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Synthesis and Structural Revision of Symbiodinolide C23−C34 Fragment

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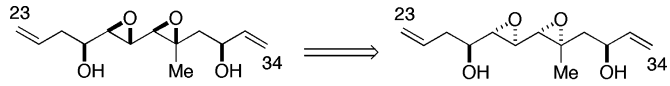

Stereoselective synthesis of the C23−C34 fragment of symbiodinolide, which possesses the originally proposed stereochemistry, and its diastereomers was achieved in 19 steps from L-aspartic acid, respectively. Comparison of spectroscopic data of the synthetic products with those of the degraded product of symbiodinolide led to a structural revision of the C23−C34 fragment.

Introduction

Various secondary metabolites have been isolated from marine organisms.[1] In particular, huge polyol and polyether compounds, such as palytoxins and halichondrins, are some of the most attractive molecules due to their remarkable biological activities and chemical structures.[2] Although the biological activities of these compounds have been well investigated, the true physiological functions have rarely been clarified.

Symbiodinolide (**1**), a novel polyol compound, has been recently isolated from the marine dinoflagellate *Symbiodinium* sp., which exhibits a voltage-dependent N-type Ca^{2+} channel-opening activity at 7 nM and COX-1 inhibitory effect at 2 μM (Figure 1).[3] The planar structure and partial stereochemistry of **1** were elucidated by spectroscopic analysis[3] and chemical synthesis.[4] Previously, we obtained the C23−C34 fragment **2** by the degradation of **1** via the cross-metathesis with ethylene using Grubbs' second-generation catalyst[5] (Scheme 1).[3] Relative stereochemistry of **2** was elucidated to be as shown in Scheme 1 by $^1H-^1H$ coupling constants and NOE correlations. Herein, we report the enantio- and stereocontrolled synthesis of **2** possessing the originally proposed stereochemistry and its diastereomers, which has resulted in the structural revision of the C23−C34 fragment.

Results and Discussion

Determination of the Absolute Stereochemistries at the C26 and C32 Positions. First, the absolute stereochemistries of the C26 and C32 positions of the degraded product **2** were determined by the modified Mosher method.[6,7] Figure 2 depicts the selected $\Delta\delta_{S-R}$ values of the corresponding bis-(*S*)- and (*R*)-MTPA esters, (*S*)-**3** and (*R*)-**3**, prepared from **2** by the standard procedures (MTPACl/Et_3N/DMAP). The signs at the C23, C24, and C25 positions showed negative, and those of the C33 and C34 positions exhibited positive. Therefore, the absolute stereochemistries of the C26 and C32 positions were assigned to be 26*S* and 32*S*, respectively.

Synthesis of the Diepoxide 2. Our synthetic plan of **2** is outlined in Scheme 2. We envisaged that **2** would be synthesized from aldehyde **4** through a stereoselective allylation. The

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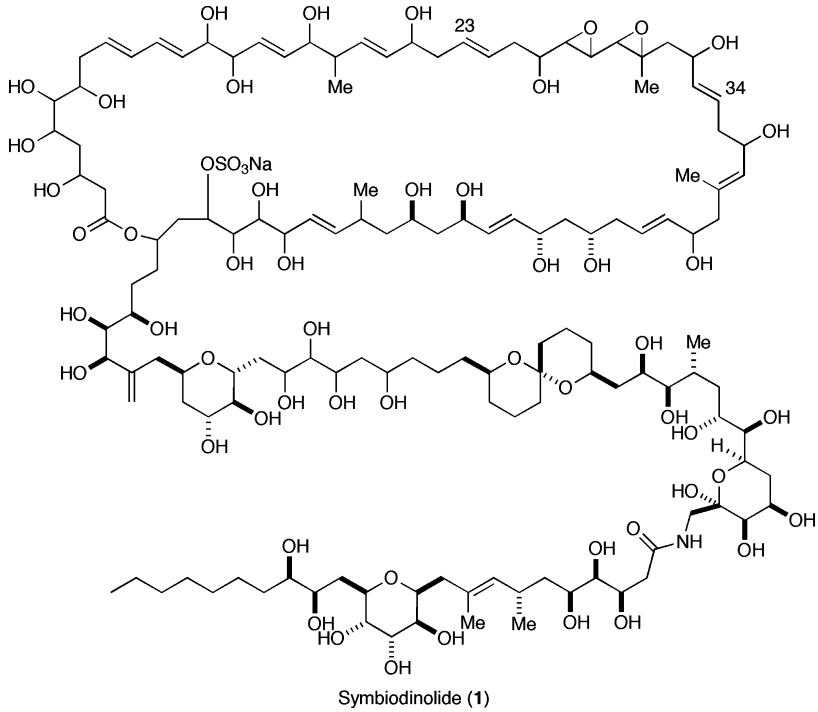

FIGURE 1. Structure of symbiodinolide (**1**).

SCHEME 1. Cross-Metathesis Degradation of 1 with Ethylene

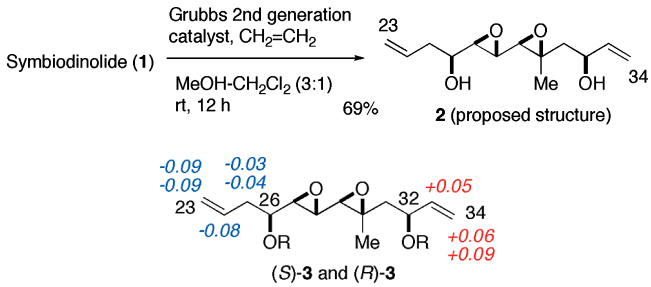

FIGURE 2. Chemical shift differences ($\Delta\delta_{S-R}$) of bis-MTPA esters derived from **2**. R = MTPA. MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl.

construction of the diepoxide moiety was based on the stepwise chain elongation−epoxidation process of allylic alcohol **5**, which might be readily prepared from L-aspartic acid.

The synthesis of **2** commenced from L-aspartic acid which was converted to epoxide **6** by the standard procedures (Scheme 3).[8] Treatment of the epoxide **6** with the lithium acetylide, derived from ethyl propiolate, gave acetylenic alcohol **7**.[9] The resulting hydroxy moiety of **7** was protected to give TBS ether **8**. Conjugate addition of benzenethiol to **8** provided the corresponding (*Z*)-thioether, which was reacted with MeMgBr and CuI to give (*E*)-α,*β*-unsaturated ester **9** with complete configurational retention at the alkene.[10] Ester **9** was reduced with DIBALH to afford allylic alcohol **10**. The allylic alcohol **10** was subjected to Sharpless asymmetric epoxidation using D-(−)-diethyl tartrate to give desired epoxy alcohol **11**, stereoselectively (dr = 12:1).[11] The alcohol **11** was converted to allylic alcohol **12** by the following three-step sequence: (1) Swern oxidation,[12] (2) Horner−Wadsworth−Emmons olefination,[13] and (3) DIBALH reduction of the resulting α,*β*-unsaturated ester. Sharpless asymmetric epoxidation was utilized for the stereoselective construction of contiguous epoxide moiety of **13**. However, chemical yield and stereoselectivity were extremely low. Therefore, we carried out *m*-CPBA epoxidation of **12** to give diepoxides **13*β*** and **13α** in 90% yield at a 1:1 diastereomeric ratio.[14]

The diepoxide **13*β***, which possesses the absolute stereochemistries at C27 and C28 positions corresponding to those of **2**, was derivatized for the structural elucidation (Scheme 4). Thus, regioselective Red-Al reduction of **13*β*** proceeded smoothly to give 1,3-diol **14**.[15] Intramolecular etherification of **14** took place in $CDCl_3$ to yield five-membered ether **15**. Treatment of the resulting diol **15** with carbonyl diimidazole provided bicyclic carbonate **16*β***. The stereostructure of **16*β*** was determined by coupling constant and NOE correlation. The large magnitude of $J_{a,b}$ (11.7 Hz) indicated that Ha and Hb were in an *anti* orientation to each other. The observed NOE between C30-Me and Ha confirmed that they were in a *syn* relationship.

Completion of the synthesis of **2** is described in Scheme 5. The alcohol **13*β*** was oxidized under Swern conditions,[12] followed by Roush's asymmetric allylation[16] to furnish homoallylic alcohol **17**.[17] The resulting hydroxy group was

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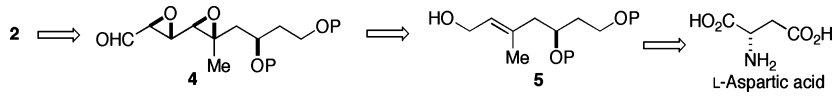
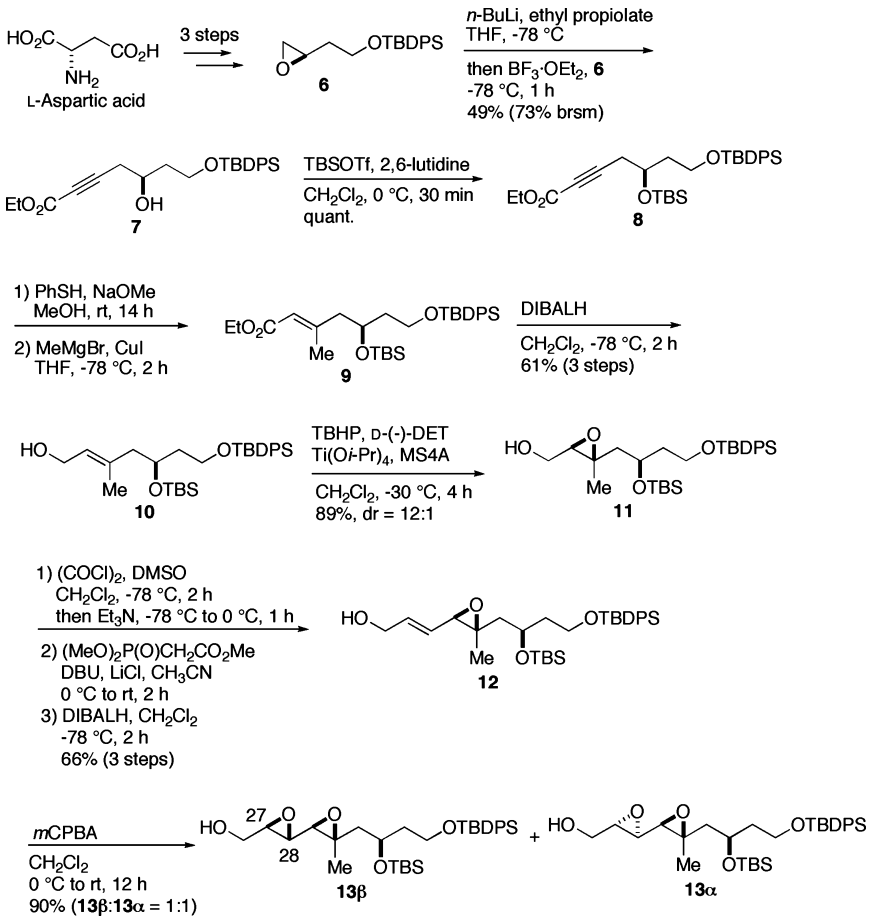
(17) The absolute stereochemistry at C26 position was determined by the modified Mosher method.

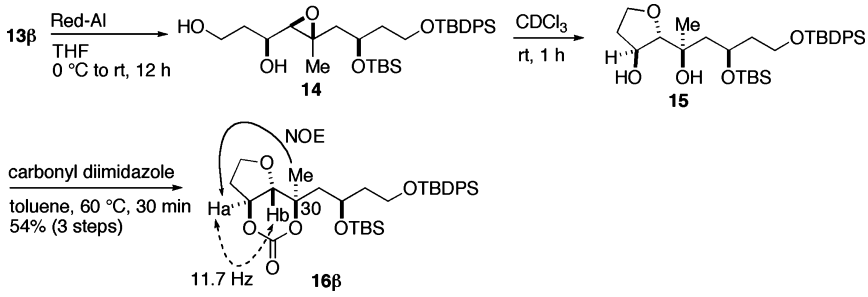
SCHEME 2. Synthetic Plan of 2



SCHEME 3. Synthesis of 13*β*



SCHEME 4. Structural Determination of 13*β*



protected with TBSOTf/2,6-lutidine affording silyl ether **18**. Selective removal of TBDPS group with NH_4F in methanol[18] gave alcohol **19**. Treatment of **19** with *o*-NO_2PhSeCN/*n*-Bu_3P followed by oxidative workup[19] gave the corresponding alkene. Final desilylation with TBAF provided diol **2**.

Unfortunately, however, the ^{1}H NMR spectrum of the synthetic **2** was different from that of the degraded product of natural symbiodinolide (**1**). Since the absolute configurations of C26 and C32 positions were unambiguously elucidated by modified Mosher method, the absolute stereochemistry of the diepoxide moiety was deemed to be misassigned. Therefore, we decided to synthesize the other three possible diastereomers **20**−**22** in Scheme 6.

Synthesis of the Diepoxides 20−22. Synthesis of epoxy alcohol **26**, the key synthetic intermediate for the synthesis of the diepoxide **21**, is described in Scheme 7. Sharpless asymmetric epoxidation[11a] of the allylic alcohol **10** with L-(+)-diethyl tartrate provided epoxy alcohol **23** in a 20:1 diastereoselectivity. Further transformation toward **26** is analogous to that toward **13*β***. Swern oxidation[12] of **23** and

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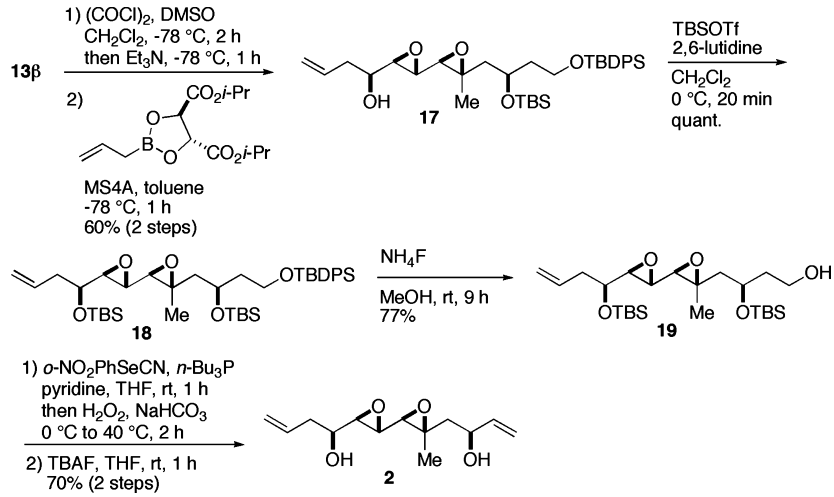
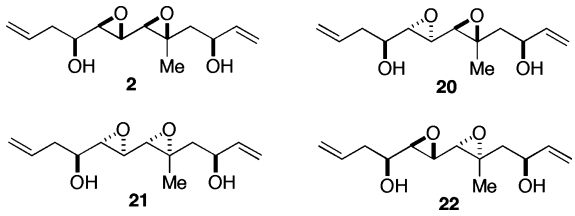
SCHEME 5. Synthesis of 2



SCHEME 6. Possible Stereoisomers of the C23−C34 Fragment



subsequent Horner−Wadsworth−Emmons olefination[13] gave α,β-unsaturated ester **24**. DIBALH reduction of **24** provided allylic alcohol **25**. The allylic alcohol **25** was epoxidized with *m*-CPBA to give the epoxy alcohol **26** and its 27,28-epimer with a 1:1 ratio.

The epoxy alcohol **26** was derivatized for structural determination of the 27,28-epoxide moiety as shown in Scheme 8. Thus, Red-Al reduction of **26** gave 1,3-diol **27**.[15] The primary hydroxy group of **27** was selectively protected to give the corresponding TBDPS ether. The resulting alcohol was converted to MTPA esters (*S*)-**28** and (*R*)-**28**. Figure 3 describes the $\Delta\delta_{S-R}$ values of (*S*)-**28** and (*R*)-**28**. The signs at the C26 and C27 showed positive, and the signs at the C29 and C31−C34 exhibited negative. Thus, the absolute stereochemistry at the C28 position of **27** was elucidated to be 28*R*.[6] From this result, the absolute configuration of the 27,28-epoxide moiety was determined to be that described in **26**.

Scheme 9 describes the synthesis of the diepoxide **21**.[20] Swern oxidation[12] of **26** and subsequent asymmetric allylation[16] afforded homoallylic alcohol **29**.[17] The resulting alcohol was protected to give TBS ether **30**. Selective desilylation of TBDPS group with NH_4F[18] provided alcohol **31**. Terminal olefin was introduced by Grieco's protocol[19] to give alkene **32**. Final deprotection with TBAF provided diol **21**. The synthetic C23−C34 fragment **21** was identical to the degraded C23−C34 fragment of symbiodinolide (**1**) in all aspects (^{1}H NMR, HRMS, and optical rotation[21]) indicating the absolute configuration of this fragment was that described in **21**.[22]

(20) For the synthesis of **20** and **22**, see the Supporting Information.

(21) The degraded C23−C34 fragment: $[\alpha]^{21}_D$ −11.2 (*c* 0.05, CH_3OH). The synthetic C23−C34 fragment **21**: $[\alpha]^{24}_D$ −14.2 (*c* 0.20, CH_3OH).

(22) The ^{1}H NMR spectra of the synthetic **20** and **22** were clearly different from those of the degraded C23−C34 fragment, respectively.

Conclusion

We have determined the absolute configurations at C26 and C32 by applying modified Mosher method to the degraded C23−C34 fragment. Furthermore, we have synthesized the possible four diastereomers of the diepoxide moiety, **2**, **20**, **21**, and **22**, based on the chain extension−epoxidation approach. Comparison of the spectroscopic data of the synthetic four diastereomers to those of the degraded product unambiguously elucidated that the correct absolute configuration of the C23−C34 fragment of **1** was that described in **21**. Further structural and synthetic studies on **1** are underway in our laboratories.

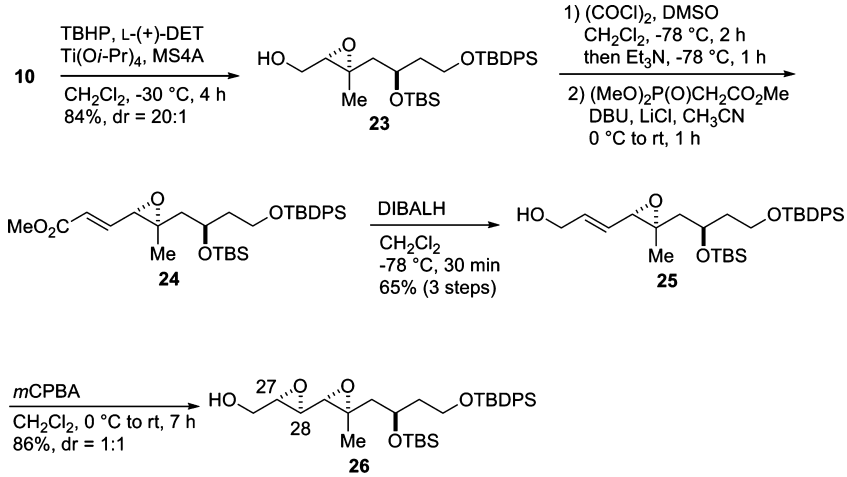
Experimental Section

Allylic Alcohol 12. To a solution of oxalyl chloride (0.32 mL, 3.78 mmol) in CH_2Cl_2 (11 mL) was added DMSO (0.54 mL, 7.56 mmol) dropwise at −78 °C. After 30 min, epoxy alcohol **11** (1.00 g, 1.89 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at −78 °C for 2 h before Et_3N (1.6 mL, 11.3 mmol) was added slowly. The mixture was stirred for 20 min at −78 °C and then allowed to reach 0 °C for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with water and brine and dried over $MgSO_4$. Concentration and short column chromatography (silica gel, EtOAc/hexane = 1:40, 1:20) afforded the corresponding aldehyde (765 mg) as a yellow oil, which was used immediately in the next reaction without further purification.

To a stirred suspension of LiCl (74 mg 1.75 mmol) and the aldehyde (765 mg) obtained above in CH_3CN (7.5 mL) was added trimethyl phosphonoacetate (0.28 mL, 1.75 mmol). The mixture was cooled to 0 °C, and DBU (0.26 mL, 1.75 mmol) was added. The mixture was stirred for 10 min at 0 °C and then allowed to reach room temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed successively with water and brine and dried over Na_2SO_4. Concentration and short column chromatography (silica gel, EtOAc/hexane = 0:1, 1:30) afforded the corresponding α,β-unsaturated ester (822 mg) as a light yellow oil, which was used in the next reaction without further purification.

To a solution of the α,β-unsaturated ester (822 mg) obtained above in CH_2Cl_2 (12 mL) was added DIBALH (1.0 M solution in hexane, 2.9 mL, 2.96 mmol) dropwise at −78 °C. After being stirred for 2 h at −78 °C, the solution was poured directly into a stirring mixture of saturated sodium potassium tartrate aqueous solution and MeOH. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4.

SCHEME 7. Synthesis of 26



SCHEME 8. Synthesis of (*S*)-28 and (*R*)-28

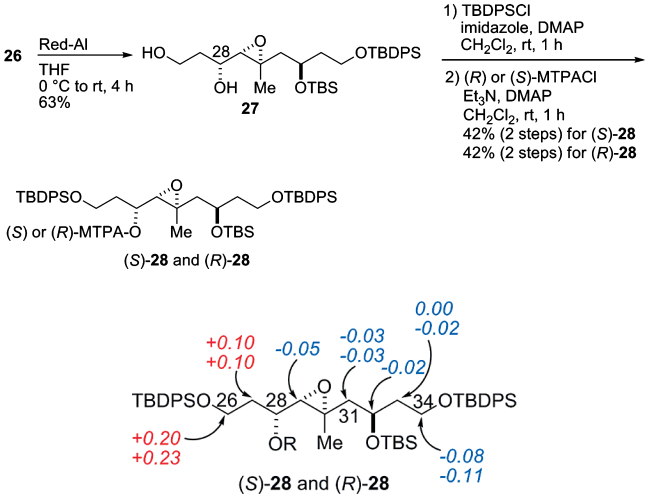


FIGURE 3. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)-**28** and (*R*)-**28**. R = MTPA. MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl.

Concentration and column chromatography (silica gel, EtOAc/hexane = 1:15) afforded allylic alcohol **12** (690 mg, 66% in three steps) as a light yellow oil: $[\alpha]^{25}_D$ +8.5 (*c* 0.42, $CHCl_3$); IR (neat) 3437, 2958, 2858, 1472, 1428, 1388, 1253, 1111 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4 H), 7.44−7.40 (m, 2 H), 7.39−7.35 (m, 4 H), 6.03 (dt, *J* = 15.5, 5.2 Hz, 1 H), 5.61 (ddt, *J* = 15.5, 7.5, 1.2 Hz, 1 H), 4.21 (dd, *J* = 5.2, 1.2 Hz, 2 H), 4.10−4.05 (m, 1 H), 3.78−3.68 (m, 2 H), 3.22 (d, *J* = 7.5 Hz, 1 H), 2.03 (dd, *J* = 13.8, 5.5 Hz, 1 H), 1.77−1.71 (m, 1 H), 1.66−1.59 (m, 1 H), 1.50 (dd, *J* = 13.8, 8.0 Hz, 1 H), 1.29 (s, 3 H), 1.04 (s, 9 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.6, 134.0, 129.7, 127.8, 126.3, 67.0, 63.1, 61.2, 60.7, 46.7, 40.1, 27.0, 26.0, 19.3, 18.1, 17.8, −4.2, −4.4; HRMS (FAB) calcd for $C_{32}H_{51}O_4Si_2$ (M + H)$^+$ 555.3326, found 555.3314.

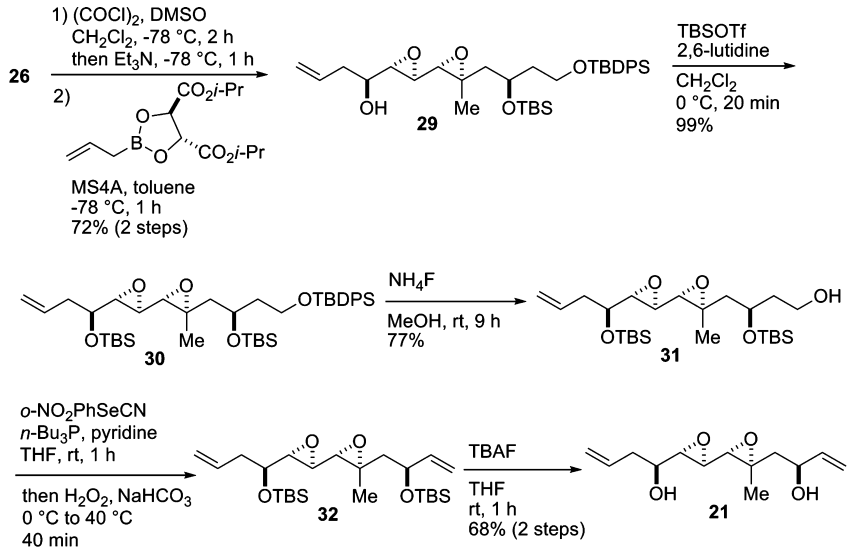
Epoxy Alcohols 13*β* and 13α. To a solution of allylic alcohol **12** (1.41 g, 2.54 mmol) in CH_2Cl_2 (35 mL) was added *m*-CPBA (1.25 g, 5.58 mmol) at 0 °C. After the solution was stirred at room temperature for 12 h, to it were added dimethyl sulfide and saturated aqueous $NaHCO_3$ at 0 °C. After being stirred for 10 min, the aqueous layer was extracted with Et_2O. The organic layer was washed with water and brine and dried over $MgSO_4$. Concentration and column chromatography (silica gel, EtOAc/hexanes = 1:8) afforded epoxy alcohols **13*β*** (655 mg, 45%) and **13α** (655 mg, 45%), respectively, as a light yellow oil. Epoxy alcohol **13*β***: $[\alpha]^{25}_D$ −14.8 (*c* 0.42, $CHCl_3$); IR (neat) 3448, 2953, 2929, 2857, 2359, 1471, 1428, 1387, 1255, 1111 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.65−7.63 (m, 4 H), 7.44−7.41 (m, 2 H), 7.39−7.36 (m, 4 H), 4.08−4.04 (m, 1 H), 3.95 (d, *J* = 13.8 Hz, 1 H), 3.77−3.65 (m, 4 H), 3.09 (dd, *J* = 3.4, 2.8 Hz, 1 H), 2.98 (dd, *J* = 5.5, 2.8 Hz, 1 H), 2.61 (d, *J* = 5.5 Hz, 1 H), 1.97 (dd, *J* = 13.8, 5.5 Hz, 1 H), 1.77−1.69 (m, 1 H), 1.67−1.61 (m, 1 H), 1.48 (dd, *J* = 13.8, 7.6 Hz, 1 H), 1.41 (s, 3 H), 1.05 (s, 9 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 135.7, 133.9, 129.9, 127.8, 67.1, 62.0, 60.7, 60.6, 59.4, 55.5, 52.9, 46.3, 40.1, 27.0, 26.0, 19.3, 18.5, 18.1, −4.2, −4.4; HRMS (FAB) calcd for $C_{32}H_{51}O_5Si_2$ (M + H)$^+$ 571.3275, found 571.3282. Epoxy alcohol **13α**: $[\alpha]^{21}_D$ +4.3 (*c* 0.20, $CHCl_3$); IR (neat) 3448, 2953, 2929, 2857, 2359, 1471, 1428, 1387, 1255, 1111 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4 H), 7.43−7.40 (m, 2 H), 7.39−7.37 (m, 4 H), 4.12−4.07 (m, 1 H), 4.00−3.96 (m, 1 H), 3.77−3.67 (m, 4 H), 3.19 (dd, *J* = 3.4, 2.1 Hz, 1 H), 2.99 (dd, *J* = 6.2, 2.1 Hz, 1 H), 2.65 (d, *J* = 6.2 Hz, 1 H), 1.94 (dd, *J* = 13.8, 5.5 Hz, 1 H), 1.81−1.74 (m, 1 H), 1.66−1.61 (m, 1 H), 1.54 (dd, *J* = 14.4, 5.5 Hz, 1 H), 1.40 (s, 3 H), 1.05 (s, 9 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 135.7, 134.0, 133.9, 129.8, 129.7, 127.8, 127.8, 66.9, 61.0, 60.9, 60.6, 59.8, 57.2, 52.6, 46.0, 39.9, 27.0, 26.0, 19.3, 18.1, 18.0, −4.2, −4.4; HRMS (FAB) calcd for $C_{32}H_{51}O_5Si_2$ (M + H)$^+$ 571.3275, found 571.3253.

Bicyclic Carbonate 16*β*. To a solution of epoxy alcohol **13*β*** (15.0 mg, 26.3 μmol) in THF (0.5 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride solution (65% in toluene, 50 μL, 0.161 mmol) at 0 °C. After being stirred for 12 h at room temperature, the solution was poured into the saturated sodium potassium tartrate aqueous solution at 0 °C and stirred for 30 min. The aqueous layer was extracted with Et_2O. The organic layer was successively washed with water and brine, dried over Na_2SO_4, and concentrated.

The residue was dissolved in $CDCl_3$, and the solution was stirred for 1 h. Concentration and preparative TLC (silica gel, EtOAc/hexane = 1:4) afforded cyclic ether **15** (11.0 mg) as a light yellow oil, which was used immediately in the next reaction without further purification.

To a solution of diol **15** (11.0 mg) obtained above in toluene (1.0 mL) was added 1,1′-carbonyldiimidazole (9.3 mg, 57.6 μmol). The solution was stirred for 30 min at 60 °C. The crude reaction mixture was directly purified by column chromatography (silica gel, EtOAc/hexane = 1:20) afforded bicyclic carbonate **16*β*** (8.5 mg, 54% in three steps) as a light yellow oil: $[\alpha]^{24}_D$ −1.3 (*c* 0.10, $CHCl_3$); IR (neat) 2953, 2928, 2855, 2359, 1818, 1473, 1428, 1361, 1254, 1174, 1109, 1074 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.82−7.79 (m, 4 H), 7.29−7.24 (m, 6 H), 4.32−4.28 (m, 1 H), 3.89−3.86 (m, 1 H), 3.81−3.77 (m, 1 H), 3.57 (td, *J* = 11.7, 4.1 Hz, 1 H), 3.48 (d, *J* = 11.7 Hz, 1 H), 3.18 (ddd, *J* = 13.1, 4.1, 2.1 Hz, 1 H), 2.73 (td, *J* = 11.7, 2.1 Hz, 1 H), 1.99−1.94 (m, 1 H),

SCHEME 9. Synthesis of 21



1.85 (dd, J = 14.4, 4.1 Hz, 1 H), 1.79−1.74 (m, 1 H), 1.66 (dd, J = 14.4, 6.2 Hz, 1 H), 1.38−1.30 (m, 1 H), 1.23−1.17 (m, 10 H), 0.98 (s, 9 H), 0.88 (s, 3 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (200 MHz, C_6D_6) δ 153.5, 136.0, 134.3, 134.3, 130.1, 84.6, 76.1, 76.1, 65.4, 61.1, 59.4, 48.4, 42.0, 31.3, 27.2, 26.2, 19.5, 18.3, 15.2, −4.0, −4.2; HRMS (FAB) calcd for $C_{33}H_{51}O_6Si_2$ (M + H)$^+$ 599.3224, found 599.3226.

Homoallylic Alcohol 17. To a solution of oxalyl chloride (55 μL, 0.642 mmol) in CH_2Cl_2 (0.5 mL) was added DMSO (68 μL, 0.963 mmol) dropwise at −78 °C. After 30 min, alcohol **13*β*** (55.0 mg, 96.3 μmol) in CH_2Cl_2 (0.6 mL) was added dropwise. The mixture was stirred at −78 °C for 2 h before Et_3N (0.28 mL, 1.93 mmol) was added slowly. The mixture was stirred for an additional 1 h at −78 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with water and brine and dried over $MgSO_4$. Concentration and short column chromatography (silica gel, EtOAc/hexane = 1:40, 1:20) afforded the corresponding aldehyde (48.0 mg) as a yellow oil, which was used immediately in the next reaction without further purification.

To a mixture of the aldehyde (48.0 mg) obtained above and powdered molecular sieves 4A (12 mg) in toluene (1.2 mL) was added (*R*,*R*)-tartrate allylboronate (54.5 μL, 0.211 mmol) at −78 °C. The reaction was stirred for 1 h at −78 °C. Saturated aqueous $NaHCO_3$ was added, the mixture was stirred for 30 min, and then the organic phase was separated. The aqueous phase was extracted with Et_2O. The combined organic extract was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexane = 1:20, 1:10) to afford homoallylic alcohol **17** (35.0 mg, 60% in two steps) and its 26-epimer (7.0 mg, 12% in 2 steps) as a yellow oil, respectively. Homoallylic alcohol **17**: $[\alpha]^{25}_D$ +30.8 (*c* 0.50, $CHCl_3$); IR (neat) 3428, 2956, 2928, 2857, 2359, 1470, 1427, 1388, 1255, 1109 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65−7.62 (m, 4 H), 7.43−7.41 (m, 2 H), 7.39−7.36 (m, 4 H), 5.87−5.80 (m, 1 H), 5.17 (dd, J = 17.2, 1.4 Hz, 1 H), 5.15 (d, J = 10.3 Hz, 1 H), 4.06−4.02 (m, 1 H), 3.76−3.69 (m, 2 H), 3.66−3.63 (m, 1 H), 2.99 (dd, J = 4.1, 2.1 Hz, 1 H), 2.96 (dd, J = 5.5, 2.1 Hz, 1 H), 2.61 (d, J = 5.5 Hz, 1 H), 2.42−2.35 (m, 2 H), 1.96 (dd, J = 13.8, 5.5 Hz, 1 H), 1.83 (brd, J = 5.5 Hz, 1 H), 1.76−1.71 (m, 1 H), 1.67−1.62 (m, 1 H), 1.49 (dd, J = 13.8, 7.6 Hz, 1 H), 1.41 (s, 3 H), 1.05 (s, 9 H), 0.83 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7, 135.7, 133.9, 133.3, 129.8, 127.8, 127.8, 118.9, 69.4, 67.0, 61.8, 60.7, 59.4, 57.9, 53.6, 46.3, 40.0, 39.4, 27.0, 26.0, 19.3, 18.5, 18.1, −4.2, −4.4; HRMS (FAB) calcd for $C_{35}H_{55}O_5Si_2$ (M + H)$^+$ 611.3588, found 611.3575.

Silyl Ether 18. To a mixture of homoallylic alcohol **17** (10.0 mg, 16.4 μmol) and 2,6-lutidine (9.0 μL, 75.3 μmol) in CH_2Cl_2 (0.5 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (13 μL, 56.5 μmol) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and then quenched by the addition of MeOH. The mixture was diluted with Et_2O and extracted. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexane = 1:40) afforded silyl ether **18** (12.0 mg, quant) as a light yellow oil: $[\alpha]^{23}_D$ +32.6 (*c* 0.33, $CHCl_3$); IR (neat) 2956, 2929, 2854, 2351, 1729, 1471, 1426, 1389, 1359, 1255, 1111 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66−7.62 (m, 4 H), 7.43−7.40 (m, 2 H), 7.39−7.36 (m, 4 H), 5.83−5.77 (m, 1 H), 5.08 (dd, J = 17.2, 1.4 Hz, 1 H), 5.05 (d, J = 10.3 Hz, 1 H), 4.04−4.00 (m, 1 H), 3.74−3.67 (m, 2 H), 3.42 (q, J = 6.2 Hz, 1 H), 2.94 (dd, J = 6.2, 2.1 Hz, 1 H), 2.77 (dd, J = 6.2, 2.1 Hz, 1 H), 2.56 (d, J = 6.2 Hz, 1 H), 2.33−2.30 (m, 2 H), 1.94 (dd, J = 13.8, 4.8 Hz, 1 H), 1.78−1.73 (m, 1 H), 1.67−1.62 (m, 1 H), 1.48 (dd, J = 13.8, 7.6 Hz, 1 H), 1.39 (s, 3 H), 1.05 (s, 9 H), 0.90 (s, 9 H), 0.82 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7, 135.7, 134.0, 133.9, 133.9, 129.8, 129.8, 127.8, 127.8, 117.9, 73.4, 67.0, 62.3, 60.7, 59.0, 58.9, 54.0, 46.3, 39.9, 39.8, 27.1, 26.0, 19.3, 18.6, 18.3, 18.1, −4.2, −4.3, −4.4, −4.8; HRMS (FAB) calcd for $C_{41}H_{69}O_5Si_3$ (M + H)$^+$ 725.4453, found 725.4479.

Alcohol 19. To a solution of TBDPS ether **18** (10.0 mg, 13.8 μmol) in MeOH (0.5 mL) was added NH_4F (10 mg, 0.276 mmol). After stirring for 9 h at room temperature, the reaction mixture was quenched by the addition of a saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O and the organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexane = 1:30, 1:10) afforded alcohol **19** (5.2 mg, 77%) as a yellow oil: $[\alpha]^{24}_D$ −2.9 (*c* 0.10, $CHCl_3$); IR (neat) 2951, 2928, 2854, 2364, 1472, 1387, 1255, 1103 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86−5.77 (m, 1 H), 5.10 (d, J = 17.2 Hz, 1 H), 5.08 (d, J = 9.7 Hz, 1 H), 4.04−4.00 (m, 1 H), 3.79−3.72 (m, 2 H), 3.44 (q, J = 6.3 Hz, 1 H), 2.92 (dd, J = 6.3, 2.3 Hz, 1 H), 2.76 (dd, J = 6.3, 2.3 Hz, 1 H), 2.55 (d, J = 6.3 Hz, 1 H), 2.33−2.30 (m, 2 H), 2.04 (dd, J = 13.8, 4.6 Hz, 1 H), 1.87−1.81 (m, 1 H), 1.65−1.55 (m, 2 H), 1.40 (s, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.0, 117.8, 73.2, 68.9, 62.6, 60.0, 58.9, 58.7, 54.0, 45.9, 39.8, 38.6, 25.9, 18.6, 18.1, 18.0, −4.3, −4.3, −4.6, −4.8; HRMS (FAB) calcd for $C_{25}H_{51}O_5Si_2$ (M + H)$^+$ 487.3275, found 487.3254.

Diepoxide 2. To a mixture of alcohol **19** (3.5 mg, 7.18 μmol) and *o*-nitrophenyl selenocyanate (16 mg, 71.8 μmol) in THF (0.4 mL) were added pyridine (6.0 μL, 71.8 μmol) and tributylphosphine (18 μL, 71.8 μmol). The mixture was stirred for 1 h at room temperature. To the resulting mixture were added $NaHCO_3$ (4.8 mg, 57 μmol) and 30% H_2O_2 (100 μL) at 0 °C. The stirring was continued for 2 h at 40 °C. The mixture was diluted with Et_2O and then washed with water, saturated aqueous Na_2CO_3, and brine. Concentration and short column chromatography (silica gel, EtOAc/hexane = 1:50) gave the corresponding alkene (2.5 mg), which was used in the next reaction without further purification.

To a solution of the diene (2.5 mg) obtained above in THF was added TBAF (1.0 M solution in THF, 107 μL, 0.107 mmol), and the mixture was stirred for 1 h at room temperature. The mixture was diluted with Et_2O and then washed with water and brine. Concentration and column chromatography (silica gel, EtOAc/hexane = 1:10, 1:1) gave diepoxide **2** (1.2 mg, 70% in two steps) as a colorless oil: $[\alpha]^{24}_D$ +40.9 (*c* 0.10, CH_3OH); IR (neat) 3377, 2921, 2850, 1719, 1421, 1384, 1266, 1080 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 5.87 (ddt, J = 16.5, 10.1, 6.4 Hz, 1 H), 5.83 (ddd, J = 16.5, 10.1, 6.4 Hz, 1 H), 5.24 (dt, J = 16.5, 1.4 Hz, 1 H), 5.15 (dq, J = 16.5, 1.4 Hz, 1 H), 5.11−5.07 (m, 2 H), 4.18−4.15 (m, 1 H), 3.47−3.45 (m, 1 H), 2.95 (dd, J = 5.5, 1.8 Hz, 1 H), 2.88 (dd, J = 6.4, 1.8 Hz, 1 H), 2.65 (d, J = 6.4 Hz, 1 H), 2.36−2.33 (m, 2 H), 1.98 (dd, J = 13.8, 7.3 Hz, 1 H), 1.54 (dd, J = 13.8, 6.4 Hz, 1 H), 1.43 (s, 3 H); ^{13}C NMR (200 MHz, CD_3OD) δ 142.3, 135.3, 118.0, 115.2, 72.0, 70.9, 63.7, 60.3, 59.6, 55.0, 46.4, 39.9, 18.7; HRMS (FAB) calcd for $C_{13}H_{20}NaO_4$ $(M + Na)^+$ 263.1259, found 263.1245.

Diepoxide 21. The title compound was synthesized from **10** following a procedure similar to that used for the synthesis of **2**: $[\alpha]^{24}_D$ −14.2 (*c* 0.20, CH_3OH); IR (neat) 3411, 2916, 2857, 1642, 1422, 1387, 1258, 1067 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 5.91 (ddt, J = 17.4, 10.1, 7.3 Hz, 1 H), 5.88 (ddd, J = 17.4, 10.1, 5.5 Hz, 1 H), 5.25 (d, J = 17.4 Hz, 1 H), 5.15 (dd, J = 17.4, 1.8 Hz, 1 H), 5.09−5.07 (m, 2 H), 4.26−4.24 (m, 1 H), 3.66−3.64 (m, 1 H), 2.98 (dd, J = 4.6, 1.8 Hz, 1 H), 2.94 (dd, J = 6.4, 1.8 Hz, 1 H), 2.65 (d, J = 6.4 Hz, 1 H), 2.40−2.36 (m, 1 H), 2.31−2.28 (m, 1 H), 1.92 (dd, J = 13.8, 3.7 Hz, 1 H), 1.46 (s, 3 H), 1.43 (dd, J = 13.8, 10.1 Hz, 1 H); ^{13}C NMR (200 MHz, CD_3OD) δ 142.5, 135.3, 117.9, 114.4, 70.7, 70.1, 64.5, 60.6, 58.8, 54.5, 46.9, 39.8, 17.9; HRMS (FAB) calcd for $C_{13}H_{20}NaO_4$ $(M + Na)^+$ 263.1259, found 263.1260.

Diepoxide 20. The title compound was synthesized from **13α** following a procedure similar to that used for the synthesis of **2**: $[\alpha]^{21}_D$ +6.4 (*c* 0.13, $CHCl_3$); IR (neat) 3451, 2925, 2851, 1736, 1458, 1375, 1262, 1066 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 5.94−5.82 (m, 2 H), 5.24 (dt, J = 17.2, 1.4 Hz, 1 H), 5.13−5.07 (m, 3 H), 4.22−4.18 (m, 1 H), 3.56−3.53 (m, 1 H), 3.04 (dd, J = 4.8, 2.1 Hz, 1 H), 2.99 (dd, J = 4.8, 2.1 Hz, 1 H), 2.83 (d, J = 4.8 Hz, 1 H), 2.37−2.34 (m, 2 H), 1.93 (dd, J = 14.4, 7.6 Hz, 1 H), 1.59 (dd, J = 14.4, 6.2 Hz, 1 H), 1.44 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 142.2, 135.4, 117.8, 114.9, 70.8, 61.8, 60.3, 54.5, 49.6, 46.2, 39.8, 30.8, 18.1; HRMS (ESI) calcd for $C_{13}H_{20}NaO_4$ $(M + Na)^+$ 263.1259, found 263.1244.

Diepoxide 22. The title compound was synthesized from **10** following a procedure similar to that used for the synthesis of **2**: $[\alpha]^{21}_D$ −9.6 (*c* 0.13, $CHCl_3$); IR (neat) 3357, 2921, 2851, 1736, 1459, 1375, 1262, 1087 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 5.92−5.86 (m, 2 H), 5.25 (dd, J = 17.2, 1.4 Hz, 1 H), 5.14 (dd, J = 17.2, 1.4 Hz, 1 H), 5.09−5.06 (m, 2 H), 4.28−4.25 (m, 1 H), 3.53−3.50 (m, 1 H), 3.04−3.02 (m, 2 H), 2.80 (d, J = 4.8 Hz, 1 H), 2.37−2.31 (m, 2 H), 1.87 (dd, J = 14.4, 4.1 Hz, 1 H), 1.52 (dd, J = 14.4, 9.6 Hz, 1 H), 1.44 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 142.5, 135.2, 118.0, 114.4, 71.5, 70.7, 62.6, 61.0, 54.3, 46.6, 39.8, 30.8, 17.5; HRMS (ESI) calcd for $C_{13}H_{20}NaO_4$ $(M + Na)^+$ 263.1259, found 263.1231.

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Supporting Information Available: Experimental procedures and spectral and analytical data for new compounds not given in the Experimental Section and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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