral media at room temperature. In contrast to the successful formation of **4a–c**, the three-



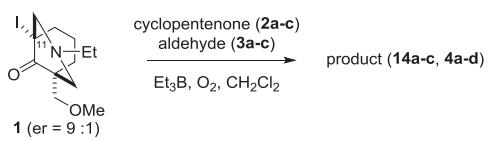
Scheme 3 Rationale of the different reactivity between **2a** and **2c**, and the stereoselectivity of the three-component coupling reaction.

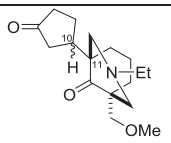
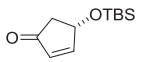
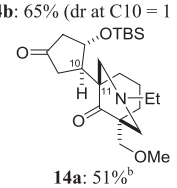
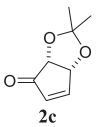
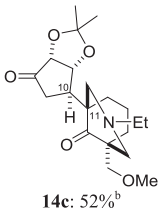
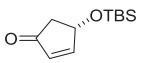
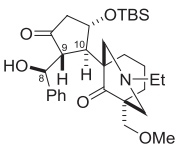
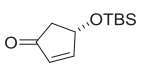
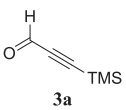
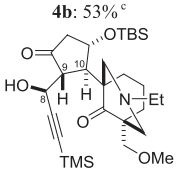
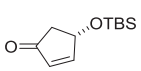
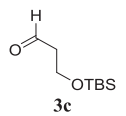
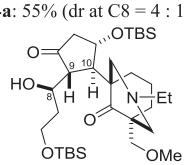
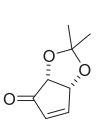
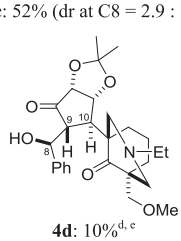
component adduct **4d** was obtained from **1**, **2c** and **3b** in only 10% yield, and the two-component adduct **14c** was mainly generated in 36% yield (entry 7). The distinct behavior of **2a** and **2c** indicated that the C-ring structure influenced the efficiency of the aldol reaction.

The reaction mechanism of the selective generation of **4b** and **14c** from **2a** and **2c**, respectively, is outlined in Scheme 3. Addition of bridgehead radical **A** to **2a** from the opposite side of the TBS-oxy group installs the C10-stereochemistry. After the formation of boron enolate **Ca**, aldehyde **3b** approaches from the less hindered face to avoid the bulky AE-ring, and forms the boron-chelating 6-membered transition state **Ea**, from which the C8,9-stereochemistry of **4b** is established.[39,40] In the case of **2c**, the radical reaction of **2c** and the radical termination of Et_3B occurred similarly to **2a**, producing **Cc**. The approach of **3b** toward one face of the enolate **Cc**, however, is blocked by the AE-ring, and the approach toward the other face is hindered by the acetonide-protected 1,2-diol. Because of the structural differences in the Y,Z-functionalities between **Ec** and **Ea**, the aldol reaction via **Ec** becomes less efficient compared with **Ea**. As a result, the yield of the three-component coupling adduct **4d** is significantly decreased, and hydrolysis of **Cc** mainly occurs to produce the two-component adduct **14c**.

In conclusion, we investigated the two- and three-component reactions of **1**, and realized the expeditious assembly of the functionalized ACE-ring substructure **4a** of the C19-diterpene alkaloids by applying the radical–polar crossover reaction. AE-ring **1**, C-ring **2a** and C6-8 chain **3a** were coupled to generate **4a** using Et_3B and O_2 through formation of the bridgehead radical from iodide **1**, radical addition to cyclopentenone **2a** and polar addition of the resultant boron enolate to aldehyde **3a**. Remarkably, this operationally simple reaction enabled connection of the hindered C10-11 and C8-9 bonds, and installation of the C8,9,10-stereocenters under mild conditions in a single step. As the thus obtained **4a** bears the C4,11-quaternary and C10-tertiary carbon centers, and the C6-8 chain of the C19-diterpene alkaloids, the compound would function as a valuable advanced intermediate for their total syntheses.

Table 1 The two- and three-component radical coupling reactions of 1[a]



Entry	Cyclopentenone	Aldehyde	Results
1	 **2b**	-	 **14b**: 65% (dr at C10 = 1 : 1)
2	 **2a**	-	 **14a**: 51%[b]
3	 **2c**	-	 **14c**: 52%[b]
4	 **2a**	 **3b**	 **4b**: 53%[c]
5	 **2a**	 **3a**	 **4a**: 55% (dr at C8 = 4 : 1)[c]
6	 **2a**	 **3c**	 **4c**: 52% (dr at C8 = 2.9 : 1)[c]
7	 **2c**	**3b**	 **4d**: 10%[d,e]

[a]Conditions: **1** (er = 9:1, 1 equiv), **2a-c** (3 equiv), **3a-c** (0 or 3 equiv), Et_3B (3 equiv), CH_2Cl_2, O_2, room temperature.
[b]The product contained a small amount of the diastereomer that would be derived from the minor enantiomer of **1** (**14a**: its diastereomer = 9.1:1, **14c**: its diastereomer = 14:1).
[c]The product did not contain the diastereomer derived from the minor enantiomer of **1**.
[d]**14c** was generated in 36% yield.
[e]The yield was calculated by ^1H NMR analysis, because **4d** and **14c** were inseparable.

EXPERIMENTAL PROCEDURES

General methods

All reactions sensitive to air or moisture were carried out under argon atmosphere in dry solvents under anhydrous conditions, unless otherwise noted. THF, CH_2Cl_2 and Et_2O were purified by Glass Contour solvent dispensing system (Nikko Hansen, Osaka, Japan). All other reagents were used as supplied unless otherwise stated. Analytical TLC was performed using E. Merck Silica gel 60 F254 precoated plates (Merck, Darmstadt, Germany). Preparative TLC was performed using E. Merck Silica gel 60 F254 precoated plates with 0.50 mm thickness. Flash chromatography was performed using 40–50 μm Silica Gel 60N (Kanto Chemical, Tokyo, Japan), 40–100 μm Silica Gel 60N (Kanto Chemical), 100–210 μm Silica Gel 60N (Kanto Chemical) and 32–53 μm Silica gel BW-300 (Fuji Silysia Chemical, Aichi, Japan). Optical rotations were measured on a JACSO P-200 Digital Polarimeter at room temperature using the sodium D line (JASCO, Tokyo, Japan). IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-ECX-500 (500 MHz), a JNM-ECA-500 (500 MHz) or a JNM-ECS-400 (400 MHz) spectrometer (JEOL, Tokyo, Japan). Chemical shifts were reported in ppm on the δ scale relative to $CHCl_3$ (δ = 7.26 for ^{1}H NMR), $CDCl_3$ (δ = 77.0 for ^{13}C NMR), C_6D_5H (δ = 7.16 for ^{1}H-NMR) and C_6D_6 (δ = 128.0 for ^{13}C-NMR) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. The numbering of compounds corresponds to that of natural product. Electrospray ionization mass spectra were measured on a JEOL JMS-T100LP or a Bruker microTOF II instrument.

Iodide (±)-10

Br_2 (200 μl, 7.96 mmol) was added to a solution of **7** (1.13 g, 7.24 mmol) in Et_2O (4.8 ml) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. Then, saturated aqueous $NaHCO_3$ (5 ml) was added. The resulting mixture was extracted with Et_2O (5 ml × 3), and the combined organic layers were washed with brine (10 ml), dried over Na_2SO_4, filtered and concentrated to afford the crude bromide **8**. The crude **8** was divided into three equal parts. One-third of the crude **8** was used in the next iodination.

NaI (470 mg, 3.13 mmol) was added to a solution of one-third of the above crude bromide **8** (2.41 mmol) in acetone (4.8 ml) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h. Then, the reaction mixture was filtered through a pad of Celite and the filter cake was washed with acetone. The resultant solution was concentrated to afford the crude **9** that was used in the next reaction without further purification.

Aqueous $EtNH_2$ (70% in water, 465 μl, 7.23 mmol) was added to a solution of the above crude **9** in MeOH (8.0 ml) and aqueous HCHO (37% in water, 2.3 ml, 28.9 mmol) at 0 °C over 3 h. The reaction mixture was warmed to 45 °C and stirred for 5 h. After the mixture was cooled to room temperature, H_2O (16 ml) was added. The resultant mixture was extracted with EtOAc (8 ml × 3), and the combined organic layers were washed with brine (5 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (100 g, hexane/EtOAc 50:1 to 5:1) to afford iodide (±)-**10** (703 mg, 2.00 mmol). The yield was determined to be 83% yield over 3 steps based on one-third amount of the starting compound **7**: pale yellow oil; IR (film) ν 2969, 2949, 2932, 2811, 1739, 1731, 1454, 1435, 1292, 1259, 1224, 1208, 1175, 1131, 1112, 1098, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, t, *J* = 7.3 Hz, NCH_2CH_3), 1.51 (1H, m), 2.30 (1H, dddd, *J* = 14.2, 6.4, 2.3, 2.3 Hz), 2.43 (2H, m, NCH_2CH_3), 2.57 (1H, m), 2.80 (1H, m), 2.99 (1H, dddd, *J* = 13.7, 5.9, 2.3, 2.3 Hz), 3.03 (1H, dd, *J* = 11.9, 2.3 Hz, NCH_AH_B), 3.16 (1H, m, NCH_AH_B), 3.18 (1H, m), 3.30 (1H, dd, *J* = 11.9, 2.3 Hz, NCH_AH_B), 3.74 (1H, dd, *J* = 8.7, 2.8 Hz), 3.76 (3H, s, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 24.4, 36.6, 49.4, 50.3, 52.5, 56.2, 59.0, 61.2, 71.6, 170.5, 203.1; HRMS (ESI) calcd for $C_{12}H_{18}INO_3Na$ $[M+Na]^+$ 374.0224, found 374.0225.

Diol (±)-11

DIBAL-H (1.0 M in hexane, 9.2 ml, 9.2 mmol) was added to a solution of (±)-**10** (536 mg, 1.53 mmol) in THF (15 ml) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. Then, saturated aqueous NH_4Cl (10 ml), saturated aqueous potassium sodium tartrate (15 ml) and EtOAc (15 ml) were successively added. After being stirred at room temperature for 1 h, the resultant mixture was extracted with EtOAc (10 ml × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane/EtOAc 50:1 to 5:1) to afford a 1:1 C5-diastereomeric mixture of diol (±)-**11** (431 mg, 1.33 mmol) in 87% yield: yellow oil; IR (film) ν 3403, 2970, 2925, 2809, 1471, 1452, 1394, 1327, 1291, 1227, 1146, 1076, 1025, 959, 943 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H × 1/2, t, *J* = 6.8 Hz, N(CH_2CH_3), 1.04 (3H × 1/2, t, *J* = 7.2 Hz, N(CH_2CH_3), 1.32–1.50 (2H and 1H × 1/2, m), 1.44–1.48 (1H × 1/2, m), 2.03–2.10 (1H, m), 2.23–2.40 (3H, m), 2.54 (1H × 1/2, d, *J* = 9.2 Hz), 2.58–2.93 (5H and 1H × 1/2, m), 2.97 (1H × 1/2, dd, *J* = 8.7 1.9 Hz), 3.18 (1H, m), 3.34 (1H, m), 3.43 (1H × 1/2, d, *J* = 8.7 Hz), 3.48 (1H × 1/2, d, *J* = 9.2 Hz), 3.59 (1H × 1/2, dd, *J* = 9.2, 1.8 Hz), 3.88 (1H × 1/2, s), 3.89 (1H × 1/2, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (1C × 1/2), 12.6 (1C × 1/2), 24.8 (1C × 1/2), 25.3 (1C × 1/2), 25.4 (1C × 1/2), 33.9 (1C), 38.9 (1C × 1/2), 42.3 (1C × 1/2), 45.9 (1C × 1/2), 51.2 (1C × 1/2), 51.7 (1C × 1/2), 53.0 (1C × 1/2), 60.4 (1C × 1/2), 62.5 (1C × 1/2), 63.4 (1C × 1/2), 69.0 (1C × 1/2), 70.3 (1C × 1/2), 70.9 (1C × 1/2), 80.3 (1C), 81.1 (1C × 1/2); HRMS (ESI) calcd for $C_{11}H_{21}INO_2$ $[M+H]^+$ 326.0611, found 326.0622.

Diol (−)-11 and butyrate (+)-12

Lipase from *C. rugosa* (1009 U mg^{-1}, 1.27 g) and vinyl butyrate (1.2 ml, 9.7 mmol) were successively added to a solution of diol (±)-**11** (1.27 g, 3.91 mmol) in *i*-Pr_2O (40 ml) at 28 °C. The reaction mixture was stirred at 28 °C for 1 h. Then, the mixture was filtered through a pad of Celite with Et_2O. After the filtrate was concentrated, brine (15 ml) was added. The resultant solution was extracted with EtOAc (15 ml × 3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 50:1 to 1:1) to afford a 1:1 C5-diastereomeric mixture of diol (−)-**11** (491 mg, 1.51 mmol) and a 1.7:1 C5-diastereomeric mixture of butyrate (+)-**12** (632 mg, 1.54 mmol) in 39% and 39% yields, respectively. The enantiopurity of (−)-**11** and (+)-**12** was evaluated by the chiral HPLC analysis of compound **13** derived from (−)-**11** and (+)-**12**, respectively (see Scheme 2). The enantiomeric ratio (er) of **13a/13b** from (−)-**11** was 9:1 and that from (+)-**12** was 1:5.5. The analytical detail was described in the Supplementary Information. Diol (−)-**11**: yellow oil; $[\alpha]_D^{23}$ −3.5 (*c* 1.00, $CHCl_3$). Butyrate (+)-**12**: $[\alpha]_D^{26}$ 8.0 (*c* 1.00, $CHCl_3$); IR (film) ν 3500, 2966, 2931, 2875, 2807, 1739, 1454, 1416, 1384, 1304, 1261, 1181, 1132, 1081, 1048, 1091, 991 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H × 5/8, t, *J* = 7.4 Hz, $COCH_2CH_2CH_3$), 1.03 (3H × 3/8, t, *J* = 7.3 Hz, NCH_2CH_3), 1.33 (1H × 3/8, m), 1.42-1.46 (2H × 5/8, m), 1.67 (2H, qt, *J* = 7.4, 7.4 Hz, $COCH_2CH_2CH_3$), 1.77 (1H, m), 2.19–2.33 (5H, m), 2.40 (1H × 3/8, d, *J* = 11.0 Hz, NH_AH_B), 2.55 (1H × 5/8, d, *J* = 11.0 Hz, NH_AH_B), 2.56–2.70 (1H, m), 2.72–2.90 (3H, m), 2.95 (1H × 5/8, d, *J* = 11.0 Hz, NH_AH_B), 3.19 (1H × 5/8, s, H-5), 3.56 (1H × 5/8, d, *J* = 11.0 Hz, NH_AH_B), 3.74-3.80 (1H and 1H × 3/8, m), 4.06 (1H × 5/8, d, *J* = 11.0 Hz, H-18a), 4.10 (1H × 3/8, d, *J* = 11.0 Hz, H-18a); ^{13}C NMR (125 MHz, C_6D_6) δ 12.5, 12.6, 13.77, 13.79, 18.7, 18.8, 25.5, 25.7, 25.8, 33.8, 36.1, 36.2, 39.4, 41.9, 42.1, 46.6, 51.4, 51.8, 53.6, 60.8, 61.8, 63.0, 63.1, 69.36, 69.39, 69.9, 76.9, 78.2, 173.1, 173.2; HRMS (ESI) calcd for $C_{15}H_{27}INO_3$ $[M+H]^+$ 396.1030, found 396.1017.

Iodide 1

$Me_3O{\bullet}BF_4$ (564 mg, 3.81 mmol) was added to a solution of a 1:1 C5-diastereomeric mixture of diol (−)-**11** (620 mg, 1.91 mmol) and 2,6-di-*tert*-butylpyridine (1.3 ml, 5.7 mmol) in CH_2Cl_2 (38 ml) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. Then, saturated aqueous $NaHCO_3$ (20 ml) was added. The resultant mixture was extracted with EtOAc (15 ml × 3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 50:1 to 5:1) to afford the crude methyl ether that was used in the next reaction without further purification.

CuCl (227 mg, 2.29 mmol) and AZADO (87.2 mg, 573 μmol) were successively added to a solution of the above crude methyl ether, DMAP (93.3 mg, 764 μmol) and 2,2′-bipyridine (59.7 mg, 382 μmol) in CH_3CN (9.6 ml) at room temperature. The reaction mixture was stirred at room temperature for 15 min. Then, saturated aqueous $Na_2S_2O_3$ (10 ml) was added. The resultant

mixture was extracted with Et_2O (10 ml ×3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane/EtOAc 80:1 to 10:1) to afford iodide **1** (309 mg, 916 μmol) in 48% yield over 2 steps: colorless oil; $[\alpha]_D^{22}$ −0.59 (*c* 1.00, $CHCl_3$); IR (film) ν 2973, 2925, 2894, 2807, 1727, 1452, 1385, 1348, 1318, 1289, 1235, 1202, 1164, 1112, 1020, 965, 935 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, *J*=7.3 Hz, NCH_2CH_3), 1.44 (1H, m), 1.75 (1H, ddd, *J*=13.3, 13.3, 2.3 Hz), 2.34–2.40 (4H, m), 2.74 (1H, ddd, *J*=13.3, 13.3, 2.3 Hz), 2.97 (1H, m), 3.09 (1H, d, *J*=11.0 Hz), 3.18 (1H, m), 3.31–3.37 (2H, m), 3.34 (3H, s, OMe), 3.44 (1H, d, *J*=9.6 Hz), 3.73 (1H, dd, *J*=11.0, 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 24.6, 37.5, 49.8, 50.3, 51.6, 59.2, 59.4, 61.9, 71.7, 76.2, 207.3; HRMS (ESI) calcd for $C_{12}H_{20}INO_2$ $[M+Na]^+$ 360.0431, found 360.0432.

General procedure A: two-component radical coupling reaction

Compound 14b

Et_3B (0.99 M in hexane, 370 μl, 370 μmol) was added to a solution of cyclopentenone **2b** (31 μl, 370 μmol) and iodide **1** (41.3 mg, 123 μmol) in CH_2Cl_2 (250 μl) at 0 °C over 30 min. The mixture was warmed to room temperature under air and stirred for 30 min. Then, saturated aqueous $NaHCO_3$ (2 ml) was added. The resultant mixture was extracted with EtOAc (2 ml ×3), and the combined organic layers were passed through a pad of silica gel with EtOAc. After the filtrate was concentrated, the residue was purified by flash column chromatography on silica gel (4 g, hexane/EtOAc 100:1 to 1:1) to afford a 1:1 C10-diastereomeric mixture of **14b** (23.4 mg, 79.8 μmol) in 65% yield: $[\alpha]_D^{26}$ −0.43 (*c* 1.00, $CHCl_3$); IR (film) ν 2957, 2930, 1731, 1710, 1459, 1362, 1330, 1208, 1165, 1112, 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H ×1/2, t, *J*=6.9 Hz, NCH_2CH_3), 1.09 (3H ×1/2, t, *J*=6.9 Hz, NCH_2CH_3), 1.40–1.50 (1H, m), 1.63–1.70 (1H, m), 1.73–1.80 (2H, m), 1.95-2.07 (2H, m), 2.10-2.19 (2H, m), 2.21–2.27 (1H, m), 2.29–2.42 (7H, m), 2.72–2.90 (1H, m), 2.92 (1H ×1/2, dd, *J*=11.0, 1.8 Hz, NH_AH_B), 3.01 (1H ×1/2, dd, *J*=11.0, 1.8 Hz, NH_AH_B), 3.14 (1H ×1/2, dd, *J*=11.5 Hz, NH_AH_B), 3.17 (1H ×1/2, dd, *J*=11.5 Hz, NH_AH_B), 3.29 (1H ×1/2, d, *J*=9.2 Hz, H-18a), 3.30 (1H ×1/2, d, *J*=9.2 Hz, H-18a), 3.34 (3H, s, OMe), 3.38 (1H, d, *J*=9.2 Hz, H-18b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.56, 12.57, 20.36, 20.37, 20.53, 20.54, 23.4, 23.7, 35.9, 36.3, 36.41, 36.42, 36.52, 36.53, 38.5, 38.7, 39.5, 39.8, 40.9, 41.2, 50.8, 50.9, 51.1, 52.3, 59.2, 59.3, 61.5, 61.6, 63.2, 63.6, 212.5, 212.6, 218.5, 218.7; HRMS (ESI) calcd for $C_{17}H_{27}NO_3Na$ $[M+Na]^+$ 316.1883, found 316.1880.

Compound 14a

According to the general procedure A, a 9.1:1 mixture of **14a** and the diastereomer presumably originated from the minor enantiomer of **1** (25.7 mg, 60.7 μmol) was obtained in 51% yield by using cyclopentenone **2a** (enantiopure, 75.8 mg, 359 μmol), iodide **1** (er=9:1, 40.1 mg, 119 μmol) and Et_3B (0.99 M in hexane, 360 μl, 360 μmol) in CH_2Cl_2 (240 μl). The crude was purified by flash column chromatography on silica gel (4 g, CH_2Cl_2/EtOAc 100:1 to 1:1). $[\alpha]_D^{26}$ 23.0 (*c* 1.00, $CHCl_3$); IR (film) ν 2950, 2929, 2895, 2808, 1747, 1707, 1470, 1389, 1361, 1254, 1204, 1164, 1112, 1007, 979, 940, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *peaks of the major isomer*: δ 0.03 (3H, s, CH_3 of TBS), 0.07 (3H, s, CH_3 of TBS), 0.86 (9H, s, *t*-Bu of TBS), 1.09 (3H, t, *J*=7.3 Hz, NCH_2CH_3), 1.46 (1H, m), 1.65–1.82 (2H, m), 2.15–2.28 (5H, m), 2.33 (1H, d, *J*=7.8 Hz), 2.36 (2H, q, *J*=7.3 Hz, NCH_2CH_3), 2.58 (1H, d, *J*=11 Hz, NCH_AH_B), 2.70 (1H, dd, *J*=17.8, 7.4 Hz), 2.84 (1H, m), 2.95 (1H, dd, *J*=11.0, 2.3 Hz, NCH_AH_B), 3.14 (1H, ddd, *J*=11.4, 1.8, 1.8 Hz, NCH_AH_B), 3.32 (1H, d, *J*=9.6 Hz, H-18a), 3.33 (3H, s, OMe), 3.37 (1H, d, *J*=9.6 Hz, H-18b), 4.50 (1H, dd, *J*=6.0, 6.0 Hz, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) *peaks of the major isomer*: δ −4.7, −3.9, 12.8, 17.7, 20.4, 25.7, 37.9, 40.3, 40.6, 49.3, 50.4, 50.8, 51.4, 52.0, 59.6, 62.3, 62.8, 70.9, 76.0, 216.1, 217.2; HRMS (ESI) calcd for $C_{23}H_{41}NO_4SiNa$ $[M+Na]^+$ 446.2697, found 446.2708.

Compound 14c

According to the general procedure A, a 14:1 mixture of **14c** and the diastereomer presumably originated from the minor enantiomer of **1** (23.4 mg, 64.0 μmol) was obtained in 52% yield by using cyclopentenone **2c** (enantiopure, 56.8 mg, 368 μmol), iodide **1** (er=9:1, 41.4 mg, 123 μmol) and Et_3B (0.99 M in hexane, 370 μl, 370 μmol) in CH_2Cl_2 (250 μl). The crude was purified by flash column chromatography on silica gel (4 g, CH_2Cl_2 to CH_2Cl_2/EtOAc 10:1). $[\alpha]_D^{22}$ -65.0 (*c* 1.00, $CHCl_3$); IR (film) ν 2979, 2934, 2810, 1757, 1706, 1453, 1381, 1242, 1210, 1157, 1112, 1041, 1004, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *peaks of the major isomer*: δ 1.10 (3H, t, *J*=7.5 Hz, NCH_2CH_3), 1.33 (3H, s, acetonide), 1.43 (3H, s, acetonide), 1.50 (1H, m), 1.67 (1H, ddd, *J*=12.6, 12.6, 6.3 Hz), 1.81 (1H, ddd, *J*=13.2, 13.2, 6.3 Hz), 1.97 (1H, m), 2.04 (1H, m), 2.22 (1H, m), 2.38–2.45 (3H, m), 2.53 (1H, d, *J*=11.5 Hz, NCH_AH_B), 2.63 (1H, dd, *J*=19.5, 10.3 Hz), 2.67 (1H, m), 2.76 (1H, d, *J*=11.5 Hz, NCH_AH_B), 2.97 (1H, dd, *J*=11.5, 1.7 Hz, NCH_AH_B), 3.09 (1H, dd, *J*=11.5, 1.2 Hz, NCH_AH_B), 3.26 (1H, d, *J*=9.8 Hz, H-18a), 3.32 (3H, s, OMe), 3.36 (1H, d, *J*=9.8 Hz, H-18b), 4.61 (1H, d, *J*=6.9 Hz, H-12), 4.68 (1H, d, *J*=6.9 Hz, H-13); ^{13}C NMR (100 MHz, $CDCl_3$) *peaks of the major isomer*: δ 12.6, 19.6, 24.7, 26.9, 37.2, 37.8, 38.9, 45.7, 50.2, 51.2, 51.7, 59.6, 62.2, 63.0, 75.8, 79.65, 79.68, 111.8, 212.8, 217.4; HRMS (ESI) calcd for $C_{20}H_{31}NO_5Na$ $[M+Na]^+$ 388.2094, found 388.2088.

General procedure B: three-component coupling reaction

Compound 4b

Et_3B (0.99 M in hexane, 350 μl, 350 μmol) was added to a solution of cyclopentenone **2a** (enantiopure, 75.4 mg, 355 μmol), aldehyde **3b** (36 μl, 350 μmol) and iodide **1** (er=9:1, 39.9 mg, 118 μmol) in CH_2Cl_2 (240 μl) at 0 °C over 30 min. The reaction mixture was warmed to room temperature under air and stirred for 30 min. Then, saturated aqueous $NaHCO_3$ (2 ml) was added. The resultant mixture was extracted with EtOAc (2 ml ×3), and the combined organic layers were passed through a pad of silica gel with EtOAc. After the filtrate was concentrated, the residue was purified by flash column chromatography on silica gel (4 g, CH_2Cl_2/EtOAc 100:1 to 1:1) to afford **4b** (33.2 mg, 62.7 μmol) in 53% yield: colorless oil; $[\alpha]_D^{26}$ 3.13 (*c* 1.00, $CHCl_3$); IR (film) ν 3462, 2952, 2928, 2894, 2857, 2807, 1708, 1472, 1456, 1388, 1253, 1172, 1113, 1061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.11 (3H, s, CH_3 of TBS), 0.19 (3H, s, CH_3 of TBS), 0.94 (9H, s, *t*-Bu of TBS), 0.98 (3H, t, *J*=6.9 Hz, NCH_2CH_3), 1.34-1.38 (1H, m), 1.44-1.53 (2H, m), 1.61 (1H, ddd, *J*=12.0, 12.0, 6.3 Hz), 1.68 (1H, br d, *J*=10.9 Hz), 2.12-2.19 (5H, m), 2.34 (1H, d, *J*=18.9 Hz), 2.36 (1H, m), 2.64 (1H, dd, *J*=11.4, 1.8 Hz), 2.64-2.74 (2H, m), 3.02 (1H, dd, *J*=11.4, 1.4 Hz), 3.13 (1H, d, *J*=9.6 Hz, H-18a), 3.33 (3H, s, OMe), 3.39 (1H, d, *J*=9.6 Hz, H-18b), 4.43 (1H, d, *J*=6.0 Hz), 4.48 (1H, s), 4.92 (1H, d, *J*=7.8 Hz), 7.29-7.38 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, 12.5, 17.8, 20.0, 25.7, 37.3, 37.4, 49.6, 50.3, 51.2, 52.1, 55.3, 56.7, 59.5, 62.1, 63.1, 71.1, 76.0, 76.3, 127.2, 127.8, 128.2, 141.2, 216.4, 220.4; HRMS (ESI) calcd for $C_{30}H_{47}NO_5SiNa$ $[M+Na]^+$ 552.3116, found 552.3117.

Compound 4a

According to the general procedure B, C8(*S*)-**4a** (29.0 mg, 52.7 μmol) and C8 (*R*)-**4a** (7.4 mg, 13.5 μmol) were obtained in 44% and 11% yields, respectively, by using cyclopentenone **2a** (enantiopure, 76.7 mg, 361 μmol), aldehyde **3a** (53 μl, 361 μmol), iodide **1** (er=9:1, 40.6 mg, 120 μmol) and Et_3B (0.99 M in hexane, 370 μl, 370 μmol) in CH_2Cl_2 (240 μl). The crude was purified by flash column chromatography on silica gel (4 g, CH_2Cl_2/EtOAc 100:1 to 5:1). C8(*S*)-**4a**: $[\alpha]_D^{26}$ −0.11 (*c* 1.00, $CHCl_3$); IR (film) ν 3454, 2955, 2929, 2897, 2857, 2809, 2175, 1743, 1709, 1472, 1462, 1388, 1361, 1286, 1251, 1172, 1112, 1066, 1006, 976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s, CH_3 of TBS), 0.13 (3H, s, CH_3 of TBS), 0.16 (9H, s, CH_3 of TMS), 0.86 (9H, s, *t*-Bu of TBS), 1.09 (3H, t, *J*=6.8 Hz, NCH_2CH_3), 1.49 (1H, m), 1.66 (1H, m), 1.87 (1H, m), 2.02 (1H, m), 2.22-2.41 (7H, m), 2.54 (1H, d, *J*=11.0 Hz, NCH_AH_B), 2.81 (2H, dd, *J*=18.3, 5.5 Hz), 3.01 (1H, d, *J*=11.0 Hz, NCH_AH_B), 3.13 (1H, d, *J*=11.0 Hz, NCH_AH_B), 3.26 (1H, d, *J*=9.6 Hz, H-18a), 3.32 (3H, s, OMe), 3.36 (1H, d, *J*=9.2 Hz, H-18b), 3.70 (1H, s, O*H*), 4.43 (1H, d, *J*=5.5 Hz, H-12), 4.66 (1H, d, *J*=7.8 Hz, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.5, −0.2, 12.7, 17.7, 20.0, 25.6, 37.4, 38.9, 49.1, 50.4, 51.3, 52.3, 55.3, 55.5, 59.6, 62.2, 63.8, 65.3, 71.0, 75.9, 91.0, 103.6, 216.7, 218.6; HRMS (ESI) calcd for $C_{29}H_{51}NO_5Si_2Na$ $[M+Na]^+$ 572.3198, found 572.3192. C8(*R*)-**4a**: $[\alpha]_D^{25}$ 5.21 (*c* 1.00, $CHCl_3$); IR (film) ν 3441, 2955, 2929, 2898, 2857, 2810, 2172, 1743, 1713, 1471, 1459, 1389, 1250, 1173, 1113, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s, CH_3 of TBS), 0.14 (3H, s, CH_3 of TBS), 0.16 (9H, s, CH_3 of TMS), 0.87 (9H, s, *t*-Bu of TBS), 1.08 (3H, t, *J*=7.3 Hz, NCH_2CH_3), 1.25 (1H, s, O*H*),

1.45, (1H, m), 1.71 (1H, m), 1.94 (1H, m), 2.13 (1H, m), 2.23-2.44 (7H, m), 2.49 (1H, d, J = 11.0 Hz, NCH_AH$_B$), 2.69 (1H, m), 2.80 (1H, dd, J = 19.2, 6.4 Hz), 2.88 (1H, dd, J = 11.0, 1.8 Hz, NCH$_A$$H_B$), 3.12 (1H, dd, J = 11.0, 1.4 Hz, NCH$_A$$H_B$), 3.29 (1H, d, J = 9.6 Hz, H-18a), 3.32 (3H, s, OMe), 3.34 (1H, d, J = 9.6 Hz, H-18b), 4.39 (1H, d, J = 4.4 Hz, H-12), 4.70 (1H, d, J = 7.8 Hz, H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ − 4.8, − 4.5, − 0.2, 12.6, 17.7, 20.4, 25.7, 37.4, 38.5, 49.0, 50.3, 51.3, 52.4, 55.2, 55.3, 59.6, 62.0, 63.6, 65.2, 70.8, 75.8, 77.3, 103.6, 217.0, 218.4, one ^{13}C peak was not observed; HRMS (ESI) calcd for $C_{29}H_{51}NO_5Si_2Na$ $[M+Na]^+$ 572.3198, found 572.3200.

Compound 4c

According to the general procedure B, a 2.9:1 C8-diastereomeric mixture of **4c** (39.2 mg, 64.0 μmol) was obtained in 52% yield by using cyclopentenone **2a** (enantiopure, 78.4 mg, 369 μmol), aldehyde **3c** (69.5 mg, 369 μmol), iodide **1** (er = 9:1, 41.5 mg, 123 μmol) and Et_3B (0.99 M in hexane, 380 μl, 380 μmol) in CH_2Cl_2 (250 μl). The crude was purified by flash column chromatography on silica gel (4 g, CH_2Cl_2/EtOAc 100:1 to 5:1). $[\alpha]_D^{26}$ 2.48 (*c* 1.00, $CHCl_3$); IR (film) ν 3471, 2953, 2930, 2892, 2857, 2810, 1740, 1470, 1387, 1362, 1295, 1254, 1188, 1171, 1006, 973, 938 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *peaks of the major isomer*: δ 0.04 (6H, s, CH_3 of TBS × 2), 0.06 (3H, s, CH_3 of TBS), 0.11 (3H, s, CH_3 of TBS), 0.87 (18H, s, *t*-Bu of TBS × 2), 1.06 (3H, t, J = 7.3 Hz, NCH$_2$CH_3), 1.42–1.44 (1H, m), 1.60–1.80 (3H, m), 1.93 (1H, m), 2.02–2.06 (1H, m), 2.13 (1H, s), 2.20–2.37 (6H, m), 2.47 (1H, d, J = 11.0 Hz, NCH_AH$_B$), 2.67–2.73 (1H, m), 2.82 (1H, m), 2.96 (1H, d, J = 11.0 Hz, NCH$_A$$H_B$), 3.14 (1H, dd, J = 11.4, 1.8 Hz, NCH$_A$$H_B$), 3.26 (1H, d, J = 10.1 Hz, H-18a), 3.31 (3H, s, OMe), 3.35 (1H, d, J = 9.6 Hz, H-18b), 3.80 (2H, m), 3.84 (1H, s, O*H*), 4.02-4.05 (1H, m), 4.40 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ − 5.5 (2C × 3/4), -5.4 (2C × 1/4), − 4.8 (1C × 1/4), -4.7 (1C × 3/4), -4.4 (1C × 1/4), − 4.3 (1C × 3/4), 12.61 (1C × 3/4), 12.64 (1C × 1/4), 17.7 (1C), 18.20 (1C × 1/4), 18.21 (1C × 3/4), 20.2 (1C × 3/4), 20.4 (1C × 1/4), 25.66 (3C × 1/4), 25.69 (3C × 3/4), 25.9 (3C × 3/4), 26.0 (3C × 1/4), 36.5 (1C), 37.2 (1C × 1/4), 37.5 (1C × 3/4), 39.0 (1C × 3/4), 50.0 (1C × 1/4), 50.1 (1C × 3/4), 50.2 (1C × 1/4), 50.3 (1C × 3/4), 51.2 (1C × 1/4), 51.3 (1C × 3/4), 53.1 (1C × 1/4), 53.2 (1C × 3/4), 55.9 (1C × 3/4), 56.5 (1C × 1/4), 56.6 (1C × 3/4), 59.5 (1C), 61.3 (1C × 1/4), 61.5 (1C × 3/4), 62.1 (1C × 3/4), 62.4 (1C × 1/4), 63.3 (1C × 3/4), 63.5 (1C × 1/4), 70.8 (1C), 73.0 (1C × 1/4), 73.2 (1C × 3/4), 75.8 (1C × 1/4), 75.9 (1C × 3/4), 216.8 (1C × 3/4), 217.7 (1C × 3/4), 218.1 (1C × 1/4), 221.0 (1C × 1/4), two ^{13}C peaks of the minor diastereomer were not observed; HRMS (ESI) calcd for $C_{32}H_{61}NO_6Si_2Na$ $[M+Na]^+$ 634.3930, found 634.3943.

Compound 4d

According to the general procedure B, a 3.6:1 mixture of **14c** and **4d** (22.3 mg, 44.9 μmol for **14c**, 12.5 μmol for **4d**) was obtained by using cyclopentenone **2c** (enantiopure, 57.8 mg, 375 μmol), aldehyde **3b** (38 μl, 370 μmol), iodide **1** (er = 9:1, 42.1 mg, 125 μmol) and Et_3B (0.99 M in hexane, 380 μl, 380 μmol) in CH_2Cl_2 (250 μl). The crude was purified by flash column chromatography on silica gel (4 g, CH_2Cl_2/EtOAc 100:1 to 5:1). The yields were calculated to be 36% for **14c** and 10% for **4d**, respectively. A small amount of the mixture was repurified by flash column chromatography to obtain pure **4d** for characterization. $[\alpha]_D^{25}$ 9.1 (*c* 0.60, $CHCl_3$); IR (film) ν 3491, 2974, 2934, 2812, 1736, 1705, 1455, 1382, 1243, 1207, 1156, 1114, 1042, 915 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, t, J = 7.5 Hz, NCH$_2$CH_3), 1.20–1.32 (3H, m), 1.35 (3H, s, acetonide), 1.45–1.49 (1H, m), 1.59 (3H, s, acetonide), 1.77 (1H, br s, O*H*), 2.04–2.07 (1H, m), 2.25–2.30 (2H, m), 2.33–2.40 (1H, m), 2.49 (1H, d, J = 10.3 Hz, H-9), 2.85–2.87 (2H, m), 2.86 (1H, d, J = 11.5 Hz), 3.19 (1H, d, J = 9.8 Hz, H-18a), 3.29 (3H, s, OMe), 3.31 (1H, d, J = 9.8 Hz, H-18b), 4.00 (1H, s), 4.65-4.69 (2H, m, H-12 and H-13), 4.75 (1H, d, J = 10.3 Hz, H-8), 7.26–7.37 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 14.1, 18.4, 22.3, 24.1, 26.5, 37.2, 49.9, 51.0, 51.7, 56.5, 59.5, 61.7, 62.4, 76.0, 79.4, 80.2, 111.5, 127.7, 128.2, 128.3, 140.3, 216.1, 217.4; HRMS (ESI) calcd for $C_{27}H_{37}NO_6Na$ $[M+Na]^+$ 494.2513, found 494.2497.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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