Formal Synthesis of Salinosporamide A Starting from D-Glucose

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Abstract: A formal synthesis of salinosporamide A is described. The tertiary alcohol function in salinosporamide A was stereoselectively generated via the substrate control by the reaction of a cyclic ketone derived from D-glucose with Me_3Al, and subsequent Overman rearrangement of an allylic trichloroacetimidate effectively constructed the tetrasubstituted carbon with nitrogen. Formation of γ-lactam, followed by the introduction of a cyclohexenyl unit furnished the Corey's intermediate of salinosporamide A.

Key words: stereoselective synthesis, carbohydrates, chiral pool, rearrangements, pericyclic reactions

Salinosporamide A (**1**, Figure 1), isolated by Fenical and co-workers in 2003 from the marine bacterium *Salinospora tropica*,[1] is a highly potent inhibitor of the 20S proteasome, and recently expected to be a promising anticancer therapeutic agent.[2] The structure of salinosporamide A, a highly functionalized γ-lactam bearing a tetrasubstituted carbon with nitrogen (α-substituted α-amino acid structure), is structurally related to omuralide (**2**) and lactacystin[3] (**3**), which are also known as potent useful covalent inhibitors of proteasome function. The important biological activities[4] as well as intriguing structures of these natural products have naturally received considerable attention from the synthetic community, and a number of synthetic studies and total syntheses have been reported to date.[5,6] In this paper, we disclose a formal synthesis of salinosporamide A starting from D-glucose.

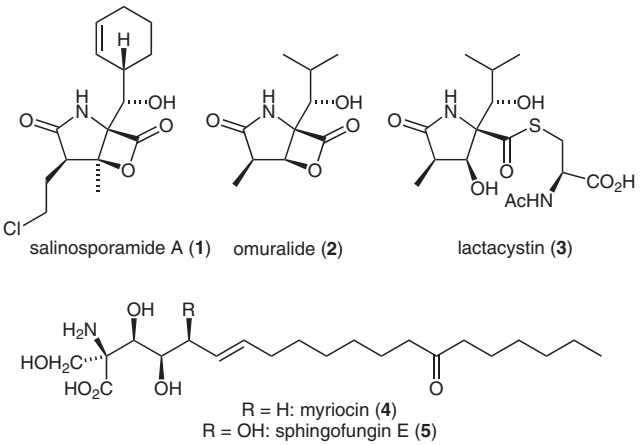

Figure 1 Structures of representative natural products possessing α-substituted α-amino acid structures

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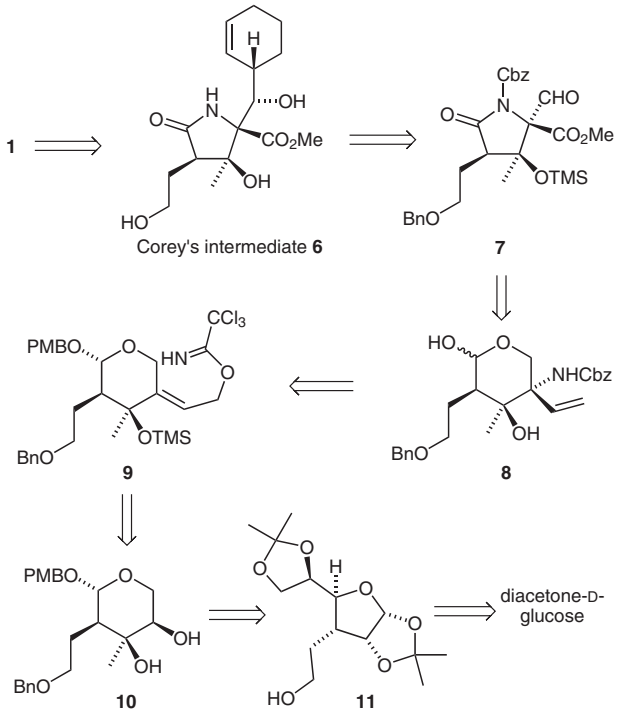
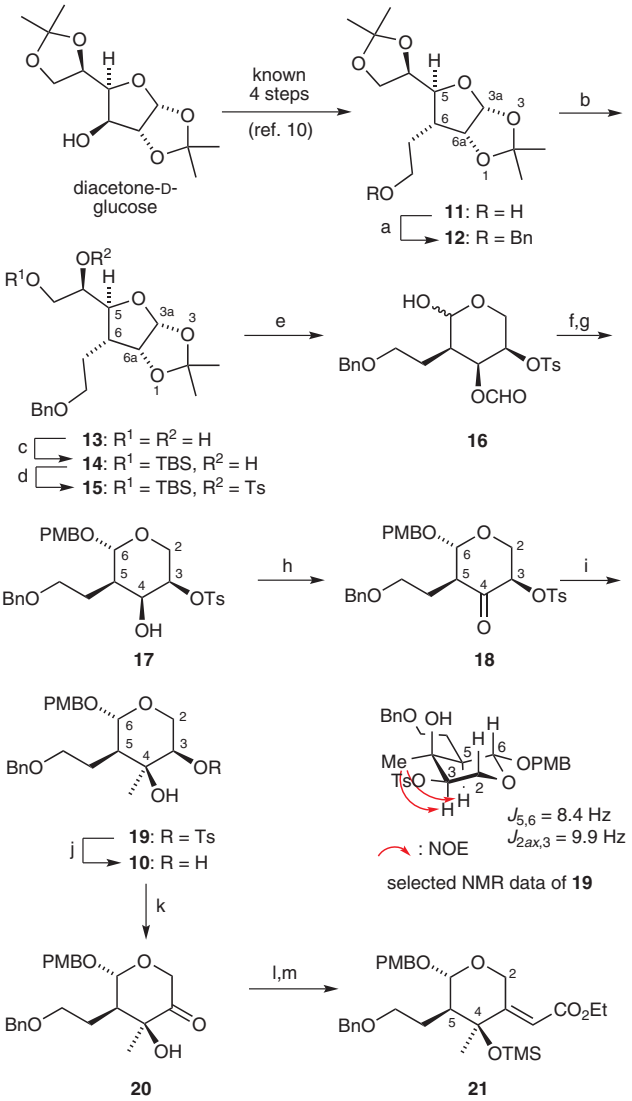
Our previous total syntheses of lactacystin[7a,b] (**3**), (+)-myriocin[7c,e] (**4**), and (–)-sphingofungin E[7d,e] (**5**) starting from aldohexoses revealed that the methodology involving Overman rearrangement[8] on sugar scaffolds, followed by further manipulation by use of the residual functional groups in sugars, is effective for the chiral synthesis of natural products possessing complex α-substituted α-amino acid structures.[7] These successful results led us to apply a similar methodology to the synthesis of salinosporamide A starting from carbohydrates. Our retrosynthetic analysis, taking into account previous successful total syntheses by Corey,[6a,c] Pattenden,[6d,i] and Hayakeyama,[6j] suggested that the Corey's intermediate **6**[6a] would be a suitable target molecule (Scheme 1). Compound **6** was expected to be prepared by the reaction of aldehyde **7** with cyclohex-2-enylzinc reagent following the Corey's procedure.[6a] The formation of the γ-lactam skeleton in **7** was planned by conversion of hemiacetal **8** to hemiaminal, followed by oxidation. The tetrasubstituted carbon with nitrogen in **8** was envisioned to be generated by Overman rearrangement of allylic trichloroacetimidate **9**.[9] The compound **9**, in turn, was planned to be synthesized from the known furanose derivative **11**[10] via diol **10**. The stereoselective construction of the tertiary alcohol function in **10** would also be an important task.



Scheme 1 Retrosynthetic analysis of salinosporamide A

Protection of a primary alcohol in the known compound **11**, that was prepared from diacetone-D-glucose in 4 step reactions,[10] afforded **12** in 90% yield (Scheme 2). The exocyclic acetonide was selectively cleaved to give diol **13** in 93% yield, whose primary hydroxy group was converted into a TBS ether, and the secondary one was protected as a *p*-toluenesulfonyl ester to give **15** in 80% yield from **13**. Hydrolysis of the remaining acetonide group, followed by glycol cleavage afforded pyranose derivative **16**, which was then transformed into PMB β-glycoside via an α-trichloroacetimidate intermediate.[11] Removal of the *O*-formyl group provided the properly protected PMB pyranoside **17** in 79% overall yield from **15**. Oxidation of **17** with DMSO–Ac_2O[12] afforded ketone **18** (90% yield), which was then reacted with Me_3Al in toluene at –40 to –5 °C to give tertiary alcohol **19** as the sole product in 88% yield. The substrate control, namely, the presence of bulky neighboring substituents (alkyl side chain and OTs groups) to the ketone carbonyl would be responsible for the observed high stereoselectivity. The structure of compound **19** was confirmed by ^{1}H NMR analyses; the observed large coupling constants ($J_{2ax,3}$ and $J_{5,6}$) revealed that **19** has a chair conformation and the substituents on C-3, C-5 and C-6 are all in the equatorial positions, and the observed NOEs between C-4 methyl and H-3, and those between C-4 methyl and H-5 clearly assigned the stereochemistry of the tertiary alcohol at C-4 as *S*. The tosyl group in **19** was then deprotected by the action of Mg in MeOH[13] to give **10** in 81% yield. Oxidation of the secondary alcohol afforded ketone **20** (73% yield), whose Horner–Wadsworth–Emmons reaction, followed by silylation of a tertiary alcohol function provided *E*-alkene **21** as a single isomer in 84% yield. The *E*-geometry of the double bond in **21** was confirmed by the observed NOEs between a vinyl proton and C-4 methyl, as well as methyl groups in OTMS. Reduction of the ester function in **21** with DIBAL-H smoothly gave primary alcohol **22** in 97% yield, which was converted into trichloroacetimidate **9** by the action of trichloroacetonitrile and DBU (97% yield) (Scheme 3). When imidate **9** was heated in *tert*-butylbenzene at 150 °C in the presence of Na_2CO_3[14] in a sealed tube for 2 days, the crucial Overman rearrangement successfully took place to provide rearranged products, **23** and *epi*-**23** in 69% and 16% isolated yields from **22**, respectively. The structure of the major rearranged product **23** was confirmed by NOE experiments as shown in Scheme 3; especially the observed NOEs between a vinyl proton and H-2, and those between NH and C-4 methyl clearly revealed that the newly formed tetrasubstituted carbon in **23** has an *S*-configuration. The steric and electronic factors might account for the observed stereoselectivity (**23**/*epi*-**23** = 4.3:1). There would be two plausible chair-like transition models in the Overman rearrangement[8a] of **9**, TS-a and TS-b, where the tetrahydropyran rings adopt the stable chair conformation (Figure 2). In TS-b, which gives rise to *epi*-**23**, an axially oriented OTMS group at C-4 would hinder the attack of the imino nitrogen from the upper side, and the electrostatic repulsion (and/or dipole-dipole interaction) between the axial oxygen and the imino nitrogen would also render the TS-b less favorable. On the other hand, the TS-a that generates **23**, has the similar gauche interactions between an equatorial methyl group at C-4 and the imino nitrogen, however, does not suffer repulsive electronic interactions between the OTMS group and the nitrogen.



Scheme 2 Synthesis of intermediate *E*-alkene **21**. *Reagents and conditions*: (a) BnBr, NaH, DMF, 90%; (b) AcOH–H_2O (4:1), 50 °C, 93%; (c) TBSCl, Et_3N, DMAP, CH_2Cl_2, 96%; (d) TsCl, Et_3N, DMAP, CH_2Cl_2, 83%; (e) aq 6 M HCl, THF, then $NaIO_4$, aq THF, 96%; (f) Cl_3CCN, DBU, CH_2Cl_2, then PMBOH, TMSOTf, CH_2Cl_2; (g) K_2CO_3, MeOH, 82% from **15**; (h) Ac_2O, DMSO, 50 °C, 90%; (i) Me_3Al, toluene, –40 to –5 °C, 88%; (j) Mg, MeOH, 81%; (k) SO_3·py, DMSO, Et_3N, 73%; (l) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 96%; (m) TMSOTf, py, CH_2Cl_2, 87%.

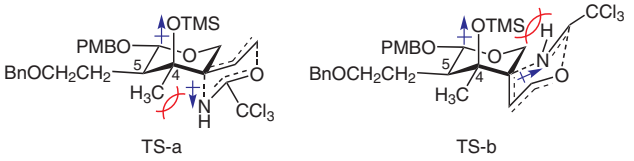
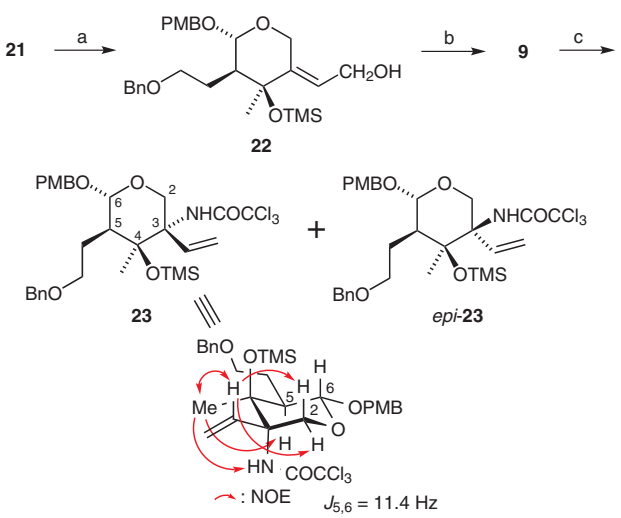
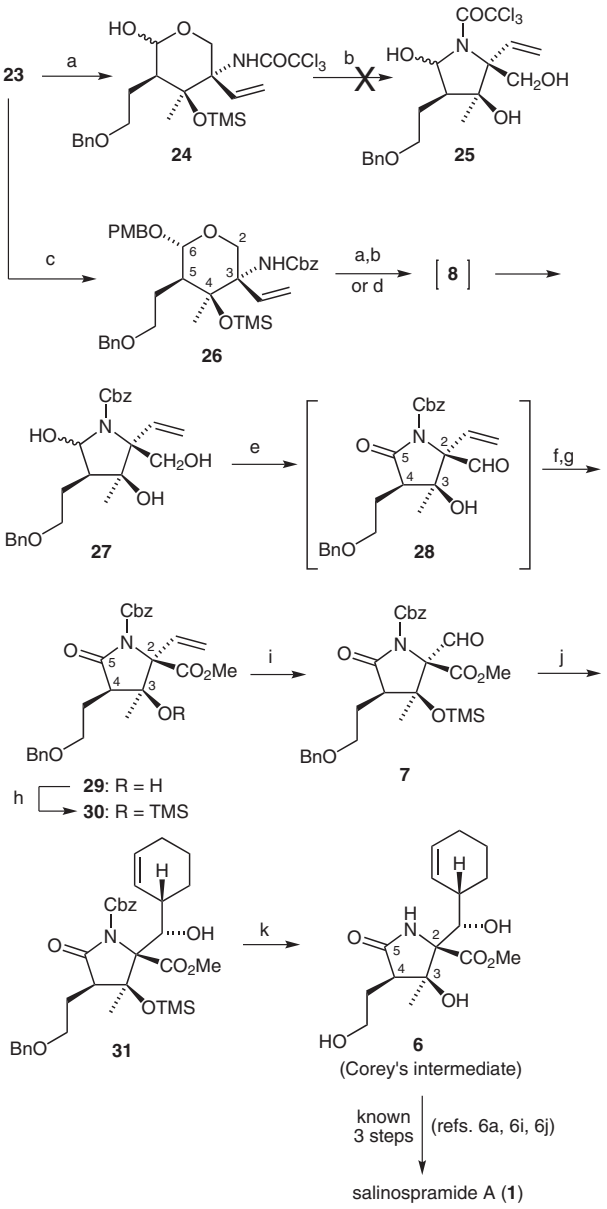


Figure 2 Transition models of Overman rearrangement of **9**



Scheme 3 Formation of **23** and *epi*-**23** from **21**. *Reagents and conditions*: (a) DIBAL-H, toluene, –50 °C, 97%; (b) Cl_3CCN, DBU, CH_2Cl_2, 97%; (c) Na_2CO_3, *tert*-butylbenzene, 150 °C, in a sealed tube, 2 d, 85% from **22** (**23**: 69%, *epi*-**23**: 16%).

With rearranged product **23** in hand, we turned our attention to conversion of **23** to Corey's intermediate **6** (Scheme 4). Treatment of **23** with DDQ smoothly afforded hemiacetal **24**, however, attempted conversion of **24** to hemiaminal **25** by the treatment with TBAF or TFA proved unsuccessful. This result led us to exchange the protecting group of the nitrogen. The trichloroacetyl group in **23** was removed by the action of DIBAL-H[7d,e] and the resulting amine was protected with CbzCl to give **26** (ca. 100% yield for 2 steps). Removal of the PMB group in **26** with DDQ, and subsequent treatment with TBAF afforded **8**, which spontaneously turned into 5-membered hemiaminal **27** under the reaction conditions (67% yield from **26**). Alternatively, **27** was also obtained in 96% yield in one step by the treatment of **26** with aqueous TFA in CH_2Cl_2 at 0 °C. Jones oxidation of hemiaminal **27** afforded γ-lactam aldehyde **28** in 67% crude yield. It is interesting to note that aldehyde **28** did not undergo further oxidation to carboxylic acid under the conditions of Jones oxidation; the severe steric hindrance around the aldehyde carbonyl group would inhibit the formation of a bulky chromate ester. Fortunately, aldehyde **28** could be oxidized by $NaClO_2$, and the product was esterified to provide methyl ester **29** in 44% overall yield from **26**. Protection of a tertiary alcohol in **29** afforded **30** in 98% yield. Oxidative cleavage of the vinyl function in **30** with OsO_4 and $NaIO_4$[15] gave aldehyde **7** in 62% yield. Reaction of **7** with cyclohex-2-enylzinc chloride as described by the Corey group[6a] gave **31** as the sole product in 90% yield. Finally, deprotection of Cbz, Bn, and TMS groups in **31** by treatment with BCl_3 furnished Corey's intermediate **6** in 78% yield. The spectral (^1H and ^{13}C NMR) data as well as the $[\alpha]_D$ value of the synthetic specimen showed a good accord with those reported by Hatakeyama.[6j] Since the three-steps conversion of compound **6** into salinosporamide A (**1**) has already been described by the groups of



Scheme 4 Synthesis of Corey's intermediate **6**. *Reagents and conditions*: (a) DDQ, aq CH_2Cl_2; (b) TBAF, THF; (c) DIBAL-H, toluene, –78 °C, then CbzCl, EtOAc, 0.5 M aq NaOH, 100%; (d) TFA–H_2O (4:1), CH_2Cl_2, 0 °C, 96%; (e) Jones reagent, aq acetone, 0 °C; (f) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, aq *t*-BuOH; (g) MeI, K_2CO_3, DMF, 44% from **26**; (h) TMSOTf, py, CH_2Cl_2, 98%; (i) OsO_4, $NaIO_4$, py, 1,4-dioxane, 60 °C, 62%; (j) cyclohex-2-eneylzinc chloride, THF, –78 °C, 90%; (k) BCl_3, CH_2Cl_2, 0 °C, then MeOH, 78%.

Corey,[6a] Pattenden,[6i] and Hatakeyama,[6j] the synthesis of **1** in the formal sense has been accomplished.

In summary, the stereoselective formal synthesis of salinosporamide A (**1**) starting from D-glucose has been accomplished. This work proved that the methodology involving Overman rearrangement of allylic alcohols derived from carbohydrates, followed by further manipulation by use of the residual functional groups in carbohydrates, is quite effective for the chiral synthesis of natural products possessing complex α-substituted α-amino acid structures with multi functionalities.

The melting points were determined on a Mitamura-riken micro hot stage and are uncorrected. ^{1}H NMR spectra were measured with a JEOL ECA-500 (500 MHz) or a Varian MVX-300 (300 MHz) spectrometers, with TMS as the internal standard for solutions in $CDCl_3$ at r.t., unless otherwise noted. Chemical shifts are reported as δ values in ppm. ^{13}C NMR spectra were taken on a JEOL ECA-500 (125 MHz) or a Varian MVX-300 (75 MHz) spectrometers, in $CDCl_3$ at r.t., unless otherwise noted. Chemical shifts are reported as δ values in ppm. Mass spectra (EI and FAB) were measured by a JEOL GC-Mate spectrometer, and those of ESI were measured by a JMS-T100LC spectrometer. Optical rotations were measured with a JASCO DIP-370 instrument with 1 dm tube and values of $[\alpha]_D$ are recorded in units of 10^{-1} deg·cm^2·g^{-1}. IR spectra were taken with a JASCO FT/IR-200 spectrometer. Organic extracts were dried over anhyd Na_2SO_4 and concentrated below 40 °C under reduced pressure. Benzene, toluene, and DMF were distilled from CaH_2. MeOH was distilled from $CaSO_4$ (Drierite®). AcOH was distilled from Ac_2O and $KMnO_4$. EtOH (95%, dried over 3Å molecular sieves), Et_2O (anhyd), THF (anhyd, stabilizer free), and CH_2Cl_2 (anhyd) were purchased from Kanto Chemical Co., Inc., Japan. For column chromatography, Merck silica gel 60 (230–400 mesh) was used, unless otherwise noted. For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} on glass plates, 0.25 mm) were used.

(3a*R*,5*S*,6*R*,6a*R*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuro[2,3-*d*][1,3]dioxole (12)

To a solution of alcohol **11** (17.3 g, 60.0 mmol) and BnBr (8.6 mL, 72.0 mmol) in DMF (170 mL) was added NaH (1.73 g, 72.0 mmol) in DMF (30 mL) at 0 °C. After stirring for 10 min at 0 °C, the reaction mixture was further stirred at r.t. for 1.5 h. The mixture was quenched with EtOH (30 mL) at 0 °C and diluted with H_2O (800 mL). The products were extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with brine (500 mL), dried, and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:5 → 1:3) to afford **12** (20.4 g, 90%) as a colorless syrup; $[\alpha]_D^{25}$ +48.0 (*c* 2.85, $CHCl_3$).

IR (neat): 2985, 2940, 2880, 1460, 1380, 1370 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H, C_6H_5), 5.73 (d, *J* = 4.0 Hz, 1 H, H-3a), 4.59 (dd, *J* = 4.0, 4.0 Hz, 1 H, H-6a), 4.56 (d, *J* = 12.3 Hz, 1 H, PhC*H*$_2$), 4.50 (d, *J* = 12.3 Hz, 1 H, PhC*H*$_2$), 4.07 (dd, *J* = 8.0, 6.3 Hz, 1 H, Me_2COCH_2), 4.02 (m, 1 H, Me_2COCH), 3.92 (dd, *J* = 8.0, 5.5 Hz, 1 H, Me_2COCH_2), 3.79 (dd, *J* = 9.7, 6.6 Hz, 1 H, H-5), 3.64–3.60 (m, 2 H, BnOC*H*$_2$), 2.13–1.98 (m, 2 H, H-6 and $BnOCH_2CH_2$), 1.88 (m, 1 H, $BnOCH_2CH_2$), 1.50 (s, 3 H, CCH_3), 1.41 (s, 3 H, CCH_3), 1.34 (s, 3 H, CCH_3), 1.30 (s, 3 H, CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.5, 128.3, 127.6, 127.5, 111.7, 109.5, 105.0, 81.9, 81.5, 77.7, 72.7, 68.5, 67.4, 45.4, 26.8, 26.5, 26.4, 25.3, 25.1.

HRMS-ESI: *m*/*z* [M + Na$^+$] calcd for $C_{21}H_{30}O_6$ + Na: 401.1940; found: 401.1933.

(*R*)-1-{(3a*R*,5*S*,6*R*,6a*R*)-6-[2-(Benzyloxy)ethyl]}-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethane-1,2-diol (13)

A solution of **12** (20.4 g, 53.9 mmol) in AcOH (200 mL) and H_2O (50 mL) was stirred at 50 °C for 1 h. The reaction mixture was concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:1 → 1:0) to give **13** (16.9 g, 93%) as a colorless syrup; $[\alpha]_D^{25}$ +51.8 (*c* 2.35, $CHCl_3$).

IR (neat): 3440, 2980, 2940, 2860, 1455, 1375 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H, C_6H_5), 5.73 (d, *J* = 4.0 Hz, 1 H, H-3a), 4.57 (dd, *J* = 4.0, 4.0 Hz, 1 H, H-6a), 4.54 (d, *J* = 12.0 Hz, 1 H, PhC*H*$_2$), 4.50 (d, *J* = 12.0 Hz, 1 H, PhC*H*$_2$), 3.88 (dd, *J* = 10.1, 4.9 Hz, 1 H, H-5), 3.72–3.68 (m, 2 H, HOC*H*$_2$ and HOC*H*), 3.66–3.61 (m, 2 H, HOC*H*$_2$ and BnOC*H*$_2$), 3.54–3.59 (m, 1 H, BnOC*H*$_2$), 2.10–2.04 (m, 1 H, H-6), 1.92–1.95 (m, 2 H, $BnOCH_2CH_2$), 1.48 (s, 3 H, CCH_3), 1.29 (s, 3 H, CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.0, 128.4, 127.8, 127.7, 111.7, 104.6, 82.6, 81.6, 73.2, 73.0, 68.6, 63.7, 44.1, 26.7, 26.3, 25.2.

HRMS-ESI: *m*/*z* [M + Na$^+$] calcd for $C_{18}H_{26}O_6$ + Na: 361.1627; found: 361.1632.

(*R*)-1-{(3a*R*,5*S*,6*R*,6a*R*)-6-[2-(Benzyloxy)ethyl]}-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-*tert*-butyldimethylsilyloxyethanol (14)

To a solution of alcohol **13** (2.11 g, 6.24 mmol) in CH_2Cl_2 (40 mL) at 0 °C were added Et_3N (1.3 mL, 9.33 mmol), TBSCl (1.13 g, 7.48 mmol), and DMAP (76 mg, 0.624 mmol), and the mixture was stirred at r.t. for 16 h. The mixture was washed successively with aq 0.2 M HCl (40 mL) and brine (40 mL). The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (EtOAc–hexane, 1:6 → 1:4) to give **14** (2.72 g, 96%) as a colorless syrup; $[\alpha]_D^{27}$ +42.1 (*c* 2.55, $CHCl_3$).

IR (neat): 3500, 2960, 2940, 2860, 1460, 1370 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 5 H, C_6H_5), 5.72 (d, *J* = 3.9 Hz, 1 H, H-3a), 4.60 (dd, *J* = 3.9, 3.9 Hz, 1 H, H-6a), 4.56 (d, *J* = 12.0 Hz, 1 H, PhC*H*$_2$), 4.51 (d, *J* = 12.0 Hz, 1 H, PhC*H*$_2$), 3.82–3.76 (m, 2 H, H-5 and TBSOC*H*$_2$), 3.67–3.60 (m, 4 H, TBSOC*H*$_2$, HOC*H* and BnOC*H*$_2$), 2.62 (d, *J* = 4.2 Hz, 1 H, OH), 2.17–2.09 (m, 2 H, H-6 and $BnOCH_2CH_2$), 1.91 (m, 1 H, $BnOCH_2CH_2$), 1.49 (s, 3 H, CCH_3), 1.30 (s, 3 H, CCH_3), 0.90 (s, 9 H, *t*-C_4H_9), 0.07 (s, 6 H, $SiCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.5, 128.3, 127.6, 127.4, 111.5, 104.8, 81.6, 81.0, 74.0, 72.6, 68.7, 64.5, 44.9, 26.8, 26.4, 25.8, 25.3, 18.2, –5.40, –5.43.

HRMS-EI: *m*/*z* [M$^+$] calcd for $C_{24}H_{40}O_6Si$: 452.2594; found: 452.2594.

(*R*)-1-{(3a*R*,5*S*,6*R*,6a*R*)-6-[2-(Benzyloxy)ethyl]}-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-*tert*-butyldimethylsilyloxyethyl 4-Methylbenzenesulfonate (15)

To a solution of alcohol **14** (3.82 g, 8.44 mmol) in pyridine (40 mL) at r.t. were added TsCl (3.22 g, 16.9 mmol) and DMAP (103 mg, 0.844 mmol), and the mixture was stirred at 60 °C for 30 h. The mixture was concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:6 → 1:3) to give **15** (4.27 g, 83%) as a colorless syrup; $[\alpha]_D^{25}$ +32.0 (*c* 0.92, $CHCl_3$).

IR (neat): 2960, 2940, 2860, 1460, 1370 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.4 Hz, 2 H, C_6H_5), 7.36–7.27 (m, 7H, C_6H_5), 5.48 (d, *J* = 3.3 Hz, 1 H, H-3a), 4.64 (ddd, *J* = 5.7, 5.7, 3.3 Hz, 1 H, TsOC*H*), 4.56–4.47 (m, 3 H, H-6a and PhC*H*$_2$), 4.06 (dd, *J* = 10.5, 3.3 Hz, 1 H, H-5), 3.77 (d, *J* = 5.7 Hz, 2 H, TBSOC*H*$_2$), 3.60–3.55 (m, 2 H, BnOC*H*$_2$), 2.42 (s, 3 H, PhC*H*$_3$), 2.19 (m, 1 H, $BnOCH_2CH_2$), 1.87–1.80 (m, 2 H, H-6 and $BnOCH_2CH_2$), 1.40 (s, 3 H, CCH_3), 1.26 (s, 3 H, CCH_3), 0.83 (s, 9 H, *t*-C_4H_9), 0.07 (s, 6 H, $SiCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 138.7, 134.6, 129.8, 128.5, 128.1, 127.7, 127.6, 111.9, 104.9, 82.5, 81.5, 80.1, 72.9, 68.5, 61.4, 42.7, 27.0, 26.7, 25.9, 25.5, 21.7, 18.3, –5.4, –5.5.

HRMS-ESI: *m*/*z* [M + Na$^+$] calcd for $C_{31}H_{46}O_8SSi$ + Na: 629.2580; found: 629.2570.

(3*R*,4*S*,5*R*,6*R*)-5-[2-(Benzyloxy)ethyl]-4-hydroxy-6-(4-methoxybenzyloxy)tetrahydro-2*H*-pyran-3-ol 4-Methylbenzenesulfonate (17)

To a solution of **15** (4.20 g, 6.92 mmol) in 1,4-dioxane (40 mL) at r.t. was added aq 6 M HCl (40 mL), and the mixture was stirred for 3 h. After the addition of aq 5 M NaOH (40 mL) at 0 °C, the mixture was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (40 mL), dried, and concentrated to give the crude triol as a pale yellow syrup. To a solution of the crude tirol in THF–H_2O (1:1, 60 mL) at r.t. was added a solution of $NaIO_4$ (4.44 g, 20.8 mmol) in H_2O (30 mL), and the mixture was stirred for 2 h. The mixture was diluted with EtOAc (50 mL), and washed successively with H_2O (40 mL) and brine (60 mL). The organic layer was dried and concentrated to give a residue, which was roughly purified by silica gel column chromatography (EtOAc–hexane, 1:2 → 1:1) to give crude **16** (2.98 g, 96%) as a colorless syrup. To a solution of crude **16** (2.98 g, 6.62 mmol) in CH_2Cl_2 (56 mL) at 0 °C were added Cl_3CCN (1.99 mL, 19.8 mmol) and DBU (0.10 mL 0.67 mmol) and the mixture was stirred for 30 min at 0 °C. The mixture was diluted with toluene (40 mL) and roughly purified by filtration through a pad of silica gel (EtOAc–hexane, 1:3, 0.5% Et_3N) to give the intermediate imidate as a colorless syrup (3.47 g, 88%). To a solution of the crude imidate (3.47 g, 5.83 mmol) in CH_2Cl_2 (62 mL) at 0 °C were added 4-methoxybenzyl alcohol (0.80 mL, 6.43 mmol) and a solution of TMSOTf (21 μL, 0.11 mmol) in CH_2Cl_2 (7 mL), and the mixture was stirred for 1.5 h at 0 °C. The mixture was quenched with Et_3N (33 μL, 0.23 mmol), and then washed successively with H_2O (50 mL) and brine (50 mL). The organic layer was dried and concentrated to give a colorless residue. This residue was dissolved in MeOH (40 mL), and to this solution was added K_2CO_3 (403 mg, 2.92 mmol) at r.t. After 30 min, the mixture was concentrated and then diluted with EtOAc (70 mL). The mixture was washed successively with H_2O (50 mL) and brine (50 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:6 → 1:3) to give **17** (2.95 g, 79% from **15**) as a colorless syrup; $[\alpha]_D^{27}$ –28.5 (*c* 0.6, $CHCl_3$).

IR (neat): 3460, 2920, 2880, 1730, 1520, 1380 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.1 Hz, 2 H, C_6H_5), 7.38–7.26 (m, 7 H, C_6H_5), 7.20 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 6.84 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 4.68 (d, *J* = 11.4 Hz, 1 H, PhC*H*$_2$), 4.59 (d, *J* = 6.6 Hz, 1 H, H-6), 4.50 (m, 1 H, H-3), 4.45 (s, 2 H, PhC*H*$_2$), 4.38 (d, *J* = 11.4 Hz, 1 H, PhC*H*$_2$), 4.16 (m, 1 H, H-4), 3.82 (dd, *J* = 11.7, 8.7 Hz, 1 H, H-2), 3.79 (s, 3 H, OCH_3), 3.65 (dd, *J* = 11.7, 4.5 Hz, 1 H, H-2), 3.54–3.42 (m, 2 H, BnOC*H*$_2$), 3.00 (d, *J* = 3.9 Hz, 1 H, OH), 2.43 (s, 3H, PhC*H*$_3$), 1.86–1.78 (m, 3 H, H-5 and $BnOCH_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 145.1, 137.8, 133.4, 130.0, 129.6, 129.4, 128.4, 127.8, 113.8, 99.9, 77.3, 73.0, 70.2, 68.0, 67.1, 60.8, 55.2, 43.2, 26.6, 21.6.

HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{29}H_{34}O_8S$ + Na: 565.1872; found: 565.1871.

(3*R*,5*R*,6*R*)-5-[2-(Benzyloxy)ethyl]-6-(4-methoxybenzyloxy)-4-oxotetrahydro-2*H*-pyran-3-ol 4-Methylbenzenesulfonate (18)

A solution of alcohol **17** (4.22 g, 7.78 mmol) in DMSO (40 mL) and Ac_2O (16 mL) was stirred for 1.5 h at 50 °C. The reaction mixture was diluted with EtOAc (150 mL), and washed successively with H_2O (150 mL) and brine (150 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:6 → 1:3) to give **18** (3.80 g, 90%) as a pale yellow syrup; $[\alpha]_D^{27}$ –23.6 (*c* 1.06, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.1 Hz, 2 H, C_6H_5), 7.36–7.20 (m, 9 H, C_6H_5), 6.85 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 4.93 (dd, *J* = 8.1, 6.6 Hz, 1 H, H-3), 4.75 (d, *J* = 5.7 Hz, 1 H, PhC*H*$_2$), 4.49–4.34 (m, 5 H, H-2, H-6 and PhC*H*$_2$), 3.80 (s, 3 H, OCH_3), 3.61 (dd, *J* = 11.7, 8.4 Hz, 1 H, H-2), 3.52–3.38 (m, 2 H, BnOC*H*$_2$), 2.75 (ddd, *J* = 7.2, 7.2, 4.8 Hz, 1 H, H-5), 2.44 (s, 3 H, PhC*H*$_3$), 2.05 (m, 1 H, $BnOCH_2CH_2$), 1.76 (m, 1 H, $BnOCH_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.5, 159.5, 145.3, 138.2, 132.9, 129.9, 129.8, 128.6, 128.3, 128.0, 127.6, 127.5, 113.9, 102.6, 77.4, 72.6, 70.3, 67.3, 63.8, 55.2, 52.6, 24.4, 21.7.

HRMS-FAB: *m*/*z* [M + Na^+] calcd for $C_{29}H_{32}O_8S$ + Na: 563.1716; found: 563.1713.

(3*R*,4*S*,5*R*,6*R*)-5-[2-(Benzyloxy)ethyl]-4-hydroxy-6-(4-methoxybenzyloxy)-4-methyltetrahydro-2*H*-pyran-3-ol 4-Methylbenzenesulfonate (19)

To a solution of ketone **18** (2.38 g, 4.40 mmol) in toluene (40 mL) was added Me_3Al (2 M in toluene, 6.6 mL, 13.2 mmol) at –40 °C over 5 min. The mixture was warmed to –5 °C and further stirred at –5 °C for 1 h. The reaction was quenched with aq 1 M HCl (15 mL) at –5 °C and diluted with EtOAc (40 mL). The EtOAc layer was washed successively with aq 1 M HCl (40 mL), aq sat. $NaHCO_3$ (40 mL), and brine (40 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:5 → 1:2) to give **19** (2.13 g, 88%) as a pale yellow oil; $[\alpha]_D^{27}$ –34.3 (*c* 0.95, $CHCl_3$).

IR (neat): 3450, 2940, 2880, 1515, 1360, 1250, 1180 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.1 Hz, 2 H, C_6H_5), 7.36–7.25 (m, 7 H, C_6H_5), 7.17 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 6.84 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 4.70 (d, *J* = 11.4 Hz, 1 H, PhC*H*$_2$), 4.56 (d, *J* = 8.4 Hz, 1 H, H-6), 4.41 (s, 2 H, PhC*H*$_2$), 4.36 (d, *J* = 11.4 Hz, 1 H, PhC*H*$_2$), 4.30 (dd, *J* = 9.9, 5.7 Hz 1 H, H-3), 3.79 (s, 3 H, OCH_3), 3.78 (dd, *J* = 10.8, 9.9 Hz, 1 H, H-2), 3.70 (dd, *J* = 10.8, 5.7 Hz, 1 H, H-2), 3.43–3.37 (m, 2 H, BnOC*H*$_2$), 2.93 (s, 1 H, OH), 2.45 (s, 3 H, PhC*H*$_3$), 1.93 (m, 1 H, $BnOCH_2CH_2$), 1.68 (m, 1 H, $BnOCH_2CH_2$), 1.57 (m, 1 H, H-5), 1.13 (s, 3 H, CCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 145.2, 138.0, 133.4, 129.9, 129.6, 129.4, 128.3, 127.9, 127.6, 113.8, 100.3, 80.4, 72.8, 72.0, 70.4, 68.4, 61.7, 55.2, 47.1, 25.2, 23.8, 21.6.

HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{30}H_{36}O_8S$ + Na: 579.2029; found: 579.2020.

(3*R*,4*S*,5*R*,6*R*)-5-[2-(Benzyloxy)ethyl]-6-(4-methoxybenzyloxy)-4-methyltetrahydro-2*H*-pyran-3,4-diol (10)

To a solution of alcohol **19** (4.70 g, 8.44 mmol) in MeOH (60 mL) at r.t. was added Mg (2.1 g, 86 mmol), and the mixture was stirred for 2.5 h. The reaction was quenched with aq 1 M HCl (150 mL) at 0 °C and then diluted with EtOAc (100 mL). The organic layer was washed successively with aq 1 M HCl (100 mL), aq 0.5 M NaOH (150 mL), and brine (150 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:2 → 2:1) to give **10** (2.76 g, 81%) as a pale yellow syrup; $[\alpha]_D^{25}$ –78.7 (*c* 1.1, $CHCl_3$).

IR (neat): 3430, 2940, 2870, 1615, 1515, 1455, 1360, 1250 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.17 (m, 7 H, C_6H_5), 6.84 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 4.75 (d, *J* = 11.4 Hz, 1 H, PhC*H*$_2$), 4.60 (d, *J* = 8.7 Hz, 1 H, H-6), 4.43 (s, 2 H, PhC*H*$_2$), 4.39 (d, *J* = 11.4 Hz, 1 H, PhC*H*$_2$), 4.18 (s, 1 H, OH), 3.87 (dd, *J* = 10.5, 4.8 Hz, 1 H, H-3), 3.80 (s, 3 H, OCH_3), 3.54 (dd, *J* = 10.5, 10.5 Hz, 1 H, H-2), 3.49–3.31 (m, 3 H, H-2 and BnOC*H*$_2$), 2.17 (br s, 1 H, OH), 2.05–1.83 (m, 2 H, $BnOCH_2CH_2$), 1.66 (m, 1 H, H-5), 1.29 (s, 3 H, CCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 137.4, 129.8, 128.4, 127.7, 113.8, 99.5, 73.1, 71.7, 71.4, 70.0, 67.6, 65.1, 55.2, 47.1, 25.0, 24.0.

HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{23}H_{30}O_6$ + Na: 425.1940; found: 425.1936.

(4*S*,5*R*,6*R*)-5-[2-(Benzyloxy)ethyl]-4-hydroxy-6-(4-methoxybenzyloxy)-4-methyldihydro-2*H*-pyran-3(4*H*)-one (20)

To a solution of alcohol **10** (2.71 g, 6.73 mmol) in DMSO (30 mL) at r.t. were added Et_3N (7.5 mL, 54 mmol) and SO_3·py (5.36 g, 33.7 mmol), and the mixture was stirred for 1.5 h. The mixture was diluted with EtOAc (120 mL), and washed successively with H_2O (100 mL) and brine (100 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:4 → 1:2) to give **20** (1.96 g, 73%) as a pale yellow oil; $[\alpha]_D^{26}$ –88.0 (*c* 1.1, $CHCl_3$).

IR (neat): 3480, 2940, 2870, 1730, 1615, 1515, 1460, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.35 (m, 7 H, C_6H_5), 6.88 (d, *J* = 8.6 Hz, 2 H, C_6H_5), 4.90 (d, *J* = 3.2 Hz, 1 H, H-6), 4.71 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.47 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.45 (d, *J* = 12.0 Hz, 1 H, PhC*H*$_2$), 4.31 (d, *J* = 12.0 Hz, 1 H, PhC*H*$_2$), 4.36 (d, *J* = 16.0 Hz, 1 H, H-2), 4.01 (d, *J* = 16.0 Hz, 1 H, H-2), 3.81 (s, 3 H, OCH_3), 3.63 (s, 1 H, OH), 3.53–3.44 (m, 2 H, m, BnOC*H*$_2$), 2.31 (dt, *J* = 3.2, 7.7 Hz, 1 H, H-5), 2.00–1.94 (m, 1 H, BnOCH$_2$C*H*$_2$), 1.71–1.64 (m, 1 H, BnOCH$_2$C*H*$_2$), 1.53 (s, 3 H, CCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.3, 159.4, 138.1, 129.5, 129.2, 128.4, 127.7, 127.6, 113.9, 100.7, 75.3, 72.9, 69.8, 68.3, 65.5, 55.2, 49.3, 27.5, 26.1.

HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{23}H_{28}O_6$ + Na: 423.1784; found: 423.1788.

Ethyl (*E*)- 2-{(4*S*,5*R*,6*S*)-5-[2-(Benzyloxy)ethyl]}-6-(4-methoxybenzyloxy)-4-methyl-4-trimethylsilyloxydihydro-2*H*-pyran-3(4*H*)-ylidene)acetate (21)

To a solution of triethyl phosphonoacetate (0.390 mL, 1.97 mmol) in THF (5 mL) at 0 °C was added NaH (47.0 mg, 1.96 mmol) and the mixture was stirred for 10 min. A solution of ketone **20** (392 mg, 0.979 mmol) in THF (2 × 3 mL) was added to the reaction mixture at 0 °C, and the resulting mixture was warmed to r.t. After stirring for 2 h at r.t., the mixture was diluted with EtOAc (120 mL), and washed successively with aq 0.5 M HCl (60 mL) and brine (60 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:5 → 1:2) to give the intermediate alkene (440 mg, 96%) as a pale yellow syrup. To a solution of the alkene (440 mg, 0.933 mmol) in CH_2Cl_2 (9 mL) were added pyridine (0.45 mL, 5.6 mmol) and TMSOTf (0.51 mL, 2.6 mmol) at 0 °C, and the mixture was stirred at 0 °C for 40 min. The mixture was washed successively with aq 0.5 M HCl (20 mL), aq sat. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:8 → 1:5) to give **21** (442 mg, 84% from **20**) as a colorless syrup; $[\alpha]_D^{26}$ –47.1 (*c* 0.86, $CHCl_3$).

IR (neat): 2950, 2860, 1715, 1515, 1250 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 7 H, C_6H_5), 6.86 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 6.01 (s, 1 H, C=CH), 5.04 (d, *J* = 14.7 Hz, 1 H, H-2), 4.77 (d, *J* = 3.6 Hz, 1 H, H-6), 4.72 (d, *J* = 11.4 Hz, 1 H, PhC*H*$_2$), 4.65 (d, *J* = 14.7 Hz, 1 H, H-2), 4.44 (s, 2 H, PhC*H*$_2$), 4.41 (d, *J* = 11.4 Hz, 1 H, PhC*H*$_2$), 4.17 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$CH$_3$), 3.79 (s, 3 H, OCH_3), 3.55–3.41 (m, 2 H, BnOC*H*$_2$), 2.00 (m, 1 H, BnOCH$_2$C*H*$_2$), 1.84 (m, 1 H, H-5), 1.61 (s, 3 H, CCH_3), 1.54 (m, 1 H, BnOCH$_2$C*H*$_2$), 1.30 (t, *J* = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$), 0.13 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 159.2, 158.8, 138.7, 130.1, 129.4, 128.3, 127.5, 127.4, 114.1, 113.8, 100.7, 75.6, 72.8, 69.6, 69.2, 60.1, 59.1, 55.3, 49.5, 28.1, 27.5, 14.3, 2.3.

HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{30}H_{42}O_7Si$ + Na: 565.2598; found: 565.2599.

(*E*)-2-{(4*S*,5*R*,6*S*)-5-[2-(Benzyloxy)ethyl]}-6-(4-methoxybenzyloxy)-4-methyl-4-trimethylsilyloxydihydro-2*H*-pyran-3(4*H*)-ylidene)ethanol (22)

To a solution of ester **21** (711 mg, 1.31 mmol) in toluene (14 mL) under argon was added DIBAL-H (0.99 M in toluene, 3.31 mL, 3.28 mmol) at –50 °C and the mixture was stirred at this temperature for 30 min. The reaction was quenched with aq 1 M HCl (10 mL) at –50 °C and then diluted with EtOAc (20 mL). The organic layer was washed successively with aq 1 M HCl (15 mL), aq 1 M NaOH (20 mL), and brine (20 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:2 → 2:1) to give **22** (634 mg, 97%) as a colorless oil; $[\alpha]_D^{25}$ –12.3 (*c* 2.88, $CHCl_3$).

IR (neat): 3440, 2950, 2860, 1615, 1515, 1250 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 7 H, C_6H_5), 6.85 (d, *J* = 8.4 Hz, 2 H, C_6H_5), 5.75 (t, *J* = 6.6 Hz, 1 H, C=CH), 4.75 (d, *J* = 11.1 Hz, 1 H, PhC*H*$_2$), 4.71 (d, *J* = 5.1 Hz, 1 H, H-6), 4.44 (s, 2 H, PhC*H*$_2$), 4.43 (d, *J* = 11.1 Hz, 1 H, PhC*H*$_2$), 4.37 (d, *J* = 12.9 Hz, 1 H, H-2), 4.29–4.15 (m, 3 H, 2-H and HOC*H*$_2$), 3.79 (s, 3 H, OCH_3), 3.55 (m, 1 H, BnOC*H*$_2$), 3.44 (m, 1 H, BnOC*H*$_2$), 1.96 (m, 1 H, BnOCH$_2$C*H*$_2$), 1.61–1.43 (m, 2 H, H-5 and BnOCH$_2$C*H*$_2$), 1.51 (s, 3 H, CCH_3), 0.07 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 140.9, 138.7, 130.1, 129.3, 128.3, 127.5, 127.4, 122.9, 113.7, 101.9, 75.6, 72.7, 70.1, 70.0, 59.2, 58.6, 55.2, 49.9, 27.1, 25.6, 2.2.

HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{28}H_{40}O_6Si$ + Na: 523.2492; found: 523.2490.

Overman Rearrangement of 9

To a solution of alcohol **22** (634 mg, 1.27 mmol) in CH_2Cl_2 (10 mL) were added trichloroacetonitrile (0.254 mL, 2.53 mmol) and DBU (0.019 mL, 0.13 mmol) at 0 °C. After stirring at 0 °C for 30 min, the mixture was diluted with toluene (10 mL) and roughly purified by filtration through a pad of silica gel (EtOAc–hexane, 1:4) to give crude imidate **9** as a colorless oil (791 mg, 97%). A solution of crude **9** (791 mg, 1.23 mmol) and Na_2CO_3 (204 mg, 1.92 mmol) in degassed *tert*-butylbenzene (41 mL) was heated in a sealed tube at 150 °C for 48 h. After cooling, the insoluble material was removed by filtration and the filtrate was concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:10 → 1:8) to give first, the rearranged product **23** (560 mg, 69% from **22**) as a colorless syrup. Further elution afforded *epi*-**23** (130 mg, 16% from **22**) as a colorless syrup.

23

R_f = 0.50 (EtOAc–hexane, 1:5); $[\alpha]_D^{25}$ +7.5 (*c* 2.4, $CHCl_3$).

IR (neat): 2960, 2860, 1730, 1615, 1515, 1250 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 8 H, C_6H_5 and NH), 6.86 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 6.24 (dd, *J* = 18.0, 11.1 Hz, 1 H, C*H*=CH$_2$), 5.38 (d, *J* = 11.1 Hz, 1 H, CH=C*H*$_2$), 5.18 (d, *J* = 18.0 Hz, 1 H, CH=C*H*$_2$), 4.80 (d, *J* = 11.7 Hz, 1 H, PhC*H*$_2$), 4.46 (d, 1 H, *J* = 11.7 Hz, PhC*H*$_2$), 4.45 (d, 1 H, *J* = 11.4 Hz, H-6), 4.44 (s, 2 H, PhC*H*$_2$), 4.02 (d, *J* = 11.7 Hz, 1 H, H-2), 3.92 (d, *J* = 11.7 Hz, 1 H, H-2), 3.80 (s, 3 H, OCH_3), 3.63 (m, 1 H, BnOC*H*$_2$), 3.49 (m, 1 H, BnOC*H*$_2$), 1.76 (m, 1 H, BnOCH$_2$C*H*$_2$), 1.67–1.53 (m, 2 H, H-5 and BnOCH$_2$C*H*$_2$), 1.35 (s, 3 H, CCH_3), 0.11 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 159.3, 138.7, 132.2, 129.6, 128.3, 127.4, 127.3, 117.7, 113.8, 102.7, 93.6, 80.9, 72.8, 70.5, 70.2, 66.7, 62.4, 55.3, 44.2, 26.8, 21.7, 2.8.

HRMS-ESI: *m*/*z* [M + K^+] calcd for $C_{30}H_{40}NO_6SiCl_3$ + K: 682.1328; found: 682.1322.

***epi*-23**

R_f = 0.40 (EtOAc–hexane, 1:5); $[\alpha]_D^{25}$ –65.8 (*c* 2.4, $CHCl_3$).

IR (neat): 3380, 2960, 2860, 1730, 1615, 1495, 1250 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (br s, 1 H, NH), 7.33–7.22 (m, 7 H, C_6H_5), 6.86 (d, *J* = 8.7 Hz, 2 H, C_6H_5), 5.70 (dd, *J* = 17.7, 11.1 Hz, 1 H, C*H*=CH_2), 5.32 (d, *J* = 11.1 Hz, 1 H, CH=CH_2), 5.23 (d, *J* = 17.7 Hz, 1 H, CH=CH_2), 4.85 (d, *J* = 1.8 Hz, 1 H, H-6), 4.66 (d, *J* = 11.7 Hz, 1 H, PhCH_2), 4.66 (d, *J* = 11.7 Hz, 1 H, H-2), 4.45 (d, *J* = 6.9 Hz, 1 H, PhCH_2), 4.42 (d, *J* = 6.9 Hz, 1 H, PhCH_2), 4.38 (d, *J* = 11.7 Hz, 1 H, PhCH_2), 3.89 (d, *J* = 11.7 Hz, 1 H, H-2), 3.80 (s, 3 H, OCH_3), 3.46 (m, 1 H, BnOCH_2), 3.40 (m, 1 H, BnOCH_2), 2.11–2.05 (m, 1 H, $BnOCH_2CH_2$), 1.90 (m, 1 H, H-5), 1.78–1.72 (m, 1 H, $BnOCH_2CH_2$), 1.53 (s, 3 H, CCH_3), 0.15 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.6, 159.1, 138.4, 133.2, 129.8, 129.2, 128.3, 127.5, 127.4, 117.0, 113.8, 99.6, 93.7, 76.4, 72.8, 69.3, 69.2, 62.5, 58.7, 55.2, 47.2, 28.3, 25.9, 2.3.

HRMS-ESI: *m*/*z* [M + K^+] calcd for $C_{30}H_{40}NO_6SiCl_3$ + K: 682.1328; found: 682.1319.

Benzyl(3*S*,4*S*,5*R*,6*R*)-5-[2-(Benzyloxy)ethyl]-6-(4-methoxybenzyloxy)-4-methyl-4-trimethylsilyoxy-3-vinyltetrahydro-2*H*-pyran-3-yl-carbamate (26)

To a solution of **23** (177 mg, 0.274 mmol) in toluene (3 mL) under argon was added DIBAL-H (0.99 M in toluene, 0.420 mL, 0.412 mmol) at –78 °C and the mixture was stirred at this temperature for 30 min. The reaction was quenched with aq 1 M HCl (1 mL) at –78 °C and then diluted with EtOAc (10 mL). The mixture was washed successively with aq 1 M NaOH (10 mL) and brine (10 mL). The organic layer was dried and concentrated to give the crude amine. To a solution of the crude amine in EtOAc (2 mL) and aq 0.5 M NaOH (2 mL) was added CbzCl (78 μL, 0.55 mmol) at 0 °C and the mixture was stirred for 3 h at r.t. The reaction was diluted with EtOAc (10 mL), and washed successively with H_2O (10 mL) and brine (10 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:8 → 1:4) to give **26** (174 mg, ca. 100%) as a colorless syrup; $[\alpha]_D^{24}$ +13.5 (*c* 0.97, $CHCl_3$).

IR (neat): 2960, 2860, 1740, 1510, 1250 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 12 H, C_6H_5), 6.85 (d, *J* = 8.4 Hz, 2 H, C_6H_5), 6.12 (dd, *J* = 18.0, 11.7 Hz, 1 H, C*H*=CH_2), 5.32 (d, *J* = 11.7 Hz, 1 H, CH=CH_2), 5.20 (s, 1 H, NH), 5.14 (d, *J* = 18.0 Hz, 1 H, CH=CH_2), 5.06 (d, *J* = 12.3 Hz, 1 H, PhCH_2), 5.00 (d, *J* = 12.3 Hz, 1 H, PhCH_2), 4.80 (d, *J* = 11.4 Hz, 1 H, PhCH_2), 4.47–4.42 (m, 4 H, H-6 and PhCH_2), 4.02 (d, *J* = 11.7 Hz, 1 H, H-2), 3.93 (d, *J* = 11.7 Hz, 1 H, H-2), 3.79 (s, 3 H, OCH_3), 3.64 (ddd, *J* = 8.7, 8.7, 4.5 Hz, 1 H, BnOCH_2), 3.45 (ddd, *J* = 8.7, 8.7, 8.7 Hz, 1 H, BnOCH_2), 1.72 (m, 1 H, $BnOCH_2CH_2$), 1.60 (m, 1 H, H-5), 1.37 (m, 1 H, $BnOCH_2CH_2$), 1.27 (s, 3 H, CCH_3), 0.10 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 154.3, 138.7, 136.6, 134.3, 129.6, 128.4, 128.3, 128.1, 128.0, 127.5, 127.4, 117.1, 113.8, 102.7, 80.7, 72.8, 70.6, 70.4, 66.6, 66.4, 61.0, 55.3, 43.9, 26.8, 21.2, 2.8.

HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{36}H_{47}NO_7Si$ + Na: 656.3020; found: 656.3002.

1-Benzyl 2-Methyl (2*R*,3*S*,4*R*)-4-[2-(Benzyloxy)ethyl]-3-hydroxy-3-methyl-5-oxo-2-vinylpyrrolidine-1,2-dicarboxylate (29)

To a solution of **26** (146 mg, 0.230 mmol) in CH_2Cl_2 (4 mL) were added TFA (1.6 mL) and H_2O (0.4 mL) at 0 °C, and the mixture was stirred at this temperature for 2.5 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with aq 1 M NaOH (20 mL) and brine (20 mL). The organic layer was dried and concentrated to give crude **27** (98 mg, 96%). To a solution of crude aminal **27** (98 mg, 0.22 mmol) in acetone–H_2O (4:1, 4 mL) was added Jones reagent (1.29 mL, 3.45 mmol) at 0 °C, and the mixture was stirred at this temperature for 2.5 h. The mixture was quenched with *i*-PrOH (0.5 mL) and then diluted with EtOAc (20 mL). The mixture was washed successively with H_2O (20 mL) and brine (20 mL). The organic layer was dried and concentrated to give a residue, which was roughly purified by silica gel column chromatography (EtOAc–hexane, 1:2) to give crude **28** as a pale yellow solid. To a solution of crude **28** in *t*-BuOH–H_2O (3:1, 3 mL) at r.t. were added NaH_2PO_4 (93 mg, 0.78 mmol), 2-methylbut-2-ene (0.16 mL, 1.6 mmol) and $NaClO_2$ (70 mg, 0.78 mmol). After stirring for 12 h, the reaction was diluted with EtOAc (15 mL). The mixture was washed successively with aq 5% $Na_2S_2O_3$ (15 mL) and brine (15 mL). The organic layer was dried and concentrated to give the intermediate carboxylic acid. To a solution of the crude carboxylic acid in DMF (2 mL) at r.t. were added K_2CO_3 (64 mg, 0.47 mmol) and MeI (30 μL, 0.47 mmol). After stirring for 1.5 h, the mixture was diluted with EtOAc (20 mL) and washed successively with H_2O (20 mL) and brine (20 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:2) to give **29** (48 mg, 44% from **26**) as a colorless syrup; $[\alpha]_D^{27}$ –9.9 (*c* 0.73, $CHCl_3$).

IR (neat): 3480, 2930, 1790, 1730, 1280 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 10 H, C_6H_5), 6.46 (dd, *J* = 17.7, 10.8 Hz, 1 H, C*H*=CH_2), 5.29 (d, *J* = 12.6 Hz, 1 H, PhCH_2), 5.27 (d, *J* = 10.8 Hz, 1 H, CH=CH_2), 5.21 (d, *J* = 12.6 Hz, 1 H, PhCH_2), 5.01 (d, *J* = 17.7 Hz, 1 H, CH=CH_2), 4.53 (d, *J* = 11.7 Hz, 1 H, PhCH_2), 4.46 (d, *J* = 11.7 Hz, 1 H, PhCH_2), 3.95 (br s, 1 H, OH), 3.81 (m, 1 H, BnOCH_2), 3.66 (m, 1 H, BnOCH_2), 2.70 (dd, *J* = 6.6, 5.1 Hz, 1 H, H-4), 2.09–2.01 (m, 2 H, $BnOCH_2CH_2$), 1.37 (s, 3 H, CCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 168.3, 151.0, 137.4, 135.2, 133.3, 129.5, 128.5, 128.4, 128.3, 128.1, 127.9, 114.7, 77.8, 73.2, 68.6, 68.2, 67.0, 52.5, 47.8, 23.6, 21.7.

HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{26}H_{29}NO_7$ + Na: 490.1842; found: 490.1855.

1-Benzyl 2-Methyl (2*R*,3*S*,4*R*)-4-[2-(Benzyloxy)ethyl]-3-methyl-5-oxo-3-trimethylsilyloxy-2-vinylpyrrolidine-1,2-dicarboxylate (30)

To a solution of alcohol **29** (9.4 mg, 0.020 mmol) in CH_2Cl_2 (1 mL) were added pyridine (10 μL, 0.12 mmol) and TMSOTf (11 μL, 0.055 mmol) at 0 °C. After stirring for 30 min, the mixture was diluted with CH_2Cl_2 (10 mL). The mixture was washed successively with aq 0.5 M HCl (10 mL) and brine (20 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:5 → 1:2) to give **30** (10.6 mg, 98%) as a colorless syrup; $[\alpha]_D^{25}$ +41.7 (*c* 0.88, $CHCl_3$).

IR (neat): 2960, 1800, 1770, 1730, 1290 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 10 H, C_6H_5), 6.44 (dd, *J* = 17.4, 10.5 Hz, 1 H, C*H*=CH_2), 5.28 (d, *J* = 12.3 Hz, 1 H, PhCH_2), 5.27 (d, *J* = 10.5 Hz, 1 H, CH=CH_2), 5.18 (d, *J* = 12.3 Hz, 1 H, PhCH_2), 4.99 (d, *J* = 17.4 Hz, 1 H, CH=CH_2), 4.50 (s, 2 H, PhCH_2), 3.74 (dd, *J* = 7.2, 4.8 Hz, 2 H, BnOCH_2), 3.53 (s, 3 H, CO_2CH_3), 2.60 (dd, *J* = 8.4, 3.6 Hz, 1 H, H-4), 1.96 (m, 1 H, $BnOCH_2CH_2$), 1.66 (m, 1 H, $BnOCH_2CH_2$), 1.47 (s, 3 H, CCH_3), 0.07 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 168.5, 151.1, 138.4, 135.3, 133.3, 128.4, 128.3, 128.2, 128.0, 127.6, 127.5, 114.8, 82.6, 78.2, 72.9, 68.0, 67.8, 52.3, 47.6, 24.5, 20.8, 2.5.

HRMS-FAB: *m*/*z* [M + H^+] calcd for $C_{29}H_{38}NO_7Si$: 540.2418; found: 540.2406.

1-Benzyl 2-Methyl (2*S*,3*S*,4*R*)-4-[2-(Benzyloxy)ethyl]-2-formyl-3-methyl-5-oxo-3-trimethylsilyloxypyrrolidine-1,2-dicarboxylate (7)

To a solution of **30** (22 mg, 0.041 mmol) in *t*-BuOH–H_2O (1:1, 2 mL) at r.t. were added OsO_4 (0.25 M in *t*-BuOH, 0.16 mL, 0.040 mmol), $NaIO_4$ (87 mg, 0.41 mmol), and pyridine (33 μL, 0.41 mmol). After stirring at 50 °C for 38 h, the mixture was diluted with EtOAc (10 mL) and washed successively with H_2O (10 mL) and brine (20 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:5 → 1:3) to give **7** (13.7 mg, 62%) as a colorless oil; $[\alpha]_D^{25}$ +62.7 (*c* 0.85, $CHCl_3$).

IR (neat): 2960, 2860, 1800, 1770, 1730, 1380, 1310 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.10 (s, 1 H, CHO), 7.38–7.26 (m, 10 H, C_6H_5), 5.29 (d, *J* = 12.3 Hz, 1 H, PhCH_2), 5.17 (br d, *J* = 12.3 Hz, 1 H, PhCH_2), 4.53 (d, *J* = 11.7 Hz, 1 H, PhCH_2), 4.46 (d, *J* = 11.7 Hz, 1 H, PhCH_2), 3.73–3.67 (m, 2 H, BnOCH_2), 3.65 (s, 3 H, CO_2CH_3), 2.61 (dd, *J* = 8.4, 3.9 Hz, 1 H, H-4), 1.95 (m, 1 H, $BnOCH_2CH_2$), 1.68 (m, 1 H, $BnOCH_2CH_2$), 1.53 (s, 3 H, CCH_3), 0.10 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.9, 172.9, 166.9, 138.3, 134.9, 128.6, 128.4, 128.0, 127.7, 127.6, 81.5, 81.1, 73.1, 68.7, 67.6, 52.6, 49.3, 24.6, 21.3, 2.5.

HRMS-ESI: *m*/*z* [M + H^+] calcd for $C_{28}H_{36}NO_8Si$: 542.2210; found: 542.2211.

1-Benzyl 2-Methyl (2*R*,3*S*,4*R*)-4-[2-(Benzyloxy)ethyl]-2-{(*S*)-[(*S*)-cyclohex-2-enyl)](hydroxyl)methyl}-3-methyl-5-oxo-3-trimethylsilyloxypyrrolidine-1,2-dicarboxylate (31)

To a solution of tri-*n*-butyl(cyclohex-2-enyl)stannane (131.6 mg, 0.355 mmol) in THF (3 mL) at –78 °C was added *n*-BuLi (1.59 M in hexane, 0.22 mL, 0.350 mmol). After stirring at –78 °C for 20 min, to this mixture was added $ZnCl_2$ (0.5 M in THF, 0.71 mL, 0.355 mmol) and the mixture was further stirred at –78 °C for 20 min. To the resulting solution of the cyclohex-2-enylzinc chloride at –78 °C was added a solution of aldehyde **30** (31.0 mg, 0.0572 mmol) in THF (1.2 mL) via cannula and the mixture was stirred at this temperature for 1 h. The mixture was quenched with H_2O (0.5 mL) and diluted with EtOAc (20 mL). The mixture was washed successively with aq sat. NH_4Cl (10 mL) and brine (10 mL). The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane, 1:5 → 1:3) to give **31** (32.0 mg, 90%) as a colorless syrup; $[\alpha]_D^{24}$ –11.0 (*c* 0.73, $CHCl_3$).

IR (neat): 3200, 2960, 2860, 1750, 1705, 1460, 1380, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 10 H, C_6H_5), 6.01 (s, 1 H, OH), 5.65 (m, 1 H, CH=C*H*), 5.46 (m, 1 H, CH=C*H*), 5.12 (d, *J* = 3.8 Hz, 1 H, HOC*H*), 5.09 (d, *J* = 12.0 Hz, 1 H, PhCH_2), 4.96 (d, *J* = 12.0 Hz, 1 H, PhCH_2), 4.48 (s, 2 H, PhCH_2), 3.76 (s, 3 H, OCH_3), 3.76–3.66 (m, 2 H, BnOCH_2), 2.68 (dd, *J* = 9.0, 3.6 Hz, 1 H, H-4), 2.28 (m, 1 H, CH_2CH=CHC*H*), 1.90–1.84 (m, 3 H, $BnOCH_2CH_2$ and CHCH=CHCH_2), 1.71–1.40 (m, 5 H, $BnOCH_2CH_2$ and CH_2 of cyclohexene), 1.45 (s, 3 H, CCH_3), 0.07 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.7, 169.2, 154.4, 138.8, 135.2, 130.0, 128.5, 128.3, 128.0, 127.5, 127.4, 124.8, 86.6, 80.0, 76.3, 72.9, 69.8, 68.5, 52.4, 48.5, 38.2, 27.5, 25.2, 24.5, 21.3, 20.6, 2.7.

HRMS-ESI: *m*/*z* [M + H^+] calcd for $C_{34}H_{46}NO_8Si$: 624.2993; found: 624.3006.

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To a solution of **31** (29.5 mg, 0.0472 mmol) in CH_2Cl_2 (3 mL) was added BCl_3 (1 M in heptane, 0.19 mL, 0.19 mmol) at –20 °C. The reaction mixture was warmed to 0 °C and further stirred for 30 min at 0 °C. After the addition of MeOH (0.5 mL) at 0 °C, the mixture was concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–MeOH, 1:0 → 20:1) to afford **6** (12.1 mg, 78%) as an amorphous solid; $[\alpha]_D^{24}$ –54.4 (*c* 0.60, $CHCl_3$) {Lit.[6j] $[\alpha]_D^{26}$ –50.0 (*c* 1.56, $CHCl_3$)}.

IR (neat): 3300, 2930, 2860, 1725, 1690, 1680, 1435, 1380, 1280 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.40 (br s, 1 H, NH), 6.10 (m, 1 H, HC=C*H*), 5.75 (m, 1 H, HC=C*H*), 5.19 (br s, 1 H, OH), 4.14 (br d, *J* = 8.0 Hz, 1 H, HOC*H*), 4.10 (br s, 1 H, OH), 3.84 (s, 3 H, OCH_3), 3.82 (dt, *J* = 4.9, 10.6 Hz, 1 H, HOCH_2), 3.74 (dt, *J* = 4.0, 10.6 Hz, 1 H, HOCH_2), 2.83 (dd, *J* = 2.6, 10.3 Hz, 1 H, H-4), 2.21 (m, 1H, CH_2CH=CHC*H*), 2.01 (br s, 1 H, OH), 1.98–1.93 (m, 3 H, CHCH=CHCH_2 and $HOCH_2CH_2$), 1.83–1.71 (m, 3 H, $HOCH_2CH_2$ and CH_2 of cyclohexene), 1.64–1.58 (m, 2 H, CH_2 of cyclohexene), 1.56 (s, 3 H, CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.6, 172.7, 135.3, 123.3, 81.7, 79.9, 75.3, 62.2, 52.9, 51.6, 38.6, 28.7, 26.2, 24.8, 20.3, 19.8.

HRMS-FAB: *m*/*z* [M + H^+] cacld for $C_{16}H_{26}NO_6$: 328.1760; found: 328.1750.

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