CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200800079

Enantioselective Synthesis of the Fully Functionalized ABC Ring of Zoanthenol

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: Zoanthenol, isolated from *Zoanthus sp.*, possesses an extremely complex architecture including contiguous quaternary carbons. An enantioselective synthesis of the fully functionalized ABC-ring of zoanthenol has been achieved and is described herein. The key features of the synthesis are the enzymatic kinetic optical resolution and the Mizoroki–Heck/Simmons–Smith reaction strategy used to construct the congested asymmetric quaternary carbons.

Keywords: alkaloids · enantioselectivity · natural products · palladium · total synthesis

Introduction

Zoanthamine alkaloids, which are isolated from marine zoanthid *Zoanthus sp.*, exhibit various biological activities.[1] Norzoanthamine (**1**) hydrochloride (Figure 1) possesses anti-osteoporotic activity without serious side effects and zoanthamine (**2**) (Figure 1) inhibits phorbol myristate-induced inflammation.[2] The structural features of zoanthamines are the congested quaternary carbons at C9, C12, C22 in the C-ring and the consecutive amino acetal moiety in the DEFG-ring. Their complex and unique architecture and biological activities have proven to be synthetically challenging,[3–7] and the only successful total syntheses of norzoanthamine (**1**) and zoanthamine (**2**) were reported by Miyashita and coworkers.[8] Our synthetic interest is focused on zoanthenol (**3**) (Figure 1), which is the only member of the zoanthamine family possessing an aromatized A-ring.[1h] Herein, we describe the enantioselective synthesis of the ABC-ring, a key intermediate in the total synthesis of zoanthenol (**3**).

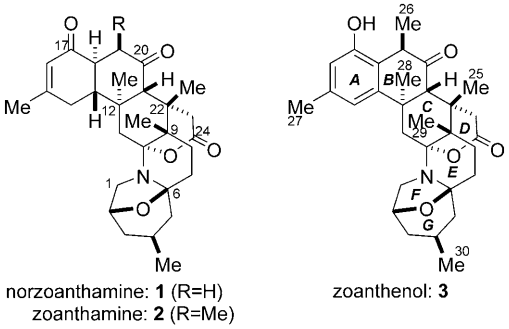

Figure 1. Structures of zoanthamine alkaloids.

Results and Discussion

The features of our synthetic strategy are illustrated in Figure 2. In our previous report, racemic **4** was prepared from **5** and **(±)-6**.[9] However, coupling with chiral amino alcohol derivatives to build the DEFG-ring of **3** led to a mixture of diastereomers which were difficult to separate. In order to avoid this problem, we decided to construct the C-ring **6** in an enantiomerically pure form by applying kinetic resolution to **(±)-7**.

We first examined the enantioselective reduction of **(±)-7** using chiral reducing agents. Borane with oxazaborolidine (**9**)[10] provided the racemic alcohol **8** even at low temperature (Table 1, entry 1). When catecholborane was used instead of BH_3·THF to decrease the reactivity, there was no reaction (Table 1, entry 2). Jacobsen's Mn-salen complex/

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asis.200800079 or from the author.

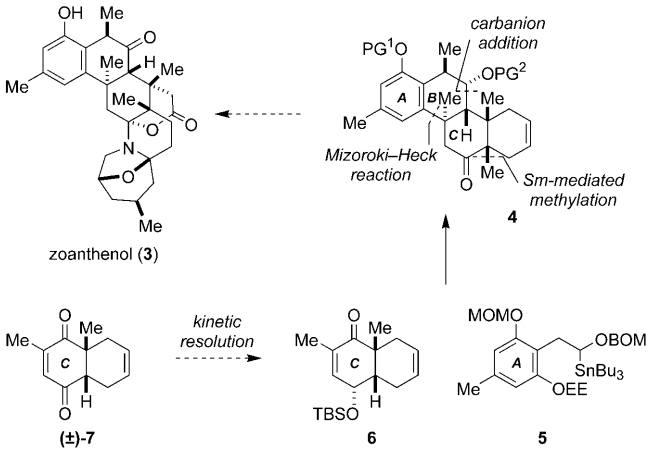
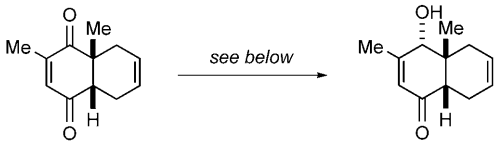


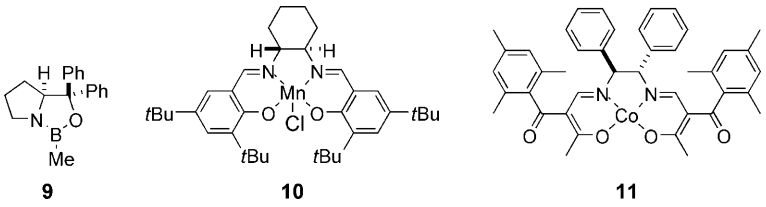
Figure 2. Synthetic plan of zoanthenol.

Table 1. Attempts at enantioselective reduction of **(±)-7**.



Entry	Chiral ligand	Reductant	Conditions	Yield [% *ee*][a]
1	**9** (0.1 eq)	BH_3·THF	THF, −78 °C	82 %, 0 % *ee*
2	**9** (0.1 eq)	catecholborane	THF, −78 to 0 °C	no reaction
3	**10** (0.04 eq)	$NaBH_4$	tetrahydrofurfuryl alcohol EtOH, $CHCl_3$, −20 °C	63 %, 32 % *ee*
4	**11** (0.05 eq)	$NaBH_4$	tetrahydrofurfuryl alcohol EtOH, $CHCl_3$, −40 °C	22 %, 5 % *ee*

[a] % *ee* was confirmed using chiral HPLC; absolute configuration was not determined.



$NaBH_4$ combination[11] afforded alcohol **8** in 63 % yield, but its enantiomeric excess was only 32 % *ee* (Table 1, entry 3). Use of Co-complex (**11**) gave an even lower enantioselectivity (Table 1, entry 4).[12]

As a result of these unsatisfactory results, we focused on the enzymatic asymmetric acetylation of the alcohols. After examining the various alcohols derived from **(±)-7**, we found that the treatment of diol **(±)-12** with lipase AK[13] in vinyl acetate at 55 °C gave rise to **(−)-12** (98 % *ee*) and the mono-acetate **(+)-13** (77 % *ee*) in 44 % and 56 % yield, respectively (Scheme 1). Enantiomerically pure **(+)-12** was obtained by the methanolysis of **(+)-13** followed by recrystallization. The absolute configuration of **(+)-12** was unambiguously determined by X-ray crystallographic analysis of its *p*-bromobenzoate derivative **(−)-14**. TBS-protection of the less hindered secondary alcohol of **(+)-12** and Dess–Martin oxidation[14] of the remaining alcohol completed the production of the enantiomerically pure C-ring **(+)-6** in 98 % yield over two steps.

With the requisite **(+)-6** in hand, the stage was now set for its assembly with the A-ring **5** (Scheme 2). Treatment of **5**[9d] with *n*BuLi in THF at −78 °C generated the corresponding α-alkoxy carbanion, and the subsequent addition of a small excess of **(+)-6** gave the adduct **15** as a 2:1 diastereomeric mixture at C20 in 95 % yield.[15] This inseparable mixture was converted to the methyl ether **16** in 99 % yield and the TBAF-promoted cleavage of the hindered TBS ether of **16** was achieved under reflux conditions in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. The resulting secondary alcohol was transformed to the α,β-unsaturated ketone **17** by Dess–Martin oxidation and elimination of the EE group in 90 % combined yield. At this stage, the C20-epimers were separable by silica gel chromatography and their configurations were confirmed after formation of the B-ring. Phenols **17-*S*** and **17-*R*** (C20-diasteromers) were treated with *N*-phenyl-bis(trifluoromethansulfonimide) and NaH to give the triflates **18-*S*** and **18-*R***, both in 97 % yield.

The key intramolecular Mizoroki–Heck reaction that was employed to construct the quaternary carbon center at C12 was examined next.[16] Upon treatment of the triflate **18-*S*** with tris(dibenzylideneacetone)dipalladium-chloroform, 1,4-bis(diphenylphosphino)butane and Et_3N in dimethyl acetamide at 120 °C,[9d] the C−C bond formation proceeded in the 6-*exo* fashion to afford the desired tetracyclic framework **19-*S*** in 86 % yield. On the other hand, the treatment of C20-epimer (**18-*R***) under the same conditions gave the cyclized product **19-*R*** (53 %) together with a significant amount of the reduced product **20-*R*** (21 %), which might have been enhanced as a result of the large steric repulsion between the C20-BOM group and the methyl group (C25).

Stereoselective reduction of the ketone **19** using L-Selectride and TBS protection of the resulting secondary alcohol furnished the TBS-ether **21**. Reductive removal of the BOM group under Birch conditions followed by Dess–Martin oxidation of the resulting alcohol afforded ketone **22**. Treatment of α-methoxyketone **22** with excess SmI_2 in the pres-

Abstract in Japanese:

ゾアンテノールは、スナギンチャクから単離された７環性アルカロイドであり、分子中央部に近接する３つの不斉第四級炭素を有する複雑な化合物である。我々は、酵素による光学分割・遷移金属を用いた第四級炭素構築を鍵とするエナンチオ選択的なゾアンテノール ABC 環部効率的合成法を開発した。

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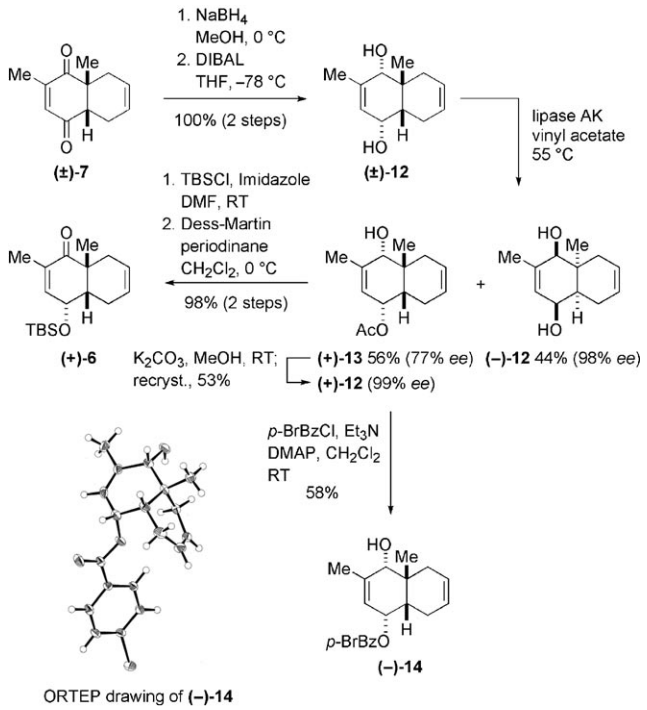


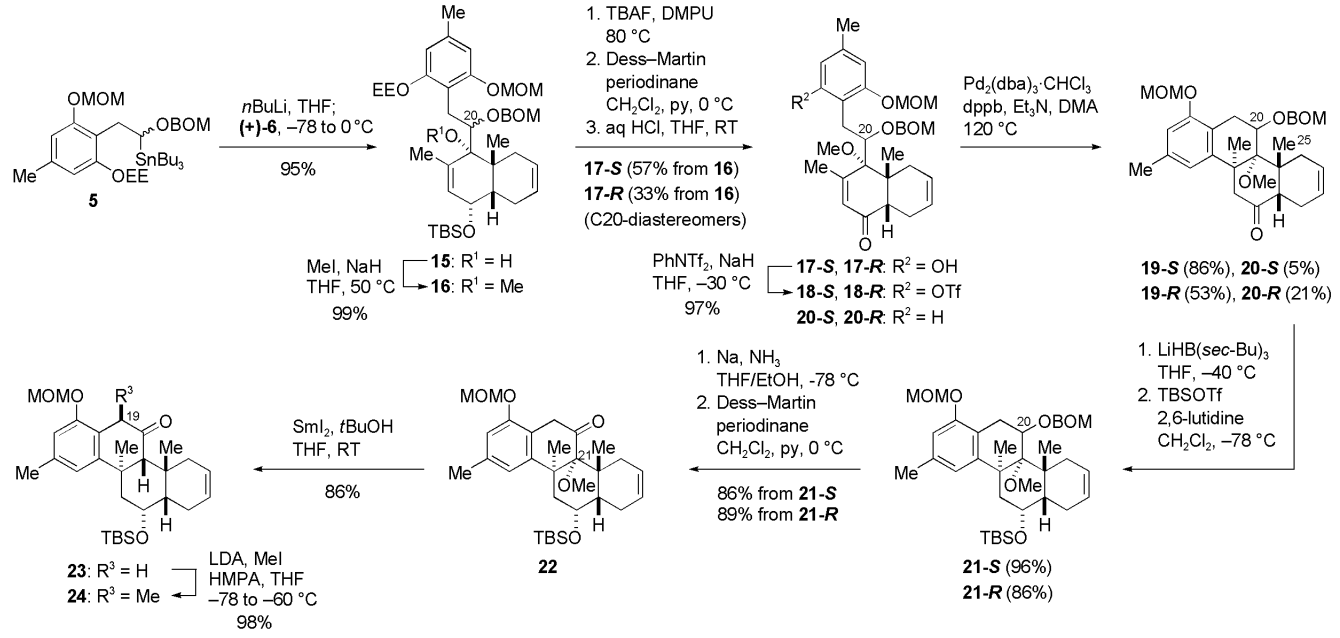
Scheme 1. Enantioselective synthesis of C-ring **6**.

ence of *t*BuOH produced deoxygenated ketone **23** in good yield.[17] Treatment of the corresponding α-hydroxyketone with SmI_2 in the absence of *t*BuOH resulted in a low yield of **23** and the generation of side products.[9d] Importantly, this deoxygenation caused a configurational change at C21 leading to the *trans*-decalin form of the BC-ring. Finally, stereoselective methylation of **23** by LDA and MeI gave **24** in 98% yield.

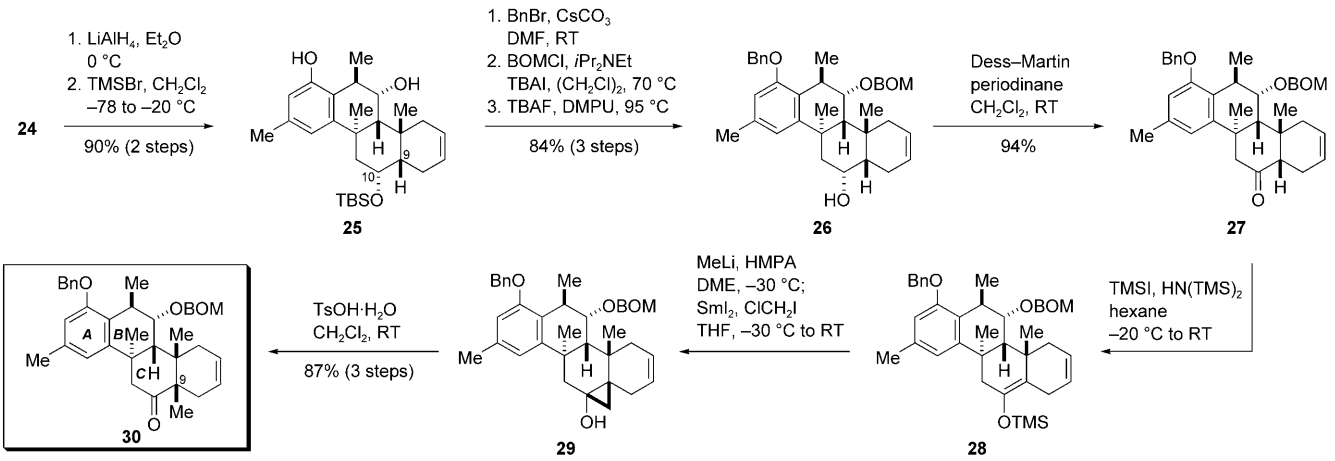
To complete the synthesis of the ABC-ring of zoanthenol, construction of the quaternary carbon at C9 was performed (Scheme 3). Reduction of the ketone **24** with $LiAlH_4$ and the removal of the MOM group by treatment with TMSBr afforded the diol **25**. Successive treatment of **25** with BnBr and BOMCl under basic conditions delivered the corresponding Bn and BOM ethers, followed by the TBAF-promoted deprotection of the C10 hydroxy group to furnish the secondary alcohol **26** in 84% overall yield. After the oxidation of alcohol **26**, the resulting ketone **27** was converted to the thermodynamically favored enol silylether **28** by treatment with TMSI in the presence of $HN(TMS)_2$ in hexane.[18] Simmons–Smith cyclopropanation of the corresponding lithium enolate of **28** using SmI_2 and chloroiodomethane proceeded in a chemo- and stereoselective fashion to provide the desired cyclopropanol **29**.[19] Acid-catalyzed regioselective cleavage of the cyclopropane of **29** generated the fully functionalized ABC-ring (**30**) of zoanthenol in 87% overall yield.

Conclusions

We have described the synthesis of the fully functionalized ABC-ring of zoanthenol in an enantioselective manner. The key features of the synthesis are kinetic enzymatic resolution, intramolecular Mizoroki–Heck reaction of β,β-disubstituted enones and Simmons–Smith reaction to introduce the consecutive chiral quaternary carbons. The application of this powerful methodology to the synthesis of zoanthenol



Scheme 2. Synthesis of ketone **24**.



Scheme 3. Synthesis of the fully functionalized ABC-ring of zoanthenol.

and other zoanthamine alkaloids is being actively investigated in our laboratory.

Experimental Section

General Methods

All air-sensitive and moisture-sensitive reactions were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF was distilled from sodium/benzophenone, dichloromethane (CH_2Cl_2), pyridine, triethylamine (Et_3N) and toluene from calcium hydride, and DMF and DMSO from calcium hydride under reduced pressure. All other reagents were used as supplied unless otherwise stated.

Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates. Flash column chromatography was performed using 40–50 μm Silica Gel 60N (Kanto Chemical Co., Inc.). ^{1}H- and ^{13}C NMR spectra were recorded on a Varian INOVA 500 (500 MHz) and a Varian Mercury 200 (200 MHz) spectrometer. Chemical shifts are reported in δ (ppm) using solvent signals as internal standard [^{1}H NMR: $CHCl_3$ (7.26), [D_6]DMSO (2.50); ^{13}C NMR: $CDCl_3$ (77.0), [D_6]DMSO (39.5)]. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. MALDI-TOF mass spectra were measured on an Applied Biosystems Voyager DE STR SI-3 instrument, and FAB-MS were measured on a JEOL JMS-HX/HX-110A mass spectrometer. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Elemental analysis was carried out on a Yanaco CHN corder MT-6.[20]

Syntheses

(±)-8: To a solution of **(±)-7** (5.34 g, 28.1 mmol) in MeOH (50 mL), $NaBH_4$ (276 mg, 7.30 mmol) was added at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was quenched with aqueous NH_4Cl, and extracted with EtOAc. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 2:1) to give **(±)-8** (5.41 g, 28.1 mmol) in 100% yield: pale yellow oil; R_f = 0.25 (hexane/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.25 (3H, s, Me25), 1.76 (1H, m, H23), 2.02 (3H, s, Me28), 2.10 (1H, m, H8), 2.15 (1H, m, H23), 2.28 (1H, m, H9), 2.84 (1H, m, H8), 4.29 (1H, s, H21), 5.60 (2H, m, H7, H24), 5.88 ppm (1H, s, H11); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.3, 21.1, 23.4, 27.4, 40.9, 50.0, 78.0, 124.4, 124.8, 125.7, 160.5, 198.6 ppm; IR (film) $\tilde{\nu}$ = 3436, 2920, 1657, 1435, 1218 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{12}H_{16}O_2Na$: 215.1043 [M+Na$^+$]; found, 215.1044.

(±)-12: To a solution of **(±)-8** (2.70 g, 14.0 mmol) in THF (70.2 mL), 0.94 M solution of DIBAL in hexane (37.4 mL, 35.1 mmol) was added at −78 °C. After being stirred for 2 h at −78 °C, the reaction mixture was quenched with EtOAc, treated with aqueous Rochelle's salt, and extracted with EtOAc. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 3:1) to give **(±)-12** (2.72 g, 14.0 mmol) in 100% yield.

(+)-13: To a solution of **(±)-12** (2.72 g, 14.0 mmol) in vinyl acetate (140 mL), lipase AK (AMANO) (2.72 g, 100% w/w) was added at room temperature. After being stirred for 4 days at 55 °C, the reaction mixture was filtered through celite and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10:1 to 2:1) to give **(+)-13** (1.85 g, 7.83 mmol) in 56% yield and **(−)-12** (1.19 g, 6.13 mmol) in 44% yield. **(+)-13**: pale yellow oil; R_f = 0.59 (hexane/EtOAc = 2:1); $[\alpha]_D^{21}$ +15.3 (c 1.00, $CHCl_3$, 77% *ee*), (calcd $[\alpha]_D^{21}$ +19.8); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.04 (3H, s, Me25), 1.83 (3H, s, Me28), 1.94 (1H, m, H23), 1.94 (1H, d, J = 6.5 Hz, OH), 2.03 (1H, m, H8), 2.04 (3H, s, Ac), 2.06 (1H, m, H9), 2.14 (1H, m, H8), 2.21 (1H, m, H23), 3.55 (1H, d, J = 6.5 Hz, H21), 5.33 (1H, s, H11), 5.49 (1H, br d, J = 1.5 Hz, H10), 5.72 (1H, m, H7), 5.78 ppm (1H, m, H24); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.5, 21.3, 24.3, 26.2, 34.0, 35.4, 37.9, 70.6, 76.8, 120.2, 126.1, 127.3, 137.5, 170.9 ppm; IR (film) $\tilde{\nu}$ = 3500, 2917, 1731, 1435, 1372, 1242 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{14}H_{20}O_3Na$: 259.1305 [M+Na$^+$]; found, 259.1306.

(+)-12: To a solution of **(+)-13** (19.2 g, 81.2 mmol) in MeOH (203 mL), K_2CO_3 (11.2 g, 81.2 mmol) was added at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was quenched with aqueous NH_4Cl, and extracted with hexane/EtOAc = 2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 3:1) to give **(+)-12** (13.4 g, 69.0 mmol) in 85% yield. After recrystalization from hexane/EtOAc = 2:1, enantio pure **(+)-12** (12.9 g, 66.4 mmol, 99% *ee*) was obtained in 62% yield. **(+)-12**: colorless solid; m.p. 142–144 °C; R_f = 0.37 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ +30.1 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.03 (3H, s, Me25), 1.82 (3H, s, Me28), 1.87 (1H, m, H9), 1.93 (1H, m, H23), 2.05 (1H, m, H8), 2.16 (1H, m, H23), 2.31 (1H, m, H8), 3.62 (1H, m, H21), 4.26 (1H, br s, H10), 5.46 (1H, s, H11), 5.84 ppm (2H, m, H7, H24); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.2, 24.2, 25.7, 32.6, 35.2, 39.8, 67.8, 77.2, 123.9, 127.27, 127.33, 136.0 ppm; IR (film) $\tilde{\nu}$ = 3324, 2875, 1434, 1060, 1027 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{12}H_{18}O_2Na$: 217.1199 [M+Na$^+$]; found, 217.1199; elemental analysis: calcd (%) for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.00, H 9.25.

(−)-14: To a solution of **(+)-12** (80.2 mg, 413 μmol), Et_3N (288 μL, 2.06 mmol) and DMAP (10.1 mg, 82.6 μmol) in CH_2Cl_2 (4.13 mL), *p*-BrBzCl (181 mg, 826 μmol) was added at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was quenched with aque-

ous $NaHCO_3$, and extracted with hexane/EtOAc = 2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to give **(−)-14** (90.2 mg, 239 μmol) in 58% yield: colorless solid; m.p. 130–131 °C; R_f = 0.64 (hexane/EtOAc = 2:1); $[\alpha]_D^{21}$ −82.2 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.12 (3H, s, Me25), 1.86 (3H, s, Me28), 1.89 (1H, d, J = 6.0 Hz, OH), 1.97 (1H, m, H23), 2.10 (1H, m, H8), 2.15 (1H, m, H9), 2.25 (1H, m, H8), 2.28 (1H, m, H23), 3.68 (1H, br d, J = 6.0 Hz, H21), 5.49 (1H, m, H11), 5.67 (1H, m, H10), 5.71 (1H, m, H7), 5.81 (1H, m, H24), 7.56 (1H, d, J = 2.0 Hz, *p*-BrBz), 7.57 (1H, d, J = 2.0 Hz, *p*-BrBz), 7.88 (1H, d, J = 2.0 Hz, *p*-BrBz), 7.90 ppm (1H, d, J = 2.0 Hz, *p*-BrBz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.4, 24.7, 25.8, 32.6, 35.5, 38.2, 71.4, 119.8, 126.4, 126.8, 128.0, 129.4, 131.3, 131.6, 138.5, 165.6 ppm; IR (film) $\tilde{\nu}$ = 3508, 2916, 1714, 1590, 1274 cm^{-1}; HRMS (FAB): m/z calcd for $C_{19}H_{21}O_3BrNa$: 399.0566 [M+Na$^+$]; found: 399.0567.

(+)-6: To a solution of **(+)-12** (12.9 g, 66.4 mmol) and imidazole (13.6 g, 199 mmol) in DMF (133 mL), TBSCl (11.0 g, 73.0 mmol) was added at room temperature. After being stirred for 2 h at room temperature, the reaction mixture was quenched with MeOH, treated with aqueous $NaHCO_3$, and extracted with hexane/EtOAc = 5:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 50:1) to give the corresponding TBS-ether (21.2 g, 68.7 mmol).

To a solution of the TBS-ether (21.2 g, 68.7 mmol) in CH_2Cl_2 (229 mL), Dess–Martin periodinane (30.6 g, 72.1 mmol) was added at 0 °C. After being stirred for 20 min at 0 °C, the reaction mixture was quenched with aqueous $NaHCO_3$, treated with aqueous $Na_2S_2O_3$, and extracted with hexane/EtOAc = 5:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 50:1) to give **(+)-6** (20.0 g, 65.2 mmol) in 98% yield from **(+)-12**: pale yellow oil; R_f = 0.64 (hexane/EtOAc, 5:1); $[\alpha]_D^{20}$ +121 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.12 (3H, s, TBS), 0.13 (3H, s, TBS), 0.92 (9H, s, TBS), 1.20 (3H, s, Me25), 1.70 (1H, m, H23), 1.77 (3H, s, Me28), 1.96 (1H, m, H8), 2.18 (1H, m, H8), 2.35 (1H, m, H9), 2.77 (1H, m, H23), 4.92 (1H, m, H10), 5.59 (2H, m, H7, H24), 6.27 ppm (1H, s, H11); ^{13}C NMR (125 MHz, $CDCl_3$) δ = −4.8, 16.0, 18.2, 23.2, 24.8, 25.8, 33.3, 45.7, 47.1, 68.0, 124.9, 125.7, 132.7, 144.0, 202.0 ppm; IR (film) $\tilde{\nu}$ = 2928, 1683, 1254, 1082 cm^{-1}; HRMS (FAB): m/z calcd for $C_{18}H_{30}O_2SiNa$: 329.1907 [M+Na$^+$]; found: 329.1907.

15: To a solution of **5** (24.2 g, 34.9 mmol) in THF (70.0 mL), 1.56 M *n*BuLi solution in hexane (26.9 mL, 41.9 mmol) was added at −78 °C. After being stirred for 5 min at −78 °C, **(+)-6** (13.9 g, 45.4 mmol) in THF (30.0 mL) was added. After being stirred for 30 min at −78 to 0 °C, the reaction mixture was quenched with H_2O, and extracted with hexane/EtOAc = 1:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 30:1) to give **15** (23.6 g, 33.2 mmol) in 95% yield as a 2:1 mixture of diastereomers at C20: pale yellow oil; R_f = 0.40 (hexane/EtOAc = 5:1); IR (film) $\tilde{\nu}$ = 3527, 2928, 1609, 1586, 1455, 1046 cm^{-1}; HRMS (FAB): m/z calcd for $C_{41}H_{62}O_8SiNa$: 733.4106 [M+Na$^+$]; found: 733.4109.

16: To a solution of **15** (26.8 g, 37.7 mmol) and NaH (4.52 g, 188 mmol) in THF (126 mL), MeI (23.5 mL, 377 mmol) was added at 0 °C. After being stirred for 30 min at 50 °C, the reaction mixture was quenched with H_2O at 0 °C, and extracted with hexane/EtOAc = 3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 35:1) to give **16** (27.0 g, 37.2 mmol) in 99% yield as a 2:1 mixture of diastereomers at C20: pale yellow oil; R_f = 0.47 (hexane/EtOAc = 5:1); IR (film) $\tilde{\nu}$ = 2927, 1609, 1586, 1455, 1155, 1046 cm^{-1}; HRMS (FAB): m/z calcd for $C_{42}H_{64}O_8SiNa$: 747.4263 [M+Na$^+$]; found, 747.4265.

17-*S* and **17-*R***: To a solution of **16** (4.46 g, 6.15 mmol) in DMPU (12.3 mL), 1.0 M TBAF solution in DMPU (18.5 mL, 18.5 mmol) was added at 0 °C. After being stirred for 30 min at 80 °C, the reaction mixture was quenched with aqueous NH_4Cl at 0 °C, and extracted with hexane/EtOAc = 2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5:1) to give an alcohol (3.69 g, 6.04 mmol) in 98% yield as a 2:1 mixture of diastereomers at C20.

To a solution of the alcohol (20.7 g, 33.9 mmol) and pyridine (27.3 mL, 339 mmol) in CH_2Cl_2 (113 mL), Dess–Martin periodinane (15.1 g, 35.6 mmol) was added at 0 °C. After being stirred for 10 min at 0 °C, the reaction mixture was quenched with aqueous $NaHCO_3$, treated with aqueous $Na_2S_2O_3$, and extracted with hexane/EtOAc = 2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to give the corresponding α,β-unsaturated ketone (19.2 g, 31.5 mmol) in 93% yield as a 2:1 mixture of diastereomers at C20.

To a solution of the α,β-unsaturated ketone (1.20 g, 1.97 mmol) in THF (19.7 mL), 0.5 N aqueous HCl (200 μL) was added at 0 °C. After being stirred for 4 h at room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$, and extracted with hexane/EtOAc = 2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (toluene/EtOAc = 30:1) to give **17-*S*** (663 mg, 1.23 mmol) in 63% yield and **17-*R*** (383 mg, 714 μmol) in 36% yield: **17-*S***: pale yellow oil; R_f = 0.44 (hexane/EtOAc = 2:1); $[\alpha]_D^{16}$ −150 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.44 (3H, s, Me25), 1.89 (1H, brdd, J = 17.5, 3.5 Hz, H23), 2.06 (3H, s, Me28), 2.06 (1H, m, H8), 2.25 (3H, s, Me27), 2.42 (1H, br d, J = 17.5 Hz, H23), 2.82 (1H, br dd, J = 18.0, 3.5 Hz, H8), 2.98 (1H, dd, J = 15.0, 7.5 Hz, H19), 3.33 (1H, dd, J = 15.0, 2.0 Hz, H19), 3.43 (1H, m, H9), 3.44 (3H, s, MeO), 3.55 (3H, s, MeO), 4.21 (1H, d, J = 11.5 Hz, BOM), 4.25 (1H, dd, J = 7.5, 2.0 Hz, H20), 4.33 (1H, d, J = 11.5 Hz, BOM), 4.75 (1H, d, J = 7.0 Hz, BOM), 4.78 (1H, d, J = 7.0 Hz, BOM), 5.13 (1H, d, J = 7.0 Hz, MOM), 5.17 (1H, d, J = 7.0 Hz, MOM), 5.52 (1H, m, H24), 5.67 (1H, m, H7), 6.19 (1H, s, H11), 6.44 (1H, s, Ar), 6.47 (1H, s, Ar), 7.10–7.28 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.5, 21.2, 21.6, 28.2, 33.0, 45.6, 48.1, 56.2, 58.0, 70.6, 83.3, 88.5, 94.7, 95.3, 106.7, 111.2, 112.9, 124.2, 124.6, 127.4, 127.6, 128.3, 132.8, 137.5, 138.4, 155.0, 155.8, 155.9, 198.9 ppm; IR (film) $\tilde{\nu}$ = 3349, 2926, 1670, 1584, 1458, 1154, 1058 cm^{-1}; HRMS (FAB): m/z calcd for $C_{32}H_{40}O_7Na$: 559.2666 [M+Na$^+$]; found: 559.2667. **17-*R***: pale yellow oil; R_f = 0.39 (hexane/EtOAc = 2:1); $[\alpha]_D^{16}$ −161 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.29 (3H, s, Me25), 1.89 (1H, m, H23), 1.93 (1H, m, H8), 2.16 (3H, s, Me28), 2.25 (3H, s, Me27), 2.47 (1H, br d, J = 17.0 Hz, H23), 2.73 (1H, br dd, J = 18.5, 4.5 Hz, H8), 2.96 (1H, br d, J = 5.5 Hz, H9), 3.03 (1H, dd, J = 15.0, 9.0 Hz, H19), 3.25 (1H, dd, J = 15.0, 3.5 Hz, H19), 3.43 (3H, s, MeO), 3.60 (3H, s, MeO), 4.20 (1H, d, J = 12.0 Hz, BOM), 4.28 (1H, d, J = 12.0 Hz, BOM), 4.47 (1H, dd, J = 9.0, 3.5 Hz, H20), 4.64 (1H, d, J = 7.0 Hz, BOM), 4.66 (1H, d, J = 7.0 Hz, BOM), 5.14 (2H, m, MOM), 5.50 (1H, m, H24), 5.64 (1H, m, H7), 6.14 (1H, s, H11), 6.44 (1H, s, Ar), 6.48 (1H, s, Ar), 7.08–7.29 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.2, 21.2, 21.6, 21.8, 27.9, 33.2, 45.6, 47.8, 56.2, 58.0, 71.0, 81.3, 88.4, 94.4, 95.2, 106.8, 111.3, 112.0, 124.4, 124.8, 127.5, 127.7, 128.3, 131.3, 137.4, 138.4, 155.4, 156.0, 198.7 ppm; IR (film) $\tilde{\nu}$ = 3351, 2925, 1664, 1592, 1454, 1155, 1057 cm^{-1}; HRMS (FAB): m/z calcd for $C_{32}H_{40}O_7Na$: 559.2666 [M+Na$^+$]; found: 559.2668.

18-*S*: To a solution of **17-*S*** (8.30 g, 15.5 mmol) and NaH (1.86 g, 77.3 mmol) in THF (155 mL), $PhNTf_2$ (8.84 g, 24.7 mmol) was added at −30 °C. After being stirred for 30 min at −30 to 0 °C, the reaction mixture was quenched with H_2O, treated with aqueous $NaHCO_3$, and extracted with hexane/EtOAc = 2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5:1) to give **18-*S*** (10.1 g, 15.1 mmol) in 97% yield: pale yellow oil; R_f = 0.50 (hexane/EtOAc = 2:1); $[\alpha]_D^{17}$ −150 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.45 (3H, s, Me25), 1.89 (1H, br dd, J = 17.5, 4.0 Hz, H23), 2.05 (1H, br d, J = 18.5 Hz, H8), 2.16 (3H, s, Me28), 2.25 (3H, s, Me27), 2.37 (1H, br d, J = 17.5 Hz, H23), 2.81 (1H, m, H8), 3.05 (1H, dd, J = 13.5, 10.5 Hz, H19), 3.08 (1H, br d, J = 6.0 Hz, H9), 3.12 (1H, dd, J = 13.5, 3.0 Hz, H19), 3.47 (3H, s, MeO), 3.50 (3H, s, MeO), 3.83 (1H, d, J =

12.0 Hz, BOM), 4.02 (1H, d, J=12.0 Hz, BOM), 4.42 (1H, d, J=6.5 Hz, BOM), 4.49 (1H, dd, J=10.5, 3.0 Hz, H20), 4.65 (1H, d, J=6.5 Hz, BOM), 5.17 (1H, d, J=6.5 Hz, MOM), 5.20 (1H, d, J=6.5 Hz, MOM), 5.53 (1H, m, H24), 5.66 (1H, m, H7), 6.19 (1H, s, H11), 6.70 (1H, s, Ar), 6.85 (1H, s, Ar), 7.06–7.29 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ=19.7, 21.3, 21.48, 21.54, 28.4, 32.9, 45.3, 48.3, 56.4, 57.5, 69.7, 80.1, 88.3, 94.6, 96.4, 114.1, 114.7, 118.7, 124.4, 124.6, 127.0, 127.3, 128.1, 131.9, 138.1, 138.9, 149.1, 156.5, 157.7, 198.8 ppm; IR (film) $\tilde{\nu}$=2928, 1671, 1420, 1215, 1142, 1027 cm^{-1}; HRMS (FAB): m/z calcd for $C_{33}H_{39}O_9F_3SNa$: 691.2159 [M+Na$^+$]; found: 691.2160.

18-*R*: Prepared by the same procedure as **18-*S*** (97% from **17-*R***): pale yellow oil; R_f=0.50 (hexane/EtOAc=2:1); $[\alpha]_D^{17}$ −109 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.32 (3H, s, Me25), 1.89 (1H, m, H23), 1.96 (1H, m, H8), 2.17 (3H, s, Me28), 2.29 (3H, s, Me27), 2.46 (1H, m, H23), 2.77 (1H, m, H8), 2.90 (1H, brd, J=5.0 Hz, H9), 3.10 (1H, dd, J=14.5, 3.0 Hz, H19), 3.26 (1H, dd, J=14.5, 10.0 Hz, H19), 3.46 (3H, s, MeO), 3.57 (3H, s, MeO), 3.92 (1H, d, J=13.0 Hz, BOM), 4.12 (1H, d, J=13.0 Hz, BOM), 4.18 (1H, d, J=7.0 Hz, BOM), 4.32 (1H, d, J=7.0 Hz, BOM), 4.70 (1H, dd, J=10.0, 3.0 Hz, H20), 5.20 (2H, s, MOM), 5.51 (1H, m, H24), 5.64 (1H, m, H7), 6.07 (1H, s, H11), 6.72 (1H, s, Ar), 6.86 (1H, s, Ar), 7.06–7.28 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ=19.2, 21.3, 21.5, 21.8, 28.8, 33.1, 45.4, 47.5, 56.4, 57.6, 70.2, 78.8, 87.7, 94.4, 95.5, 113.9, 114.9, 117.8, 119.0, 124.7, 127.4, 127.5, 128.2, 130.0, 137.7, 138.8, 149.2, 160.1, 198.9 ppm; IR (film) $\tilde{\nu}$=2927, 1669, 1418, 1214, 1143, 1027 cm^{-1}; HRMS (FAB): m/z calcd for $C_{33}H_{39}O_9F_3SNa$: 691.2159 [M+Na$^+$]; found: 691.2159.

19-*S*: To a solution of $Pd_2(dba)_3$·$CHCl_3$ (98.7 mg, 95.3 μmol) and dppb (97.6 mg, 229 μmol) in DMAc (4.00 mL) in a sealed tube, **18-*S*** (425 mg, 636 μmol) and Et_3N (886 μL, 6.36 mmol) in DMAc (8.70 mL) were added at room temperature. After being freeze-degassed (four times), the reaction mixture was stirred for 12 h at 120 °C, quenched with H_2O, and extracted with hexane/EtOAc=2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=5:1) to give **19-*S*** (285 mg, 546 μmol, 86%) and **20-*S*** (17 mg, 32 μmol, 5%). **19-*S***: pale yellow oil; R_f=0.58 (hexane/EtOAc=2:1); $[\alpha]_D^{15}$ −15.6 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.42 (3H, s, Me25), 1.58 (3H, s, Me28), 1.82 (1H, m, H23), 1.84 (1H, brs, H9), 1.99 (1H, dd, J=20.0, 2.5 Hz, H8), 2.26 (3H, s, Me27), 2.55 (1H, dd, J=17.0, 4.5 Hz, H23), 2.74 (1H, dd, J=19.0, 3.0 Hz, H19), 2.78 (1H, d, J=18.0 Hz, H11), 2.79 (1H, brd, J=20.0 Hz, H8), 3.10 (1H, dd, J=14.5, 3.0 Hz, H19), 3.10 (1H, d, J=18.0 Hz, H11), 3.35 (3H, s, MeO), 3.62 (3H, s, MeO), 3.78 (1H, dd, J=19.0, 3.0 Hz, H19), 4.40 (1H, d, J=12.0 Hz, BOM), 4.43 (1H, d, J=12.0 Hz, BOM), 4.78 (1H, dd, J=3.0, 3.0 Hz, H20), 4.91 (1H, d, J=7.5 Hz, BOM), 4.96 (1H, d, J=7.5 Hz, BOM), 4.98 (1H, d, J=7.0 Hz, MOM), 5.00 (1H, d, J=7.0 Hz, MOM), 5.52 (1H, m, H7), 5.55 (1H, m, H24), 6.64 (1H, s, Ar), 6.73 (1H, s, Ar), 7.20–7.32 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ=21.8, 22.0, 22.3, 27.0, 29.4, 34.3, 40.8, 44.2, 49.1, 49.5, 52.4, 56.0, 70.0, 74.4, 79.5, 94.4, 94.5, 111.6, 118.2, 120.6, 124.9, 125.7, 127.6, 127.7, 128.3, 136.8, 137.7, 145.2, 154.3, 211.7 ppm; IR (film) $\tilde{\nu}$=2937, 1714, 1453, 1215, 1151, 1095, 1027, 753 cm^{-1}; HRMS (FAB): m/z calcd for $C_{32}H_{40}O_6Na$: 543.2717 [M+Na$^+$]; found: 543.2717. **20-*S***: pale yellow oil; R_f=0.58 (hexane/EtOAc=2:1); $[\alpha]_D^{15}$ −144 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.44 (3H, s, Me25), 1.90 (1H, m, H23), 2.05 (1H, m, H8), 2.15 (3H, s, Me28), 2.26 (3H, s, Me27), 2.38 (1H, m, H23), 2.64 (1H, dd, J=13.5, 10.0 Hz, H19), 2.81 (1H, m, H8), 3.16 (1H, brd, J=6.0 Hz, H9), 3.28 (1H, dd, J=13.5, 2.5 Hz, H19), 3.45 (3H, s, MeO), 3.53 (3H, s, MeO), 3.90 (1H, d, J=12.0 Hz, BOM), 4.10 (1H, d, J=12.0 Hz, BOM), 4.43 (1H, d, J=7.0 Hz, BOM), 4.45 (1H, dd, J=10.0, 2.5 Hz, H20), 4.54 (1H, d, J=7.0 Hz, BOM), 5.17 (2H, s, MOM), 5.53 (1H, m, H24), 5.66 (1H, m, H7), 6.14 (1H, s, H11), 6.71–7.07 (3H, m, Ar), 7.06–7.28 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ=20.1, 21.3, 21.4, 21.7, 29.4, 33.0, 35.1, 45.2, 48.3, 56.1, 57.3, 69.8, 81.2, 87.8, 94.2, 96.4, 114.4, 122.3, 124.4, 124.8, 125.1, 127.3, 127.7, 128.1, 131.4, 131.8, 137.7, 138.2, 155.1, 158.3, 199.1 ppm; IR (film) $\tilde{\nu}$=2927, 1668, 1152, 1084, 1025 cm^{-1}; HRMS (FAB): m/z calcd for $C_{32}H_{40}O_6Na$: 543.2717 [M+Na$^+$]; found: 543.2717.

19-*R*: Prepared by the same procedure as **19-*S*** (53% from **18-*R***). **19-*R***: pale yellow oil; R_f=0.58 (hexane/EtOAc=2:1); $[\alpha]_D^{15}$ −63.1 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.55 (3H, s, Me25), 1.55 (3H, s, Me28), 1.92 (1H, m, H23), 1.96 (1H, m, H8), 2.29 (3H, s, Me27), 2.53 (1H, m, H8), 2.53 (1H, d, J=12.5 Hz, H11), 2.79 (1H, dd, J=18.0, 3.0 Hz, H19), 2.89 (1H, brd, J=18.0 Hz, H23), 3.23 (1H, brd, J=5.5 Hz, H9), 3.33 (1H, d, J=12.5 Hz, H11), 3.40 (3H, s, MeO), 3.51 (1H, dd, J=18.0, 3.0 Hz, H19), 3.53 (3H, s, MeO), 4.37 (1H, d, J=11.5 Hz, BOM), 4.40 (1H, d, J=11.5 Hz, BOM), 4.90 (1H, d, J=6.5 Hz, BOM), 4.96 (1H, d, J=6.5 Hz, BOM), 5.03 (1H, dd, J=3.0, 3.0 Hz, H20), 5.05 (1H, d, J=6.5 Hz, MOM), 5.06 (1H, d, J=6.5 Hz, MOM), 5.59 (1H, m, H24), 5.77 (1H, m, H7), 6.71 (1H, s, Ar), 6.79 (1H, s, Ar), 7.18–7.30 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ=20.8, 21.8, 24.7, 25.5, 26.5, 29.7, 31.9, 45.9, 48.9, 51.6, 53.6, 55.9, 70.6, 75.5, 77.9, 94.4, 94.6, 111.5, 118.0, 120.2, 123.9, 124.4, 127.7, 127.8, 128.4, 136.3, 137.3, 145.4, 154.4, 211.2 ppm; IR (film) $\tilde{\nu}$=2927, 1712, 1454, 1215, 1152, 1089, 1048, 1024 cm^{-1}; HRMS (FAB): m/z calcd for $C_{32}H_{40}O_6Na$: 543.2717 [M+Na$^+$]; found: 543.2717. **20-*R* :** pale yellow oil; R_f=0.58 (hexane/EtOAc=2:1); $[\alpha]_D^{15}$ −137 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.38 (3H, s, Me25), 1.91 (1H, m, H23), 1.97 (1H, m, H8), 2.16 (3H, s, Me28), 2.29 (3H, s, Me27), 2.44 (1H, brd, J=18.0 Hz, H23), 2.77 (1H, dd, J=14.0, 10.0 Hz, H19), 2.77 (1H, m, H8), 3.06 (1H, brd, J=6.0 Hz, H9), 3.34 (1H, brd, J=14.0 Hz, H19), 3.46 (3H, s, MeO), 3.61 (3H, s, MeO), 4.01 (1H, d, J=12.0 Hz, BOM), 4.17 (1H, d, J=6.5 Hz, BOM), 4.22 (1H, d, J=12.0 Hz, BOM), 4.30 (1H, d, J=6.5 Hz, BOM), 4.69 (1H, dd, J=10.0, 2.0 Hz, H20), 5.19 (2H, s, MOM), 5.52 (1H, m, H24), 5.62 (1H, m, H7), 6.07 (1H, s, H11), 6.73–7.08 (3H, m, Ar), 7.08–7.28 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ=19.7, 21.3, 21.4, 22.3, 29.7, 32.9, 35.4, 45.2, 47.7, 56.1, 56.8, 70.4, 80.0, 86.9, 94.0, 96.1, 114.2, 122.4, 124.7, 124.8, 125.0, 127.45, 127.51, 128.2, 129.6, 131.9, 137.7, 137.8, 155.0, 160.5, 199.3 ppm; HRMS (FAB): m/z calcd for $C_{32}H_{40}O_6Na$: 543.2717 [M+Na$^+$]; found: 543.2717.

21-*S*: To a solution of **19-*S*** (134 mg, 257 μmol) in THF (2.57 mL), 1.0 M solution of L-selectride in THF (772 μL, 772 μmol) was added at −40 °C. After being stirred for 4 h at −40 to −30 °C, the reaction mixture was quenched with water at −78 °C, and treated with 30% aqueous H_2O_2. After being stirred for 30 min at room temperature, the reaction mixture was treated with aqueous $Na_2S_2O_3$. After being stirred for overnight, and extracted with hexane/EtOAc=1:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=10:1) to give an alcohol (134 mg, 256 μmol) in 99% yield.

To a solution of the alcohol (4.94 g, 9.45 mmol) and 2,6-lutidine (3.12 mL, 28.3 mmol) in CH_2Cl_2 (94.5 mL), TBSOTf (2.60 mL, 11.3 mmol) was added at −78 °C. After being stirred for 30 min at −78 °C, the reaction mixture was quenched with MeOH at −78 °C, and treated with aqueous $NaHCO_3$, and extracted with hexane/EtOAc=2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=30:1) to give **21-*S*** (5.77 g, 9.06 mmol) in 96% yield: pale yellow oil; R_f=0.62 (hexane/EtOAc=5:1); $[\alpha]_D^{19}$ −12.4 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO, 130 °C) δ=0.00 (3H, s, TBS), 0.08 (3H, s, TBS), 0.86 (3H, s, Me25), 0.90 (9H, s, TBS), 1.36 (3H, s, Me28), 1.48 (1H, m, H9), 1.74 (1H, brd, J=19.0 Hz, H23), 1.98 (1H, m, H8), 2.01 (1H, m, H11), 2.23 (1H, m, H8), 2.25 (1H, m, H11), 2.28 (3H, s, Me27), 2.80 (1H, brd, J=19.0 Hz, H23), 3.05 (1H, brd, J=9.0 Hz, H19), 3.34 (1H, m, H19), 3.36 (3H, s, MeO), 3.50 (3H, s, MeO), 3.82 (1H, br, H10), 4.50 (1H, d, J=12.5 Hz, BOM), 4.54 (1H, m, H20), 4.56 (1H, d, J=12.5 Hz, BOM), 4.93 (1H, d, J=6.5 Hz, BOM), 4.96 (1H, d, J=6.5 Hz, BOM), 5.10 (1H, d, J=6.5 Hz, MOM), 5.12 (1H, d, J=6.5 Hz, MOM), 5.53 (1H, m, H24), 5.68 (1H, m, H7), 6.67 (1H, s, Ar), 6.90 (1H, s, Ar), 7.26–7.31 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ=−5.5, −5.2, −4.0, 17.0, 20.4, 23.4, 25.1, 26.5, 28.7, 30.4, 35.5, 38.2, 41.4, 44.1, 53.5, 54.9, 66.6, 69.1, 73.3, 81.0, 94.0, 94.4, 111.3, 117.4, 119.1, 124.7, 125.2, 126.6, 126.7, 127.4, 134.8, 137.5, 145.3, 153.4 ppm; IR (film) $\tilde{\nu}$=2928, 1611, 1585, 1463, 1153, 1097, 1047, 758 cm^{-1}; HRMS (FAB): m/z calcd for $C_{38}H_{56}O_6SiNa$: 659.3738 [M+Na$^+$]; found: 659.3738.

21-*R*: Prepared by the same procedure as **21-*S*** (86% from **19-*R***): pale yellow oil; R_f=0.62 (hexane/EtOAc=5:1); $[\alpha]_D^{19}$ +14.4 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO, 130°C) δ=0.04 (3H, s, TBS), 0.12 (3H, s, TBS), 0.93 (9H, s, TBS), 0.95 (3H, brs, Me25), 1.25 (3H, brs, Me28), 1.66 (1H, br, H9), 1.66 (1H, br, H23), 2.02 (1H, brd, J=12.5 Hz, H11), 2.13 (1H, br, H8), 2.23 (1H, br, H11), 2.24 (1H, br, H8), 2.28 (3H, s, Me27), 3.04 (1H, br, H19), 3.30 (1H, m, H19), 3.37 (3H, s, MeO), 3.51 (3H, s, MeO), 3.63 (1H, br, H23), 4.01 (1H, br, H10), 4.56 (1H, brd, J=11.5 Hz, BOM), 4.65 (1H, brd, J=11.5 Hz, BOM), 4.78 (1H, br, H20), 4.94 (1H, brd, J=6.0 Hz, BOM), 4.98 (1H, brd, J=6.0 Hz), 5.11 (1H, d, J=6.5 Hz, MOM), 5.13 (1H, d, J=6.5 Hz, MOM), 5.57 (1H, m, H24), 5.66 (1H, m, H7), 6.68 (1H, s, Ar), 6.84 (1H, s, Ar), 7.25–7.35 ppm (5H, m, BOM); ^{13}C NMR (125 MHz, DMSO, 130°C) δ=−5.4, −5.0, 17.0, 17.8, 20.5, 25.19, 25.22, 29.7, 42.4, 46.6, 52.9, 54.9, 69.5, 75.6, 93.9, 94.0, 111.3, 117.4, 124.0, 125.3, 126.7, 126.8, 127.4, 134.8, 137.5, 153.0 ppm; IR (film) $\tilde{\nu}$=2929, 1611, 1586, 1462, 1153, 1088, 1030, 837, 758 cm^{-1}; HRMS (FAB): m/z calcd for $C_{38}H_{56}O_6SiNa$: 659.3738 [M+Na$^+$]; found: 659.3736.

22: To a solution of **21-*S*** (745 mg, 1.17 mmol) in THF/EtOH=5:1 (11.7 mL), NH_3 (11.7 mL) and sodium was added until the color changed to blue at −78°C. After being stirred for 30 min at −78°C, the reaction mixture was quenched with solid NH_4Cl at −78°C and evaporated at room temperature. The reaction mixture was treated with aqueous NH_4Cl, and extracted with hexane/EtOAc=2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=15:1) to give a secondary alcohol (557 mg, 1.08 mmol) in 92% yield.

To a solution of the alcohol (556 mg, 1.07 mmol) and pyridine (865 μL, 10.7 mmol) in CH_2Cl_2 (10.7 mL) Dess–Martin periodinane (502 mg, 1.18 mmol) was added at 0°C. After being stirred for 30 min at 0°C, the reaction mixture was quenched with aqueous $NaHCO_3$, treated with aqueous $Na_2S_2O_3$, and extracted with hexane/EtOAc=3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=30:1) to give **22** (518 mg, 1.01 mmol) in 94% yield. From **21-*R***, **22** was prepared by the same procedure in 89% yield: pale yellow oil; R_f=0.61 (hexane/EtOAc=3:1); $[\alpha]_D^{23}$ +20.9 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.05 (3H, s, TBS), 0.14 (3H, s, TBS), 0.46 (3H, s, Me25), 0.93 (9H, s, TBS), 1.17 (3H, s, Me28), 1.34 (1H, brd, J=19.5 Hz, H23), 1.66 (1H, dt, J=11.5, 5.0 Hz, H9), 2.07 (1H, m, H8), 2.09 (1H, dd, J=13.5, 3.5 Hz, H11), 2.32 (1H, dd, J=13.5, 12.0 Hz, H11), 2.37 (3H, s, Me27), 2.37 (1H, m, H8), 2.93 (1H, brd, J=19.5 Hz, H23), 3.41 (3H, s, MeO), 3.43 (1H, d, J=23.5 Hz, H19), 3.45 (3H, s, MeO), 3.83 (1H, d, J=23.5 Hz, H19), 4.28 (1H, brddd, J=12.0, 5.0, 3.5 Hz, H10), 5.15 (1H, d, J=7.0 Hz, MOM), 5.19 (1H, d, J=7.0 Hz, MOM), 5.60 (1H, m, H24), 5.72 (1H, m, H7), 6.79 (1H, s, Ar), 6.96 ppm (1H, s, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ=−4.5, −4.4, 18.1, 21.8, 23.7, 25.9, 28.5, 29.5, 34.9, 35.6, 40.3, 42.9, 47.1, 47.4, 56.1, 58.2, 66.2, 88.3, 94.2, 112.2, 117.2, 118.4, 125.2, 125.4, 137.9, 144.4, 153.5, 208.6 ppm; IR (film) $\tilde{\nu}$=2955, 1704, 1463, 1255, 1154, 1090, 1025, 836 cm^{-1}; HRMS (FAB): m/z calcd for $C_{30}H_{46}O_5SiNa$: 537.3007 [M+Na$^+$]; found: 537.3007.

23: To a degassed solution of **22** (2.0 g, 3.89 mmol) and *t*BuOH (372 μL, 3.89 mmol) in THF (38.9 mL), 0.1 M SmI_2 solution in THF (233 mL, 23.3 mmol) was added at 0°C. After being stirred for 12 h at room temperature, the reaction mixture was treated with Al_2O_3 at −78°C, and filtered through celite and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=50:1) to give **23** (1.62 g, 3.34 mmol) in 86% yield: pale yellow oil; R_f=0.60 (toluene/EtOAc=13:1); $[\alpha]_D^{25}$ −80.3 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.07 (3H, s, TBS), 0.14 (3H, s, TBS), 0.88 (9H, s, TBS), 1.13 (3H, s, Me25), 1.25 (1H, m, H9), 1.43 (3H, s, Me28), 1.89 (1H, m, H8), 1.95 (1H, dd, J=13.5, 3.0 Hz, H11), 2.35 (1H, s, Me27), 2.46 (1H, m, H8), 2.49 (1H, dd, J=13.5, 3.0 Hz, H11), 2.62 (1H, s, H21), 2.75 (1H, m, H23), 2.83 (1H, m, H23), 3.35 (1H, d, J=22.0 Hz, H19), 3.48 (3H, s, MOM), 3.64 (1H, d, J=22.0 Hz, H19), 4.11 (1H, m, H10), 5.17 (1H, d, J=6.5 Hz, MOM), 5.20 (1H, d, J=6.5 Hz, MOM), 5.54 (1H, m, H7), 5.63 (1H, m, H24), 6.75 (1H, s, Ar), 6.78 ppm (1H, s, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ=0.00, 0.81, 22.9, 26.7, 31.0, 32.4, 32.7, 33.0, 35.5, 39.0, 45.4, 45.7, 48.7, 49.8, 61.0, 68.5, 78.7, 99.1, 116.6, 121.9, 123.5, 127.9, 131.9, 142.2, 155.8, 159.0, 214.8 ppm; IR (film) $\tilde{\nu}$=2955, 1715, 1584, 1471, 1255, 1154, 1030, 837, 758 cm^{-1}; HRMS (FAB): m/z calcd for $C_{29}H_{44}O_4SiNa$: 507.2901 [M+Na$^+$]; found: 507.2900.

24: To a solution of *i*Pr_2NH (214 μL, 1.89 mmol) in THF (3.44 mL), 1.56 M *n*BuLi solution in hexane (1.21 mL, 1.89 mmol) was added at −78°C. After being stirred for 30 min at 0°C, a solution of **23** (458 mg, 944 μmol) in THF (3.0 mL) was added at −78°C. After being stirred for 30 min at −78 to −60°C, MeI (588 μL, 9.44 mmol) and HMPA (164 μL, 944 μmol) were added at −78°C. After being stirred for 1 h at −78°C to room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$, and extracted with hexane/EtOAc=3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=20:1) to give **24** (463 mg, 929 μmol) in 98% yield: pale yellow oil; R_f=0.61 (hexane/EtOAc=5:1); $[\alpha]_D^{25}$ −65.9 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.07 (3H, s, TBS), 0.14 (3H, s, TBS), 0.88 (9H, s, TBS), 1.08 (3H, s, Me25), 1.26 (1H, m, H9), 1.39 (3H, s, Me28), 1.52 (3H, d, J=7.0 Hz, Me26), 1.90 (1H, m, H8), 1.92 (1H, dd, J=13.5, 3.0 Hz, H11), 2.33 (3H, s, Me27), 2.46 (1H, m, H8), 2.52 (1H, dd, J=13.5, 3.0 Hz, H11), 2.79 (1H, m, H23), 2.88 (1H, m, H23), 3.00 (1H, s, H21), 3.49 (3H, s, MOM), 3.52 (1H, q, J=7.0 Hz, H19), 4.11 (1H, brdd, J=3.0, 3.0 Hz, H10), 5.18 (1H, d, J=7.0 Hz, MOM), 5.20 (1H, d, J=7.0 Hz, MOM), 5.54 (1H, m, H24), 5.61 (1H, m, H7), 6.71 (1H, s, Ar), 6.80 ppm (1H, s, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ=0.00, 0.84, 22.8, 24.6, 26.6, 31.0, 32.7, 33.1, 33.9, 35.9, 38.5, 47.8, 48.5, 50.0, 51.3, 61.1, 64.6, 78.9, 99.0, 117.3, 122.5, 127.9, 128.6, 131.8, 142.5, 155.1, 159.9, 218.8 ppm; IR (film) $\tilde{\nu}$=2928, 1715, 1574, 1470, 1255, 1152, 1029, 837, 771 cm^{-1}; HRMS (FAB): m/z calcd for $C_{30}H_{46}O_4SiNa$: 521.3058 [M+Na$^+$]; found: 521.3060.

25: To a solution of $LiAlH_4$ (93.9 mg, 2.51 mmol) in Et_2O (4.36 mL), **24** (463 mg, 929 μmol) in Et_2O (2.00 mL) was added at −78°C. After being stirred for 1 h at −78 to 0°C, the reaction mixture was quenched with EtOAc at −78°C, treated with aqueous Rochelle salt, and extracted with hexane/EtOAc=3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=30:1) to give the alcohol (465 mg, 929 μmol) in 100% yield as a 9:1 mixture of diastereomers at C20, which was used in the next reaction without further purification.

To a solution of the secondary alcohol (1.92 g, 3.83 mmol) in CH_2Cl_2 (38.3 mL), TMSBr (2.53 mL, 19.2 mmol) was added at −78°C. After being stirred for 2 h at −78 to −20°C, the reaction mixture was quenched with aqueous $NaHCO_3$ at −78°C, treated with aqueous NH_4Cl, and extracted with hexane/EtOAc=3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=4:1) to give **25** (1.58 g, 3.45 mmol) in 90% yield: pale yellow oil; R_f=0.60 (hexane/EtOAc=2:1); $[\alpha]_D^{24}$ +1.48 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.09 (3H, s, TBS), 0.18 (3H, s, TBS), 0.89 (9H, s, TBS), 1.14 (3H, s, Me25), 1.24 (3H, d, J=7.0 Hz, Me26), 1.40 (1H, m, H9), 1.60 (1H, s, H21), 1.65 (1H, dd, J=14.0, 3.5 Hz, H11), 1.80 (3H, s, Me28), 1.92 (1H, m, H23), 1.96 (1H, m, H8), 2.27 (3H, s, Me27), 2.42 (1H, dd, J=14.0, 3.5 Hz, H11), 2.51 (1H, m, H8), 3.12 (1H, m, H23), 3.12 (1H, q, J=7.0 Hz, H19), 4.08 (1H, ddd, J=8.5, 3.5, 3.5 Hz, H10), 4.51 (1H, brs, H20), 5.61 (2H, m, H7, H24), 6.41 (1H, s, Ar), 6.67 ppm (1H, s, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ=−5.0, −3.7, 14.1, 17.9, 20.4, 21.2, 26.1, 28.0, 28.8, 31.0, 32.5, 35.2, 37.9, 38.3, 44.3, 47.5, 49.4, 60.5, 72.0, 74.1, 113.2, 117.5, 120.9, 124.2, 125.8, 136.3, 150.4, 154.1 ppm; IR (film) $\tilde{\nu}$=3365, 2928, 1580, 1471, 1254, 1069, 837, 771 cm^{-1}; HRMS (FAB): m/z calcd for $C_{28}H_{44}O_3SiNa$: 479.2952 [M+Na$^+$]; found: 479.2951.

26: To a solution of **25** (8.7 mg, 19 μmol) and Cs_2CO_3 (34 mg, 95 μmol) in DMF (1.0 mL), BnBr (6.8 μL, 57 μmol) was added at 0°C. After being stirred for 30 min at room temperature, the reaction mixture was quenched with MeOH, treated with aqueous $NaHCO_3$, and extracted with hexane/EtOAc=3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified

by flash column chromatography (hexane/EtOAc = 50:1) to give a Bn-ether (9.2 mg, 17 μmol) in 91% yield.

To a solution of the Bn-ether (1.37 g, 2.51 mmol), TBAI (1.85 g, 5.01 mmol) and iPr$_2$NEt (8.73 mL, 50.1 mmol) in $(CH_2Cl)_2$ (25.1 mL), BOMCl (1.74 mL, 12.5 mmol) was added at 0 °C. After being stirred for 2 h at 70 °C, the reaction mixture was quenched with aqueous $NaHCO_3$ at 0 °C, and extracted with hexane/EtOAc = 3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated to give a BOM-ether.

To a solution of the BOM-ether in DMPU (25.1 mL), 1.0 M solution of TBAF in DMPU (50.2 mL, 50.2 mmol) was added at 0 °C. After being stirred for 3 h at 95 °C, the reaction mixture was quenched with aqueous NH_4Cl, and treated with water, and extracted with hexane/EtOAc = 3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5:1) to give **26** (1.29 g, 2.33 mmol) in 93% overall yield: pale yellow oil; $R_f = 0.33$ (hexane/EtOAc = 5:1); $[\alpha]_D^{26}$ −8.52 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.15$ (3H, s, Me25), 1.25 (3H, d, $J = 7.0$ Hz, Me26), 1.48 (1H, m, H9), 1.62 (1H, m, H11), 1.67 (1H, s, H21), 1.86 (3H, s, Me28), 1.96 (1H, m, H23), 2.08 (1H, m, H8), 2.33 (3H, s, Me27), 2.62 (1H, dd, $J = 14.0$, 3.0 Hz, H11), 2.66 (1H, m, H8), 3.19 (1H, m, H23), 3.61 (1H, q, $J = 7.0$ Hz, H19), 4.16 (1H, m, H10), 4.32 (1H, brs, H20), 4.49 (1H, d, $J = 12.0$ Hz, BOM), 4.59 (1H, d, $J = 12.0$ Hz, BOM), 4.84 (1H, d, $J = 6.5$ Hz, BOM), 4.92 (1H, d, $J = 6.5$ Hz, BOM), 5.03 (1H, d, $J = 12.0$ Hz, Bn), 5.06 (1H, d, $J = 12.0$ Hz, Bn), 5.79 (2H, m, H7, H24), 6.61 (1H, s, Ar), 6.84 (1H, s, Ar), 7.22–7.41 ppm (10H, m, Bn, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 14.0$, 20.6, 20.9, 21.7, 27.6, 29.0, 29.1, 30.3, 32.3, 34.1, 34.3, 38.2, 43.7, 46.5, 48.9, 53.8, 69.5, 69.9, 74.5, 79.4, 94.9, 109.2, 118.1, 123.1, 123.5, 126.7, 127.3, 127.4, 127.7, 128.1, 128.3, 128.7, 135.9, 137.4, 137.8, 150.3, 156.5 ppm; IR (film) $\tilde{\nu} = 3573$, 2931, 1575, 1454, 1377, 1058, 734, 696 cm^{-1}; HRMS (FAB): m/z calcd for $C_{37}H_{44}O_4Na$: 575.3132 $[M+Na^+]$; found: 575.3134.

27: To a solution of **26** (1.29 g, 2.33 mmol) in CH_2Cl_2 (23.3 mL), Dess–Martin periodinane (2.97 g, 7.00 mmol) was added at 0 °C. After being stirred for 30 min at room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$, treated with aqueous $Na_2S_2O_3$, and extracted with hexane/EtOAc = 3:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to give **27** (1.21 g, 2.20 mmol) in 94% yield: pale yellow oil; $R_f = 0.44$ (hexane/EtOAc = 5:1); $[\alpha]_D^{26}$ −42.1 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.31$ (3H, d, $J = 7.5$ Hz, Me26), 1.34 (3H, s, Me25), 1.59 (3H, s, Me28), 1.88 (1H, m, H23), 2.08 (1H, m, H8), 2.24 (1H, s, H21), 2.32 (3H, s, Me27), 2.46 (1H, d, $J = 7.0$ Hz, H9), 2.56 (1H, d, $J = 11.5$ Hz, H11), 2.71 (1H, m, H8), 2.79 (1H, m, H23), 2.93 (1H, d, $J = 11.5$ Hz, H11), 3.68 (1H, q, $J = 7.5$ Hz, H19), 4.34 (1H, brs, H20), 4.45 (1H, d, $J = 12.0$ Hz, BOM), 4.54 (1H, d, $J = 12.0$ Hz, BOM), 4.82 (1H, d, $J = 7.5$ Hz, BOM), 4.90 (1H, d, $J = 7.5$ Hz, BOM), 5.02 (1H, d, $J = 12.0$ Hz, Bn), 5.07 (1H, d, $J = 12.0$ Hz, Bn), 5.54 (1H, m, H24), 5.71 (1H, m, H7), 6.64 (1H, s, Ar), 6.71 (1H, s, Ar), 7.22–7.42 ppm (10H, m, Bn, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 20.6$, 21.0, 21.8, 28.6, 29.7, 31.3, 34.1, 40.7, 43.7, 48.9, 53.9, 57.1, 69.8, 70.3, 79.3, 94.8, 110.0, 118.1, 123.3, 124.1, 124.4, 127.0, 127.6, 127.7, 127.8, 128.3, 128.5, 136.6, 137.4, 137.7, 147.0, 156.7, 209.9 ppm; IR (film) $\tilde{\nu} = 2930$, 1713, 1575, 1454, 1377, 1048, 910, 734 cm^{-1}; HRMS (FAB): m/z calcd for $C_{37}H_{42}O_4Na$: 573.2975 $[M+Na^+]$; found: 573.2976.

30: To a solution of **27** (83.5 mg, 152 μmol) in hexane (3.00 mL), HN(TMS)$_2$ (320 μL, 1.52 mmol) and TMSI (107 μL, 760 μmol) was added at −20 °C. After being stirred for 12 h at room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$ at −20 °C, and extracted with hexane/EtOAc = 5:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated to give **28**.

To a solution of **28** in DME/HMPA = 5:1 (1.85 mL), 1.0 M solution of MeLi in Et_2O (500 μL, 500 μmol) was added at −30 °C. After being stirred for 30 min at −30 °C, the reaction mixture and $ClCH_2I$ (110 μL, 1.52 mmol) were added to 0.5 M solution of SmI_2 in THF (2.90 mL) at −50 °C. After being stirred for 30 min at −30 °C to room temperature, the reaction mixture was treated with Al_2O_3 at −78 °C, and filtered through florisil and concentrated to give **29**.

To a solution of **29** in CH_2Cl_2 (2.00 mL), p-TsOH (2.9 mg, 15.2 μmol) was added at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$ at 0 °C, and extracted with hexane/EtOAc = 2:1. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 20:1) to give **30** (74.3 mg, 132 μmol) in 87% yield from **27**: colorless oil; $R_f = 0.61$ (hexane/EtOAc = 3:1); $[\alpha]_D^{24}$ −43.6 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.19$ (3H, s, Me29), 1.24 (3H, s, Me25), 1.32 (3H, d, $J = 7.0$ Hz, Me26), 1.63 (3H, s, Me28), 1.78 (1H, m, H8), 1.98 (1H, m, H23), 2.32 (3H, s, Me27), 2.64 (1H, s, H21), 2.70 (1H, m, H8), 2.77 (1H, d, $J = 12.5$ Hz, H11), 2.92 (1H, m, H23), 2.97 (1H, d, $J = 12.5$ Hz, H11), 3.66 (1H, q, $J = 7.0$ Hz, H19), 4.26 (1H, s, H20), 4.48 (1H, d, $J = 12.0$ Hz, BOM), 4.56 (1H, d, $J = 12.0$ Hz, BOM), 4.81 (1H, d, $J = 7.5$ Hz, BOM), 4.91 (1H, d, $J = 7.5$ Hz, BOM), 5.03 (1H, d, $J = 12.5$ Hz, Bn), 5.07 (1H, d, $J = 12.5$ Hz, Bn), 5.53 (1H, m, H24), 5.69 (1H, m, H7), 6.64 (1H, s, Ar), 6.69 (1H, s, Ar), 7.23–7.42 ppm (10H, m, Bn, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 15.3$, 21.0, 21.8, 24.2, 24.9, 29.8, 31.0, 33.3, 34.4, 41.3, 42.3, 43.2, 51.8, 52.9, 65.8, 69.8, 70.4, 79.6, 94.8, 110.0, 118.0, 124.0, 124.2, 124.4, 127.0, 127.6, 127.7, 127.8, 128.4, 128.5, 136.7, 137.4, 137.8, 148.0, 156.7, 212.9 ppm; IR (film) $\tilde{\nu} = 2924$, 1705, 1576, 1454, 1288, 1050, 753 cm^{-1}; HRMS (FAB): m/z calcd for $C_{38}H_{44}O_4Na$: 587.3132 $[M+Na^+]$; found: 587.3133.

Acknowledgements

This work was supported financially by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology, Japan.

[1] a) C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkateswarlu, R. M. Rosser, D. J. Faulkner, M. H. M. Chen, J. Clardy, *J. Am. Chem. Soc.* **1984**, *106*, 7983; b) C. B. Rao, A. S. R. Anjaneyulu, N. S. Sarma, Y. Venkateswarlu, R. M. Rosser, D. J. Faulkner, *J. Org. Chem.* **1985**, *50*, 3757; c) C. B. Rao, D. V. Rao, V. S. N. Raju, B. W. Sullivan, D. J. Faulkner, *Heterocycles* **1989**, *28*, 103; d) A. U. Rahman, K. A. Alvi, S. A. Abbas, M. I. Choudhary, J. Clardy, *Tetrahedron Lett.* **1989**, *30*, 6825; e) M. Kuramoto, K. Hayashi, K. Yamaguchi, M. Yada, T. Tsuji, D. Uemura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 771; f) H. Nakamura, Y. Kawase, K. Maruyama, A. Murai, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 781; g) A. H. Deranas, J. J. Fernández, J. A. Gavín, M. Norte, *Tetrahedron* **1998**, *54*, 7891; h) A. H. Deranas, J. J. Fernández, J. A. Gavín, M. Norte, *Tetrahedron* **1999**, *55*, 5539; i) R. M. Villar, J. Gil-Longo, A. H. Daranas, M. L. Souto, J. J. Fernández, S. Peixinho, M. A. Barral, G. Santafé, J. Rodríguez, C. Jiménez, *Bioorg. Med. Chem.* **2003**, *11*, 2301; j) E. Fattorusso, A. Romano, O. Taglialatela-Scafati, M. J. Achmad, G. Bavestrello, C. Cerrano, *Tetrahedron Lett.* **2008**, *49*, 2189.

[2] a) S. Fukuzawa, Y. Hayashi, D. Uemura, A. Nagatsu, K. Ijuin, *Heterocycl. Commun.* **1995**, *1*, 207; b) M. Kuramoto, K. Hayashi, Y. Fujitani, K. Yamaguchi, T. Tsuji, K. Yamada, Y. Ijuin, D. Uemura, *Tetrahedron Lett.* **1997**, *38*, 5683; c) K. Yamaguchi, M. Yada, T. Tsuji, M. Kuramoto, D. Uemura, *Biol. Pharm. Bull.* **1999**, *22*, 920.

[3] For a recent review of synthetic studies of zoanthamine alkaloids, see: D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2008**, *120*, 2400; *Angew. Chem. Int. Ed.* **2008**, *47*, 2365; D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2008**, *120*, 2400.

[4] For synthetic studies of zoanthenol, see: a) D. R. Williams, D. C. Ihle, T. A. Brugel, S. Patnaik, *Heterocycles* **2006**, *70*, 77; b) D. R. Williams, S. Patnaik, G. S. Cortez, *Heterocycles* **2007**, *72*, 213; c) D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2007**, *119*, 4155; *Angew. Chem. Int. Ed.* **2007**, *46*, 4077; D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2007**, *119*, 4155.

[5] For synthetic studies of zoanthamine, see: a) D. Tanner, P. G. Andersson, L. Tedenborg, P. Somfai, *Tetrahedron* **1994**, *50*, 9135; b) D. Tanner, L. Tedenborg, P. Somfai, *Acta Chem. Scand. Ser. A* **1997**, *51*, 1217; c) T. E. Nielsen, D. Tanner, *J. Org. Chem.* **2002**, *67*, 6366; d) T. E. Nielsen, S. Le Quement, M. Juhl, D. Tanner, *Tetrahedron* **2005**, *61*, 8013; e) M. Juhl, T. E. Nielsen, S. Le Quement, D. Tanner, *J. Org. Chem.* **2006**, *71*, 265; f) S. Ghosh, F. Rivas, D. Fischer, M. A. González, E. A. Theodorakis, *Org. Lett.* **2004**, *6*, 941; g) F. Rivas, S. Ghosh, E. A. Theodorakis, *Tetrahedron Lett.* **2005**, *46*, 5281; h) N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 6237; i) N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 6241; j) N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Chem. Pharm. Bull.* **2000**, *48*, 1370; k) D. R. Williams, T. A. Brugel, *Org. Lett.* **2000**, *2*, 1023.

[6] For synthetic studies of norzoanthamine, see: a) M. Sakai, M. Sasaki, K. Tanino, M. Miyashita, *Tetrahedron Lett.* **2002**, *43*, 1705; b) T. Irifune, T. Ohashi, T. Ichino, E. Sakia, K. Suenaga, D. Uemura, *Chem. Lett.* **2005**, 1058.

[7] For synthetic studies of zoanthamide, see: D. R. Williams, G. S. Cortez, *Tetrahedron Lett.* **1998**, *39*, 2675.

[8] a) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, K. Tanino, *Science* **2004**, *305*, 495; b) M. Miyashita, *Pure Appl. Chem.* **2007**, *79*, 651.

[9] a) G. Hirai, H. Oguri, M. Hirama, *Chem. Lett.* **1999**, 141; b) S. M. Moharram, G. Hirai, K. Koyama, H. Oguri, M. Hirama, *Tetrahedron Lett.* **2000**, *41*, 6669; c) G. Hirai, H. Oguri, S. M. Moharram, K. Koyama, M. Hirama, *Tetrahedron Lett.* **2001**, *42*, 5783; d) G. Hirai, Y. Koizumi, S. M. Moharram, H. Oguri, M. Hirama, *Org. Lett.* **2002**, *4*, 1627; e) S. M. Moharram, H. Oguri, M. Hirama, *Egypt. J. Pharm. Sci.* **2003**, *44*, 177; f) G. Hirai, H. Oguri, M. Hayashi, K. Koyama, Y. Koizumi, S. M. Moharram, M. Hirama, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2647.

[10] E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925.

[11] C.-Y. Yu, O. Meth-Cohn, *Tetrahedron Lett.* **1999**, *40*, 6665.

[12] K. D. Sugi, T. Nagata, T. Yamada, T. Mukaiyama, *Chem. Lett.* **1996**, 1081.

[13] For selected reviews on enzymatic asymmetrization, see: a) E. Scoffers, A. Golebiowski, C. R. Johnson, *Tetrahedron* **1996**, *52*, 3769; b) R. D. Schmid, R. Verger, *Angew. Chem.* **1998**, *110*, 1694; *Angew. Chem. Int. Ed.* **1998**, *37*, 1608; c) A. Ghanem, *Tetrahedron* **2007**, *63*, 1721.

[14] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.

[15] a) S. Arseniyadis, J. I. M. Hernando, J. Q. del Moral, D. V. Yashunsky, P. Potier, *Synlett* **1998**, 1010; b) J. I. M. Hernando, J. Q. del Moral, M. R. R. Ferreira, J. I. C. Lena, S. Arseniyadis, *Tetrahedron: Asymmetry* **1999**, *10*, 783.

[16] For a selected recent review, see: a) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945; For selected reports for constructing a benzylic quaternary carbon center, see: b) T. Takemoto, M. Sodeoka, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1993**, *115*, 8477; c) L. E. Overman, *Pure Appl. Chem.* **1994**, *66*, 1423; d) S. Laschat, F. Narjes, L. E. Overman, *Tetrahedron* **1994**, *50*, 347; e) J. H. Rigby, C. Deur, M. J. Heeg, *Tetrahedron Lett.* **1999**, *40*, 6887; f) E. Dras, C. Guillou, C. Thal, *Tetrahedron Lett.* **1999**, *40*, 9243; g) Y. Fukuyama, K. Matsumoto, Y. Tonoi, R. Yokoyama, H. Takahashi, H. Minami, H. Okazaki, Y. Mitsumoto, *Tetrahedron* **2001**, *57*, 7127; h) B. J. Burke, L. E. Overman, *J. Am. Chem. Soc.* **2004**, *126*, 16820.

[17] G. A. Molander, G. Hahn, *J. Org. Chem.* **1986**, *51*, 1135.

[18] R. D. Miller, D. R. Mckean, *Synthesis* **1979**, 730.

[19] a) T. Imamoto, N. Taniyama, *Tetrahedron Lett.* **1987**, *28*, 1307; b) G. A. Molander, L. S. Harring, *J. Org. Chem.* **1989**, *54*, 3525.

[20] Copies of ^{1}H- and ^{13}C NMR spectra of selected compounds and X-ray crystallographic data of compound **(−)-14** are provided in the Supporting Information.

Received: March 10, 2008

