Role of Conformational Effects on the Regioselectivity of Macrocyclic INOC Reactions: Two New Asymmetric Total Syntheses of (+)-Brefeldin A[†,1]

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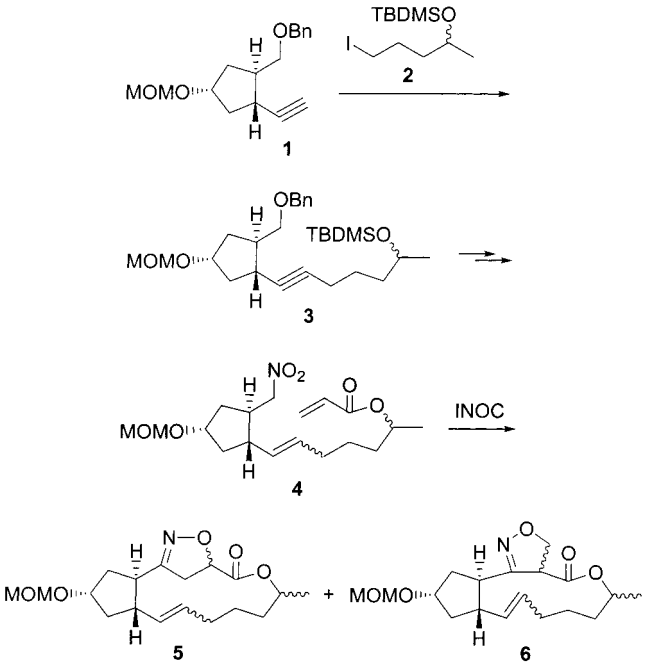
We have gained some insight into the role of conformational effects on the regioselectivity of the macrocyclic intramolecular nitrile oxide cycloaddition observed in our (+)-brefeldin A synthesis. During the course of this regiochemical study, we have developed two novel stereoselective and regioselective schemes for total synthesis of (+)-brefeldin A (i.e. intramolecular nitrile oxide cycloaddition−isomerization and intermolecular nitrile oxide cycloaddition−ring closing metathesis strategies).

Introduction

In the preceding paper[2] we described an asymmetric total synthesis of (+)-brefeldin A taking advantage of a triple chirality transfer process for remote stereocontrol. An intramolecular nitrile oxide cycloaddition (INOC) reaction was utilized for the efficient construction of the macrocycle but unfortunately was nonregioselective. The regioselectivity problem was overcome by way of intermolecular nitrile oxide cycloaddition and macrolactonization route, which is somewhat less efficient.

Previous studies on the macrocyclic INOC reactions by Asaoka showed that the regioselectivity between bridged and fused isomers is dependent upon the ring size.[3] In the case of a 13-membered ring, which is of relevance to us, the desired bridged isomers are favored over the fused isomers in the ratio of about 5:1. To understand our observed regiochemical discrepancy with Asaoka's model system (bridged isomers:fused isomer = 1:1 compared to 5:1), we decided to synthesize all four possible diastereomers of INOC substrates **4** as shown in Scheme 1. We felt that Mori-type[4] intermediate **1** would be ideal for our purposes, since we could obtain both trans and cis olefins from an acetylene functional group by either a dissolving metal reduction or a partial catalytic hydrogenation, respectively.

Scheme 1



Results and Discussion

To obtain the key intermediate **1**, we developed a shorter stereorational synthetic route rather than employing Mori's synthesis, as depicted in Scheme 2. Silyl protection of the primary alcohol of readily available lactone **7**,[5] followed by vinyl cuprate addition,[6] provided lactone **8** in 81% overall yield. Lactone opening with a catalytic amount of titanium tetraisopropoxide in methanol[7] afforded hydroxy ester **9** with minimum migration of the silyl group. After protection of the secondary

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† Dedicated to Professor Steven M. Weinreb on the occasion of his 60th birthday.

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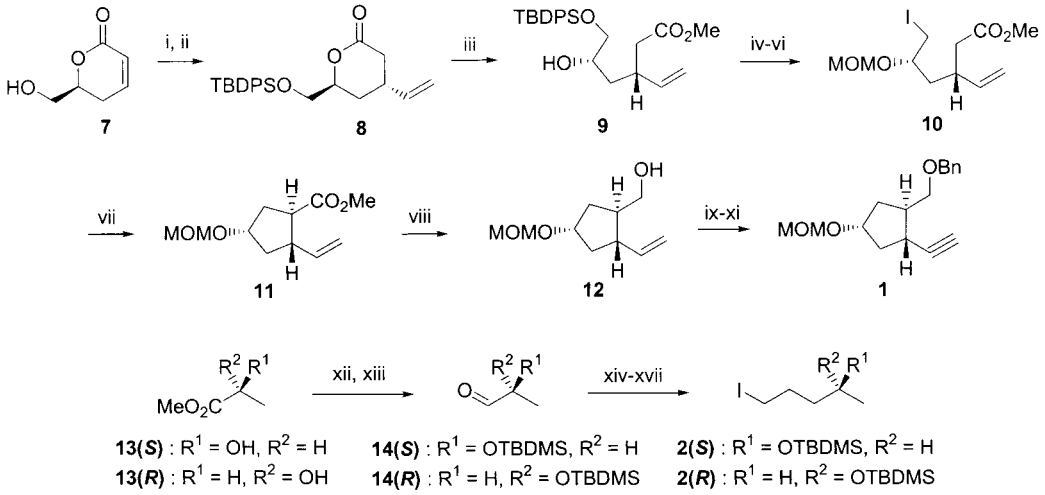
Scheme 2[a]



[a]Key: (i) TBDPSCl, DMAP, Et_3N, rt, CH_2Cl_2, 97%; (ii) CH_2=CHMgBr, CuI, slow addition for 3 h, −35 to −25 °C, 83%; (iii) Ti(O-*i*-Pr)$_4$, MeOH, reflux, overnight, 88% (based on 92% conversion); (vi) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 18 h, 98%; (v) TBAF, THF, rt, overnight, 96%; (vi) I_2, Ph_3P, imidazole, THF, rt, 3 h, 96%; (vii) LHMDS, THF, 0 °C, 30 min, 92%; (viii) $LiAlH_4$, THF, 0 °C, 2 h, 100%; (ix) BnBr, TBAI, NaH, DMF, rt, overnight, 96%; (x) pyr·HBr_3, pyridine, CH_2Cl_2, 0 °C, 40 min, 82%; (xi) $NaNH_2$, NH_3, reflux, 30 min, 81%; (xii) TBDMSCl, imidazole, DMF, rt, 1 h, 99%; (xiii) DIBALH, toluene, −78 °C, 30 min, 77%; (xiv) Ph_3P=$CHCO_2Et$, CH_2Cl_2, 40 °C, 1 h, 82−95%; (xv) H_2, Pd/Al_2O_3, hexane, rt, 5 h, 99%; (xvi) $LiAlH_4$, THF, 0 °C to room temperature, 1 h, 92%; (xvii) I_2, Ph_3P, imidazole, THF, 0 °C to room temperature, 30 min, 87−92%.

hydroxyl group of **9** as a MOM ether, deprotection of the silyl group and subsequent iodination gave the intramolecular ester enolate alkylation substrate **10**. The intramolecular cyclization of ω-iodo ester **10** was successfully performed under standard conditions[8] (LHMDS, THF, 0 °C) to produce the desired cyclopentanecarboxylate **11** with excellent stereoselectivity and in high yield (92%).

With ester **11** in hand, the elaboration of cyclopentanecarboxylate **11** to the key intermediate **1** proceeded without difficulty. First, the ester group of **11** was reduced to the corresponding alcohol **12**. After alcohol protection as a benzyl ether, the olefin moiety of compound **12** was converted to an acetylene via the dibromide,[9] furnishing the desired Mori-type[4] intermediate **1**.

We next synthesized two optically active alkylating agents **2**(*S*) and **2**(*R*) from the commercially available methyl lactates **13** via a conventional six-step sequence. Protection of the hydroxyl groups of methyl lactates **13** as the silyl ethers and subsequent reduction with DIBALH generated the corresponding known aldehydes **14**.[10] Three-step chain elongation, involving a Wittig reaction and a catalytic hydrogenation followed by reduction with $LiAlH_4$, afforded the corresponding alcohols. These alcohols were then treated with iodine and triphenylphosphine to give iodides **2**(*S*) and **2**(*R*) in good overall yield.

With all the fragments necessary for the acetylenic coupling reactions[11] in hand, we were able to synthesize all four possible isomers as planned (Scheme 3). Couplings between the lithium acetylide of **1** and the corresponding iodides, **2**(*S*) and **2**(*R*), afforded **3**(*S*) and **3**(*R*), respectively. The acetylenes **3** were reduced to the trans and cis olefins by a dissolving metal reduction and partial catalytic hydrogenation, respectively, to furnish the four isomers **15**. Access to all four INOC substrates **4** was secured by applying the following four-step sequence to **15**: iodination of the primary hydroxyl group, transformation to nitro compound **16**,[12] deprotection of the silyl ether by mild acid treatment, and acryloylation led to the requisite four INOC substrates **4**.

The four isomers **4** were then subjected to the INOC reactions,[13] and the regiochemical outcome is summarized in Scheme 3.[14] The most important isomer, **4a** (trans, C15-(*S*)), required for the synthesis of (+)-brefeldin A, exhibited the worst regioselectivity. In contrast, the desired bridged isomers were formed almost exclusively in the cases of **4b** (cis, C15-(*S*)) and **4c** (trans, C15-(*R*)). To understand the conformational effects on INOC reactions, we performed MM2 calculations as summarized in Table 1. The transition state structures were generated by a systematic multiconformer conformational search and subsequent MM2 energy minimizations using the force field methods (rigid model) described by Houk.[15] The observed stereoselectivity at C2 of the INOC reactions is consistent with the calculated results except for bridged isomers **5d** (cis, C15-(*R*)). Our regioselectivity data for the INOC reactions cannot be fully explained by calculations, which did not take the electronic effect of the carbonyl groups into account. However, it could be inferred from the calculated data that the lower energy transition states for **6a** (C2-(*S*)) compared to the fused

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(8) (a) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945. (b) Kim, D.; Kim, I. H. *Tetrahedron Lett.* **1997**, *38*, 415 and references cited.

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(13) The experimental procedure of INOC of **4a** was described in the preceding paper.[2]

(14) For the structure determination of INOC products **5a**−**d** and **6a**−**d**, see the Supporting Information.

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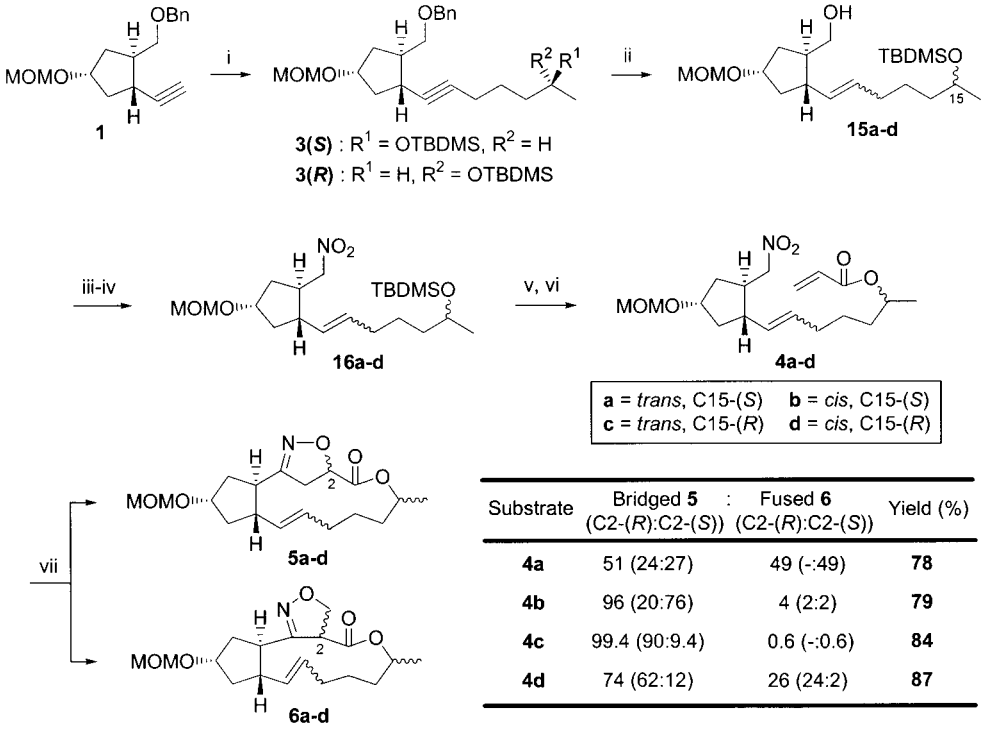
Scheme 3[a]



Substrate	Bridged **5** (C2-(*R*):C2-(*S*))	Fused **6** (C2-(*R*):C2-(*S*))	Yield (%)
4a	51 (24:27)	49 (-:49)	**78**
4b	96 (20:76)	4 (2:2)	**79**
4c	99.4 (90:9.4)	0.6 (-:0.6)	**84**
4d	74 (62:12)	26 (24:2)	**87**

[a] Key: (i) *n*-BuLi, HMPA/THF (7:11), **2(*S*)** or **2(*R*)**, 0 °C, 25 min then rt, 1 h, 78−81%; (ii) (a) Na, NH_3/THF, −78 °C, 1 h, 71% (trans), (b) Pd/$CaCO_3$/Pb, quinoline, H_2, hexane, rt, 8 h, 85−92%; Na, NH_3/THF, −78 °C, 1 h, 94−99% (cis); (iii) I_2, Ph_3P, imidazole, THF, rt, 30 min, 95−99%; (iv) $NaNO_2$, urea, DMF, rt, 12 h, 67−72%; (v) PPTS, ethanol, 50 °C, 12 h, 78−97%; (vi) CH_2=CHCOCl, *N*,*N*-dimethylaniline, CH_2Cl_2, 0 °C, 30 min, 81−89%; (vii) *p*-ClC_6H_4NCO, Et_3N, benzene, reflux, 20 h, 78−87%.

Table 1. MM2 Calculations of INOC Reactions

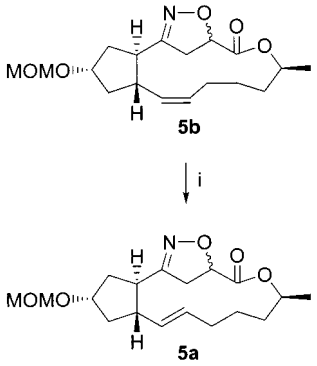
substrate	param	bridged **5** C2-(*R*):C2-(*S*)	fused **6** C2-(*R*):C2-(*S*)
4a	expt	47:53	<1:>99
	calcd	65:35	<1:>99
	energy	0.00:0.31	6.52:0.00
	(kcal/mol)	(113.86)	(53.07)
4b	expt	21:79	50:50
	calcd	30:70	23:77
	energy	−0.10:0.09	3.59:2.90
4c	expt	91:9	<1:>99
	calcd	86:14	<1:>99
	energy	−0.22:1.43	4.48:0.57
4d	expt	84:16	92:8
	calcd	22:78	88:12
	energy	0.75:0.11	1.94:3.18

isomers **6b**−**d** are responsible for the observed poor regioselectivity.

From a synthetic point of view, conversion of bridged isomers **5b** (cis, C15-(*S*)) to the corresponding isomers **5a** (trans, C15-(*S*)) as shown in Scheme 4 constitutes a regioselective synthesis of (+)-brefeldin A based on the INOC strategy. After some experimentation, we found to our delight that treatment of the cis isomers **5b** with thiophenol and AIBN in refluxing benzene[16] produced the corresponding trans isomers **5a** (82% based on 55% conversion), which have been converted to (+)-brefeldin A as described in our preceding paper.[2]

In addition, this isomerization result prompted us to test the intermolecular nitrile oxide cycloaddition−ring closing metathesis (RCM) strategy outlined in Scheme 5, which we believed might be attractive for reasons of

Scheme 4[a]



[a] Key: (i) PhSH, AIBN, benzene, reflux, 5 h, 81−82% based on 55−56% conversion.

improved brevity and efficiency. The required nitro compound **17** for this new strategy was prepared from the previously mentioned alcohol **12** in two steps in 80% yield. Routine intermolecular nitrile oxide cycloaddition between nitro compound **17** and optically active acrylate **19**[17] furnished a separable 1:1 mixture of the bridged products **20** and **21**. To our surprise, only C2-(*R*) isomer **21** provided the key (+)-brefeldin A intermediates **23** (trans:cis = 2.2:1, 42%) under typical RCM conditions.[18]

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(17) The optically active acrylate **19** was synthesized from known (*S*)-heptenol (**18**) by treatment with acryloyl chloride and *N*,*N*-dimethylamine in 83% yield. For a preparation of (*S*)-heptenol (**18**), see: Kobayashi, Y.; Watatani, K.; Kikori, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 6125.

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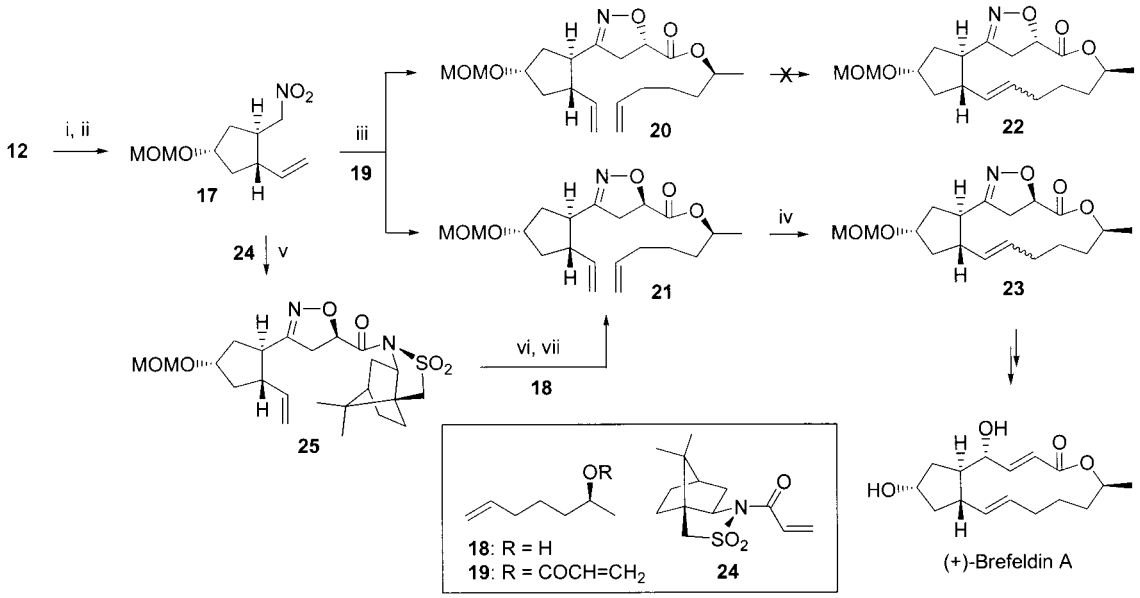
Scheme 5[a]



[a] Key: (i) I_2, Ph_3P, imidazole, THF, rt, 4 h, 93%; (ii) $NaNO_2$, urea, DMSO, rt, 6 h, 76%; (iii) *p*-ClC_6H_4NCO, Et_3N, benzene, reflux, 24 h, 85%; (iv) $Cl_2(Cy_3P)_2RuCHC_6H_5$, CH_2Cl_2, reflux, 42% (*E*/*Z* = 2.2:1); (v) *p*-ClC_6H_4NCO, Et_3N, benzene, reflux, overnight, 76%; (vi) $LiOH{\cdot}H_2O$, THF/H_2O (2:1), rt, 12 h; (vii) (a) 2,4,6-trichlorobenzoyl chloride, THF, rt, 4 h, (b) DMAP, toluene, reflux, 18 h, 72% for the two steps.

We could synthesize the important C2-(*R*) isomer **21** in a stereoselective manner by using the acrylate derivative **24** of Oppolzer's camphor sultam.[19] The intermolecular nitrile oxide cycloaddition between nitro compound **17** and acrylamide **24** yielded the bridged product **25** with high diastereoselectivity (94:6).[20] Hydrolysis of sultam **25**, followed by esterification[21] with alcohol **18**, led to the C2-(*R*) isomer **21** in high overall yield.

Conclusion

In conclusion, we have gained some insight into the role of conformational effects on the regioselectivity of the macrocyclic INOC in our (+)-brefeldin A synthesis. During the course of this regiochemical study, we have developed two novel stereoselective and regioselective schemes for total synthesis of (+)-brefeldin A (i.e. INOC isomerization and intermolecular nitrile oxide cycloaddition−RCM strategies).

Experimental Section

General Methods. All chemicals were reagent grade and used as purchased. All moisture-sensitive reactions were performed under an inert atmosphere of N_2 or Ar using distilled dry solvents. Reactions were monitored by TLC analysis using E. Merck silica gel 60 F_{254} thin layer plates. Flash chromatography was carried out on E. Merck silica gel 60 (230−400 mesh). Optical rotations were measured using sodium light (D line 589.3 nm).

(6*S*,4*R*)-6-(*tert*-Butyldiphenylsilanyloxymethyl)-4-vinyltetrahydropyran-2-one (8). 1. Protection of Hydroxyl Group. A mixture of alcohol **7** (62.0 mg, 0.48 mmol), DMAP (59 mg, 0.48 mmol), Et_3N (0.61 mL, 4.38 mmol), and TBDPSCl (0.38 mL, 1.46 mmol) in CH_2Cl_2 (2.4 mL) was stirred for 72 h at room temperature and filtered through a pad of silica gel. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to afford the silyl ether (172.0 mg, 97%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (t, J = 7.8 Hz, 2H), 7.67 (t, J = 7.7 Hz, 2H), 7.45−7.38 (m, 6H), 6.88 (ddd, J = 9.6, 6.0, 2.7 Hz, 1H), 6.00 (dd, J = 9.8, 1.9 Hz, 1H), 4.51 (dddd, J = 11.2, 4.6, 4.6, 4.6 Hz, 1H), 3.87−3.81 (m, 2H), 2.59 (dddd, J = 18.5, 11.3, 2.6, 2.6 Hz, 1H), 2.41 (ddd, J = 18.5, 4.9, 4.9 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8, 145.0, 135.44, 135.37, 132.7, 132.6, 129.8, 127.7, 120.9, 77.5, 64.5, 26.6, 25.7, 19.1; IR (neat) 1731 cm^{-1}; $[\alpha]^{20}_D = -52.3$ (c = 1.8, $CHCl_3$); HRMS (EI) calcd for $C_{21}H_{23}O_3Si$ (M^+ − Me) 351.1416, found 351.1420.

2. Cuprate Addition. To a suspension of CuI (145 mg, 0.76 mmol) in anhydrous THF (4.0 mL) was added vinylmagnesium bromide (3.8 mL, 1.0 M solution in THF) at −78 °C. After 30 min at −35 °C, the above silyl ether (557.0 mg, 1.52 mmol) in THF (8.0 mL) was added slowly to the cuprate mixture over 3 h at −35 to −25 °C. The mixture was stirred for 1 h at the same temperature and was quenched with saturated aqueous NH_4Cl solution. The mixture was filtered through a pad of Celite, and the filtrate was concentrated at reduced pressure. The resulting residue was dissolved in EtOAc, and the solution was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to afford lactone **8** (494.5 mg, 83%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67−7.65 (m, 4H), 7.46−7.39 (m, 6H), 5.81 (ddd, J = 17.0, 10.6, 6.2 Hz, 1H), 5.14 (d, J = 10.4 Hz, 1H), 5.09 (d, J = 17.2 Hz, 1H), 4.48 (dddd, J = 8.3, 4.4, 4.4, 4.4 Hz, 1H), 3.80−3.75 (m, 2H), 2.88−2.82 (m, 1H), 2.63 (dd, J = 17.2, 5.7 Hz, 1H), 2.46 (dd, J = 17.2, 7.7 Hz, 1H), 2.10 (ddd, J = 13.9, 8.2, 5.6 Hz, 1H), 1.85−1.80 (m, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 139.2, 135.5, 135.4, 132.7, 132.5, 129.8, 127.7, 115.3, 77.1, 65.2, 34.4, 32.2, 29.3, 26.6, 19.1; IR (neat) 1739 cm^{-1}; $[\alpha]^{20}_D = +25.1$ (c = 2.0, $CHCl_3$); HRMS (EI) calcd for $C_{24}H_{30}O_3Si$ (M^+) 394.1964, found 394.1956.

(3*R*)-3-[(2*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-2-hydroxypropyl]pent-4-enoi c Acid Methyl Ester (9). To a solution of lactone **8** (356.0 mg, 0.90 mmol) in dry MeOH (9.0 mL) was added Ti(O-*i*-Pr)$_4$ (0.27 mL, 0.91 mmol) at room temperature. The mixture was refluxed for 24 h and filtered through a pad of Celite. The filtrate was concentrated at

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reduced pressure, and the resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to give hydroxy ester **9** (275.6 mg, 88% based on 92% conversion): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67−7.64 (m, 4H), 7.44−7.38 (m, 6H), 5.67 (ddd, J = 17.1, 10.3, 8.3 Hz, 1H), 4.97 (d, J = 10.2 Hz, 1H), 4.95 (d, J = 17.4 Hz, 1H), 3.79−3.73 (m, 1H), 3.66 (dd, J = 10.1, 3.5 Hz, 1H), 3.63 (s, 3H), 3.49 (dd, J = 10.2, 7.4 Hz, 1H), 2.65−2.58 (m, 1H), 2.58 (d, J = 3.5 Hz, 1H), 2.41 (dd, J = 15.1, 6.0 Hz, 1H), 2.30 (dd, J = 15.0, 8.2 Hz, 1H), 1.56 (ddd, J = 13.9, 7.7, 7.7 Hz, 1H), 1.48 (ddd, J = 13.9, 6.1, 6.1 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 140.7, 135.53, 135.51, 133.09, 133.07, 129.8, 127.8, 115.2, 69.8, 67.6, 51.4, 39.5, 37.3, 37.1, 26.8, 19.2; IR (neat) 3462, 1739 cm^{-1}; $[\alpha]^{20}_D$ = +6.2 (c = 0.97, $CHCl_3$); HRMS (FAB) calcd for $C_{21}H_{25}O_4Si$ (M^+ − t-Bu) 369.1522, found 369.1515.

(3*R*)-3-[(2*S*)-3-Iodo-2-(methoxymethoxy)propyl]pent-4-enoic Acid Methyl Ester (10). 1. Protection of Hydroxyl Group. A mixture of alcohol **9** (275.6 mg, 0.65 mmol), MOMCl (0.15 mL, 1.97 mmol), and diisopropylethylamine (0.68 mL, 3.90 mmol) in CH_2Cl_2 (2.2 mL) was stirred for 18 h at room temperature and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to afford the MOM ether (276.2 mg, 91%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69−7.67 (m, 4H), 7.45−7.37 (m, 6H), 5.66 (ddd, J = 16.9, 10.5, 8.4 Hz, 1H), 4.98 (d, J = 10.0 Hz, 1H), 4.97 (d, J = 18.0 Hz, 1H), 4.77 (d, J = 6.8 Hz, 1H), 4.61 (d, J = 6.9 Hz, 1H), 3.72−3.66 (m, 1H), 3.65 (dd, J = 4.8, 2.2 Hz, 2H), 3.63 (s. 3H), 3.36 (s, 3H), 2.69−2.61 (m, 1H), 2.48 (dd, J = 14.8, 5.2 Hz, 1H), 2.26 (dd, J = 14.8, 9.2 Hz, 1H), 1.65 (ddd, J = 14.0, 6.5, 6.5 Hz, 1H), 1.58 (ddd, J = 14.0, 7.1, 7.1 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 140.6, 135.5, 133.2, 129.7, 127.7, 127.6, 115.3, 96.0, 75.5, 65.9, 55.6, 51.4, 39.4, 36.9, 36.3, 26.7, 19.1; IR (neat) 1739 cm^{-1}; $[\alpha]^{20}_D$ = −21.3 (c = 1.6, $CHCl_3$); HRMS (EI) calcd for $C_{26}H_{35}O_4Si$ (M^+ − OMe) 439.2305, found 439.2287.

2. Removal of Silyl Group. To a solution of the above silyl ether (142.5 mg, 0.30 mmol) in THF (1.0 mL) was added TBAF (0.33 mL, 1.0 M solution in THF) at room temperature. The mixture was stirred overnight and filtered through a pad of silica gel. The filtrate was concentrated at reduced pressure, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to afford the primary alcohol (67.5 mg, 96%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.67 (ddd, J = 17.3, 10.0, 8.5 Hz, 1H), 5.08 (d, J = 17.3 Hz, 1H), 5.04 (d, J = 10.0 Hz, 1H), 4.72 (d, J = 7.0 Hz, 1H), 4.67 (d, J = 7.0 Hz, 1H), 3.66 (s, 3H), 3.66−3.57 (m, 2H), 3.54−3.51 (m, 1H), 3.43 (s, 3H), 3.32 (br s, 1H), 2.68−2.61 (m, 1H), 2.43 (dd, J = 15.1, 6.0 Hz, 1H), 2.32 (dd, J = 15.1, 8.3 Hz, 1H), 1.66−1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 140.1, 115.5, 96.5, 64.8, 55.6, 51.5, 39.4, 36.9, 35.8; IR (neat) 3444, 1731 cm^{-1}; $[\alpha]^{20}_D$ = +45.1 (c = 2.4, $CHCl_3$); HRMS calcd for $C_{11}H_{19}O_4$ (M^+ −OH) 215.1283, found 215.1284.

3. Iodination. To a solution of the above primary alcohol (58.3 mg, 0.25 mmol) in THF (2.5 mL) were added Ph_3P (132 mg, 0.50 mmol), imidazole (51 mg, 0.75 mmol), and iodine (191 mg, 0.75 mmol) at 0 °C. After 3 h at room temperature, the mixture was filtered through a pad of silica gel and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to afford ω-iodo ester **10** (82.9 mg, 96%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.68 (ddd, J = 17.2, 10.1, 8.5 Hz, 1H), 5.08 (d, J = 17.2 Hz, 1H), 5.04 (d, J = 10.1 Hz, 1H), 4.69 (d, J = 7.2 Hz, 1H), 4.66 (d, J = 7.2 Hz, 1H), 3.66 (s, 3H), 3.42 (s, 3H), 3.42−3.36 (m, 2H), 3.32−3.27 (m, 1H), 2.67−2.60 (m, 1H), 2.45 (dd, J = 15.0, 5.8 Hz, 1H), 2.33 (dd, J = 15.0, 8.3 Hz, 1H), 1.74−1.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 140.0, 115.7, 95.8, 74.0, 56.1, 51.5, 39.61, 39.58, 36.9, 11.0; IR (neat) 1739, 1036 cm^{-1}; $[\alpha]^{20}_D$ = −4.7 (c = 1.8, $CHCl_3$); HRMS (FAB) calcd for $C_{11}H_{20}IO_4$ (MH^+) 343.0406, found 343.0400.

(1*R*,2*S*,4*S*)-4-(Methoxymethoxy)-2-vinylcyclopentanecarboxylic Acid Methyl Ester (11). To a solution of ω-iodo ester **10** (306 mg, 0.90 mmol) in THF (90 mL) was added LHMDS (2.7 mL, 1.0 M solution in THF). After 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and concentrated in vacuo. The resulting residue was dissolved in EtOAc, and the solution was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to afford cyclopentanecarboxylate **11** (177 mg, 92%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.82 (ddd, J = 17.2, 10.1, 7.2 Hz, 1H), 5.05 (d, J = 17.0 Hz, 1H), 4.98 (dd, J = 10.2, 1.3 Hz, 1H), 4.63 (s, 2H), 4.24 (dddd, J = 5.9, 5.2, 5.2, 5.2 Hz, 1H), 3.68 (s, 3H), 3.36 (s, 3H), 2.78−2.72 (m, 2H), 2.31 (ddd, J = 13.7, 7.5, 6.3 Hz, 1H), 2.07 (dd, J = 8.6, 5.1 Hz, 2H), 1.58 (ddd, J = 13.7, 8.9, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.5, 140.2, 114.6, 95.1, 76.9, 55.2, 51.6, 48.0, 46.3, 39.3, 36.9; IR (neat) 1732 cm^{-1}; $[\alpha]^{20}_D$ = −58.5 (c = 1.2, $CHCl_3$); HRMS (CI) calcd for $C_{11}H_{19}O_4$ (MH^+) 215.1283, found 215.1291.

[(1*R*,2*S*,4*S*)-4-(Methoxymethoxy)-2-vinylcyclopentyl]-methanol (12). A solution of cyclopentanecarboxylate **11** (189.6 mg, 0.89 mmol) in THF (3.0 mL) was added dropwise to a suspension of $LiAlH_4$ (53 mg, 1.40 mmol) in THF (4.0 mL) at 0 °C. After 2 h at the same temperature, water (0.05 mL), 3 N NaOH (0.05 mL), and water (0.15 mL) were sequentially added to the mixture. The mixture was stirred for 3 h and filtered through a pad of Celite. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to afford alcohol **12** (164.5 mg, 100%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.81 (ddd, J = 17.2, 9.9, 8.1 Hz, 1H), 5.03 (dd, J = 17.1, 1.5 Hz, 1H), 4.96 (dd, J = 10.0, 1.8 Hz, 1H), 4.64 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 7.3 Hz, 1H), 4.18−4.14 (m, 1H), 3.66 (dd, J = 10.4, 5.0 Hz, 1H), 3.50 (dd, J = 10.7, 6.4 Hz, 1H), 3.36 (s, 3H), 2.27−2.17 (m, 3H), 2.09−2.01 (m, 1H), 1.92 (ddd, J = 13.1, 8.5, 4.1 Hz, 1H), 1.67 (ddd, J = 13.5, 9.3, 7.0 Hz, 1H), 1.59−1.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.1, 114.2, 95.1, 76.9, 65.0, 55.2, 45.5, 45.2, 39.9, 35.9; IR (neat) 3444 cm^{-1}; $[\alpha]^{20}_D$ = −44.8 (c = 4.1, $CHCl_3$); HRMS (EI) calcd for $C_9H_{14}O_2$ (M^+ − MeOH) 154.0994, found 154.0981.

[(1*R*,2*R*,4*S*)-2-Ethynyl-4-(methoxymethoxy)cyclopentylmethoxymethyl]benzene (1). 1. Protection of the Hydroxyl Group. To a stirred suspension of NaH (321 mg, 7.36 mmol, 55% dispersion in oil) in THF (2.0 mL) was added dropwise a solution of alcohol **12** (914 mg, 4.91 mmol) in THF (9.8 mL). After 30 min, benzyl bromide (0.82 mL, 6.86 mmol) and tetrabutylammonium iodide (20 mg, 0.054 mmol) were added to the mixture at 0 °C. The mixture was stirred overnight at room temperature and poured into ice water. The mixture was extracted with ether (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to give the benzyl ether (1.303 g, 96%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.27 (m, 5H), 5.78 (ddd, J = 17.3, 9.9, 7.6 Hz, 1H), 4.96 (dd, J = 17.9, 1.7 Hz, 1H), 4.93 (dd, J = 10.5, 1.7 Hz, 1H), 4.63 (d, J = 6.7 Hz, 1H), 4.62 (d, J = 6.7 Hz, 1H), 4.53 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.17−4.13 (m, 1H), 3.49 (dd, J = 9.2, 4.4 Hz, 1H), 3.36 (s, 3H), 3.32 (dd, J = 9.2, 6.8 Hz, 1H), 2.25−2.18 (m, 2H), 2.14−2.08 (m, 1H), 1.98−1.92 (m, 1H), 1.78−1.71 (m, 1H), 1.59−1.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.0, 138.7, 128.3, 127.44, 127.41, 113.9, 95.2, 77.1, 73.0, 72.3, 55.2, 45.0, 43.5, 39.8, 36.5; IR (neat) 1642, 1042 cm^{-1}; $[\alpha]^{25}_D$ = −39.3 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{17}H_{24}O_3$ (M^+) 276.1725, found 276.1726.

2. Conversion of Double Bond to Triple Bond. A mixture of the above benzyl ether (4.00 g, 14.47 mmol), pyridinium tribromide (5.40 g, 15.23 mmol), and pyridine (1.2 mL, 15.23 mmol) in CH_2Cl_2 (38 mL) was stirred for 30 min at 0 °C. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to give the crude dibromide (5.50 g). To a solution of $NaNH_2$ (67.86 mmol) prepared from Na (1.56 g, 67.86 mmol) and $Fe(NO_3)_3$·$9H_2O$ (717 mg, 1.77 mmol) in refluxing ammonia (340 mL) was rapidly added a solution of the crude dibromide (5.50 g, 12.6 mmol) in THF (38 mL). The mixture was refluxed for 30 min, and to the

mixture was added portionwise NH_4Cl (1.30 g) with vigorous stirring at −78 °C. After the mixture was concentrated at reduced pressure, water and ether were added to the residue. The organic layer was separated, and the aqueous phase was reextracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give acetylene **1** (3.25 g, 82%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.26 (m, 5H), 4.63 (s, 2H), 4.54 (s, 2H), 4.15−4.10 (m, 1H), 3.58 (dd, J = 9.3, 4.3 Hz, 1H), 3.48 (dd, J = 9.3, 5.7 Hz, 1H), 3.36 (s, 3H), 2.51(ddd, J = 17.7, 9.0, 2.2 Hz, 1H), 2.48−2.37 (m, 2H), 2.07 (d, J = 2.3 Hz, 1H), 1.95−1.92 (m, 1H), 1.85−1.80 (m, 1H), 1.75−1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 128.3, 127.43, 127.39, 95.2, 87.0, 76.7, 73.0, 71.3, 68.4, 55.2, 45.1, 40.2, 35.9, 30.4; IR (neat) 3291, 2120 cm^{-1}; $[\alpha]^{27}_D$ = −70.9 (c = 1.0, CH_3OH); HRMS (EI) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1552.

(2*S*)-2-(*tert*-Butyldimethylsilanyloxy)propionaldehyde (14(*S*)). A mixture of lactate **13**(*S*) (1.00 g, 9.61 mmol), TBDMSCl (1.74 g, 11.54 mmol), and imidazole (981 mg, 14.41 mmol) in DMF (9.6 mL) was stirred for 1 h at room temperature. The mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to give the silyl ether (2.07 g, 99%). To a solution of the above silyl ether (1.00 g, 4.58 mmol) in toluene was added DIBALH (6.0 mL, 1.0 M in toluene) at −78 °C. After 30 min at the same temperature, methanol was added to the mixture. The white precipitate was filtered off using a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography (ether/hexane, 1:10) on silica gel to give lactaldehyde **14**(*S*) (664 mg, 77%) which, without characterization, was used in the next step.

***tert*-Butyl[(1*S*)-4-iodo-1-methylbutoxy]dimethylsilane (2(*S*)). 1. Wittig Reaction.** A mixture of aldehyde **14**(*S*)-(300 mg, 1.59 mmol) and (carbethoxymethylene)triphenylphosphorane (1.17 g, 3.36 mmol) in CH_2Cl_2 (3.2 mL) was refluxed for 1 h. The mixture was diluted with hexane and filtered through a short pad of silica gel. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:50) to give the α,β-unsaturated esters (336 mg, 82%). *Z*-Olefin: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.22 (dd, J = 11.6, 7.9 Hz, 1H), 5.65 (d, J = 11.6 Hz, 1H), 5.48−5.41 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.26 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9, 154.6, 116.9, 65.5, 60.1, 25.8, 23.5, 18.1, 14.2, −4.8, −4.9; IR (neat) 1717, 1652 cm^{-1}; $[\alpha]^{27}_D$ = +65.5 (c = 0.30, CH_3OH); HRMS (EI) calcd for $C_{13}H_{25}O_3Si$ (M^+ − H) 257.1573, found 257.1579. *E*-Olefin: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (dd, J = 15.5, 4.0 Hz, 1H), 5.98 (dd, J = 15.5, 1.6 Hz, 1H), 4.78−4.44 (m, 1H), 4.23−4.16 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 151.9, 118.9, 67.7, 60.3, 25.8, 23.5, 18.2, 14.2, −4.90, −4.92; IR (neat) 1716, 1660 cm^{-1}; $[\alpha]^{28}_D$ = +4.0 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{13}H_{26}O_3Si$ (M^+) 258.1651, found 258.1670.

2. Catalytic Hydrogenation. A mixture of the above α,β-unsaturated esters (336 mg, 1.30 mmol) and 5% Pd/Al_2O_3 (10 mg) in hexane (6.5 mL) was stirred under a hydrogen atmosphere for 5 h. The mixture was filtered through a short pad of Celite, and the filtrate was concentrated in vacuo to give the saturated ester (337 mg, 99%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.12 (q, J = 7.1 Hz, 2H), 3.86−3.82 (m, 1H), 2.41−2.30 (m, 2H), 1.77−1.66 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 67.4, 60.1, 34.3, 30.4, 25.8, 23.6, 18.0, 14.2, −4.5, −4.9; IR (neat) 1738 cm^{-1}; $[\alpha]^{25}_D$ = +25.0 (c = 1.0, CH_3OH).

3. $LiAlH_4$ Reduction. To a solution of the above ester (337 mg, 1.30 mmol) in THF (13 mL) was added portionwise $LiAlH_4$ (50 mg, 1.32 mmol) at 0 °C. The mixture was warmed to room temperature over 1 h and quenched with water (0.05 mL), 2 N NaOH (0.05 mL), and water (0.15 mL). The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give the alcohol (260 mg, 92%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.92−3.87 (m, 1H), 3.67−3.59 (m, 2H), 1.67−1.61 (m, 2H), 1.58−1.50 (m, 2H), 1.16 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.3, 63.0, 36.0, 28.5, 25.8, 23.2, 18.1, −4.5, −4.8; IR (neat) 3443, 1053 cm^{-1}; $[\alpha]^{25}_D$ = +11.2 (c = 1.1, C_2H_5OH); HRMS (EI) calcd for $C_{11}H_{25}O_2Si$ (M^+ − H) 217.1624, found 217.1618.

4. Iodination. To a stirred solution of the above alcohol (260 mg, 1.19 mmol) in THF (12 mL) was added imidazole (178 mg, 2.61 mmol) and Ph_3P (343 mg, 1.31 mmol). After 5 min, iodine (332 mg, 1.31 mmol) was added at 0 °C and the mixture was allowed to warm to room temperature over 30 min. The mixture was diluted with hexane and filtered through a short pad of silica gel. Concentration of the filtrate in vacuo and purification of the residue by column chromatography on silica gel (EtOAc/hexane, 1:30) afforded iodide **2**(*S*) (340 mg, 87%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.82 (sextet, J = 6.0 Hz, 1H), 3.19 (ddd, J = 7.0, 7.0, 1.4 Hz, 2H), 1.98−1.80 (m, 2H), 1.53−1.48 (m, 2H), 1.13 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 67.6, 40.3, 29.9, 25.9, 23.8, 18.1, 7.3, −4.4, −4.8; IR (neat) 2928 cm^{-1}; $[\alpha]^{25}_D$ = +13.9 (c = 1.0, C_2H_5OH); HRMS (EI) calcd for $C_{11}H_{24}IOSi$ (M^+ − H) 327.0641, found 327.0620.

{(1*S*)-6-[(1*R*,2*R*,4*S*)-2-(Benzyloxymethyl)-4-(methoxymethoxy)cyclopentyl]-1-methylhex-5-ynyloxy}-*tert*-butyldimethylsilane (3(*S*)). To a solution of acetylene **1** (1.888 g, 6.88 mmol) in THF (7.0 mL) was added dropwise *n*-BuLi (4.5 mL, 1.6 M solution in hexane) over 10 min at 0 °C. After 5 min, a solution of iodide **2**(*S*) (2.485 g, 7.60 mmol) in dry HMPA (11 mL) was added to the mixture over 10 min at 0 °C. The mixture was stirred at room temperature for 1 h, poured into ice water, and extracted with ether (100 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:13) to give acetylene **3**(*S*) (1.280 g, 81%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.33 (m, 4H), 7.29−7.26 (m, 1H), 4.62 (s, 2H), 4.53 (s, 2H), 4.13−4.09 (m, 1H), 3.81−3.76 (m, 1H), 3.60 (dd, J = 9.3, 4.0 Hz, 1H), 3.43 (dd, J = 9.3, 6.1 Hz, 1H), 3.36 (s, 3H), 2.43−2.30 (m, 3H), 2.16−2.13 (m, 2H), 1.93−1.90 (m, 1H), 1.76−1.69 (m, 2H), 1.58−1.42 (m, 4H), 1.12 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 128.3, 127.4, 95.2, 82.5, 80.5, 73.0, 71.8, 68.2, 55.3, 45.3, 40.7, 38.8, 35.9, 31.0, 25.9, 25.3, 23.8, 18.9, 18.1, −4.4, −4.7; IR (neat) 1042 cm^{-1}; $[\alpha]^{24}_D$ = −40.5 (c = 1.0, CH_3OH); HRMS (EI) calcd for $C_{24}H_{37}O_4Si$ (M^+ − *t*-Bu) 417.2461, found 417.2453.

{(1*R*)-6-[(1*R*,2*R*,4*S*)-2-(Benzyloxymethyl)-4-(methoxymethoxy)cyclopentyl]-1-methylhex-5-ynyloxy}-*tert*-butyldimethylsilane (3(*R*)). To a stirred solution of acetylene **1** (310 mg, 1.13 mmol) in THF (3.8 mL) was added dropwise *n*-BuLi (0.85 mL, 1.6 M solution in hexane) over 10 min at 0 °C. After 5 min, a solution of iodide **2**(*R*) (520 mg, 1.58 mmol) in dry HMPA (8.0 mL) was added to the mixture over 10 min at 0 °C. The mixture was stirred for 1 h at room temperature, poured into ice water, and extracted with ether (50 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 13:1) to give acetylene **3**(*R*) (416 mg, 78%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.33 (m, 4H), 7.29−7.26 (m, 1H), 4.62 (s, 2H), 4.53 (s, 2H), 4.13−4.09 (m, 1H), 3.81−3.76 (m, 1H), 3.60 (dd, J = 9.3, 4.0 Hz, 1H), 3.43 (dd, J = 9.3, 6.1 Hz, 1H), 3.36 (s, 3H), 2.43−2.30 (m, 3H), 2.16−2.13 (m, 2H), 1.93−1.90 (m, 1H), 1.76−1.69 (m, 2H), 1.58−1.42 (m, 4H), 1.12 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 128.3, 127.4, 95.2, 82.5, 80.5, 73.0, 71.8, 68.2, 55.3, 45.3, 40.7, 38.8, 36.0, 31.0, 25.9, 25.3, 23.7, 18.9, 18.1, −4.4, −4.7; IR (neat) 1042 cm^{-1}; $[\alpha]^{29}_D$ = −53.7 (c = 1.5, CH_3OH); HRMS (EI) calcd for $C_{28}H_{45}O_4Si$ (M^+ − H) 473.3087, found 473.3090.

{(1*R*,2*S*,4*S*)-2-[(1*E*,6*S*)-6-(*tert*-Butyldimethylsilanyloxy)-hept-1-enyl]-4-(methoxymethoxy)cyclopentyl}-methanol (15a). To a mixture of acetylene **3**(*S*) (974 mg, 2.05 mmol), THF (20 mL) and liquid ammonia (20 mL) was added portionwise Na (566 mg, 24.62 mmol), and the mixture was refluxed for 1 h. To the mixture was added portionwise NH_4Cl (1.00 g, 18.70 mmol) at −78 °C, and the mixture was concentrated at reduced pressure. Water and ether were added to the residue, the organic layer was separated, and the aqueous phase was reextracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give *E*-olefin **15a** (560 mg, 71%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.48−5.36 (m, 2H), 4.64 (d, J = 7.4 Hz, 1H), 4.63 (d, J = 7.4 Hz, 1H), 4.17−4.11 (m, 1H), 3.79−3.73 (m, 1H), 3.68−3.64 (m, 1H), 3.54−3.50 (m, 1H), 3.36 (s, 3H), 2.23 (ddd, J = 13.2, 6.6, 6.6 Hz, 1H), 2.18−2.10 (m, 1H), 2.06−1.96 (m, 3H), 1.92−1.88 (m, 1H), 1.67−1.60(m, 2H), 1.51 (ddd, J = 13.2, 9.8, 5.7 Hz, 1H), 1.46−1.28 (m, 4H), 1.11 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.044 (s, 3H), 0.041 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.8, 130.6, 95.2, 76.9, 68.4, 65.4, 55.2, 45.9, 44.4, 40.6, 39.1, 35.9, 32.3, 25.9, 25.6, 23.8, 18.1, −4.5, −4.8; IR (neat) 3444 cm^{-1}; $[\alpha]^{19}_D$ = −20.2 (c = 1.0, CH_3OH); HRMS (EI) calcd for $C_{19}H_{37}O_3Si$ (M^+ − MOM) 341.2512, found 341.2513.

***tert*-Butyl{(1*S*,5*E*)-6-[(1*S*,2*R*,4*S*)-(4-(methoxymethoxy)-2-(nitromethyl)cyclopentyl)]-1-methylhex-5-enyloxy}-dimethylsilane (16a). 1. Iodination.** To a solution of alcohol **15a** (440 mg, 1.14 mmol) in THF (11 mL) were added imidazole (201 mg, 2.96 mmol), Ph_3P (388 mg, 1.48 mmol), and iodine (375 mg, 1.48 mmol) at 0 °C. After 30 min, the mixture was diluted with hexane and filtered through a short pad of silica gel. Concentration of the filtrate in vacuo and purification of the residue by column chromatography on silica gel (EtOAc/hexane, 1:20) gave the iodo compound (543 mg, 96%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.45 (ddd, J = 15.2, 6.7, 6.7 Hz, 1H), 5.26 (dd, J = 15.2, 8.6 Hz, 1H), 4.63 (s, 2H), 4.16−4.14 (m, 1H), 3.79−3.75 (m, 1H), 3.39 (dd, J = 9.7, 3.3 Hz, 1H), 3.36 (s, 3H), 3.09 (dd, J = 9.7, 7.5 Hz, 1H), 2.32 (ddd, J = 13.5, 7.0, 7.0 Hz, 1H), 2.05 (ddd, J = 17.9, 8.6, 8.6 Hz, 1H), 2.01−1.96 (m, 3H), 1.82−1.75 (m, 1H), 1.62−1.58 (m, 2H), 1.46−1.31 (m, 4H), 1.12 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.1, 131.8, 95.3, 75.9, 68.5, 55.3, 47.9, 45.2, 40.9, 40.1, 39.2, 32.4, 25.9, 25.6, 23.8, 18.2, 12.8, −4.4, −4.7; IR (neat) 1047 cm^{-1}; $[\alpha]^{23}_D$ = −30.2 (c = 0.80, CH_3OH); HRMS (EI) calcd for $C_{21}H_{41}IO_3Si$ (M^+) 496.1870, found 496.1855.

2. Conversion to Nitro Compound. To a solution of the above iodo compound (540 mg, 1.09 mmol) in DMF (11 mL) were added sodium nitrite (375 mg, 5.45 mmol) and urea (457 mg, 7.63 mmol). After the reaction mixture was stirred for 12 h at room temperature, the mixture was poured into ice water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:13) to give nitro compound **16a** (307 mg, 68%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.45 (ddd, J = 15.2, 6.7, 6.7 Hz, 1H), 5.31 (dd, J = 15.2, 8.6 Hz, 1H), 4.61 (s, 2H), 4.45 (dd, J = 12.1, 4.7 Hz, 1H), 4.20−4.15 (m, 2H), 3.78 (dddd, J = 11.9, 5.9, 5.9, 5.9 Hz, 1H), 3.35 (s, 3H), 2.56−2.48 (m, 1H), 2.28 (ddd, J = 13.9, 7.8, 6.4 Hz, 1H), 2.12−2.05 (m, 2H), 2.00−1.94 (m, 2H), 1.66−1.54 (m, 3H), 1.46−1.31 (m, 3H), 1.11 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.6, 131.3, 95.3, 78.7, 77.2, 76.0, 68.4, 55.3, 45.7, 42.2, 40.2, 39.1, 37.4, 32.3, 25.9, 25.5, 23.8, 18.1, −4.4, −4.7; IR (neat) 1553, 1044 cm^{-1}; $[\alpha]^{17}_D$ = −13.2 (c = 1.5, CH_3OH); HRMS (EI) calcd for $C_{21}H_{40}NO_5Si$ (M^+ − t-Bu) 358.2050, found 358.2061.

Acrylic Acid (1*S*,5*E*)-6-[(1*S*,2*R*,4*S*)-(4-(Methoxymethoxy)-2-(nitromethyl)cyclopentyl)]-1-methylhex-5-enyl Ester (4a). 1. Removal of Silyl Group. To a solution of silyl ether 16a (200 mg, 0.48 mmol) in ethanol (32 mL) was added PPTS (242 mg, 0.96 mmol). After the mixture was stirred for 12 h at 50 °C, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give the alcohol (140 mg, 97%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.38 (ddd, J = 15.2, 6.7, 6.7 Hz, 1H), 5.26 (dd, J = 15.2, 8.6 Hz, 1H), 4.54 (s, 2H), 4.37 (dd, J = 12.1, 5.0 Hz, 1H), 4.15−4.08 (m, 2H), 3.76−3.70 (m, 1H), 3.28 (s, 3H), 2.50−2.42 (m, 1H), 2.21 (ddd, J = 14.3, 7.8, 6.4 Hz, 1H), 2.07−1.93 (m, 4H), 1.58−1.49 (m, 2H), 1.45−1.30 (m, 4H), 1.24 (br s, 1H), 1.12 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 132.2, 131.6, 95.2, 78.7, 76.0, 67.9, 55.3, 45.7, 42.1, 40.2, 38.6, 37.4, 32.2, 25.4, 23.5; IR (neat) 3412, 1553, 1040 cm^{-1}; $[\alpha]^{18}_D$ = −21.6 (c = 0.50, CH_3OH); HRMS calcd for $C_{14}H_{24}NO_4$ (M^+ − OMe) 270.1705, found 270.1702.

2. Acryloylation. To a solution of the above alcohol (93 mg, 0.47 mmol) and *N*,*N*-dimethylaniline (0.40 mL, 3.16 mmol) in CH_2Cl_2 (4.6 mL) was added dropwise acryloyl chloride (0.20 mL, 2.46 mmol). After 30 min at 0 °C, saturated aqueous NH_4Cl solution was added to the mixture. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give acrylate **4a** (93 mg, 89%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.31 (dd, J = 17.3, 1.5 Hz, 1H), 6.03 (dd, J = 17.8, 10.4 Hz, 1H), 5.72 (dd, J = 10.4, 1.4 Hz, 1H), 5.36 (ddd, J = 15.2, 6.6, 6.6 Hz, 1H), 5.26 (dd, J = 15.2, 8.6 Hz, 1H), 4.93−4.90 (m, 1H), 4.54 (s, 2H), 4.37 (dd, J = 12.1, 4.8 Hz, 1H), 4.14−4.08 (m, 2H), 3.28 (s, 3H), 2.50−2.42 (m, 1H), 2.21 (ddd, J = 13.9, 8.0, 6.3 Hz, 1H), 2.06−1.92 (m, 4H), 1.59−1.42 (m, 4H), 1.40−1.28 (m, 2H), 1.18 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.9, 132.0, 131.8, 130.2, 129.1, 95.3, 78.7, 76.0, 71.0, 55.3, 45.6, 42.1, 40.2, 37.4, 35.3, 32.0, 25.0, 19.9; IR (neat) 1721, 1553 cm^{-1}; $[\alpha]^{20}_D$ = −6.1 (c = 0.10, CH_3OH); HRMS (EI) calcd for $C_{17}H_{26}NO_5$ (M^+ − OMe) 324.1811, found 324.1818.

{(1*R*,2*S*,4*S*)-2-[(1*Z*,6*S*)-6-(*tert*-Butyldimethylsilanyloxy)-hept-1-enyl]-4-(methoxymethoxy)cyclopentyl}-methanol (15b). 1. Partial Reduction of the Triple Bond. To a stirred solution of acetylene 3(*S*) (757 mg, 1.59 mmol) in hexane (8.0 mL) were added Lindlar catalyst (378 mg, 50 wt %) and quinoline (0.35 mL, 378 mg, 50 wt %). The mixture was stirred for 8 h under a hydrogen atmosphere and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography (EtOAc/hexane, 1:15) to give the *cis*-olefin (700 mg, 92%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.29 (m, 4H), 7.28−7.25 (m, 1H), 5.38−5.27 (m, 2H), 4.63 (d, J = 6.7 Hz, 1H), 4.61 (d, J = 6.7 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 4.19−4.13 (m, 1H), 3.77−3.72 (m, 1H), 3.46 (dd, J = 9.1, 4.0 Hz, 1H), 3.35 (s, 3H), 3.29 (dd, J = 9.1, 6.7 Hz, 1H), 2.55 (quintet, J = 9.1 Hz, 1H), 2.19 (ddd, J = 13.5, 7.0, 7.0 Hz, 1H), 2.05−1.92 (m, 4H), 1.79−1.74 (m, 1H), 1.47−1.25 (m, 5H), 1.10 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 133.6, 130.0, 128.3, 127.44, 127.38, 95.2, 77.2, 73.0, 72.2, 68.5, 55.2, 44.6, 40.6, 39.3, 38.5, 36.6, 27.5, 26.1, 25.9, 23.8, 18.1, −4.4, −4.7; IR (neat) 1042 cm^{-1}; $[\alpha]^{26}_D$ = −8.0 (c = 0.80, CH_3OH); HRMS (EI) calcd for $C_{28}H_{46}O_4Si$ (M^+) 476.3322, found 476.3323.

2. Removal of Benzyl Group. To a mixture of the above benzyl ether (1.114 g, 2.34 mmol), THF (8.0 mL), and liquid ammonia (50 mL) was added portionwise Na (160 mg, 6.96 mmol). The mixture was refluxed for 30 min, quenched with NH_4Cl (300 mg, 5.61 mmol) at −78 °C, and concentrated in vacuo. The residue was dissolved in ether, and the solution was washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:5) to give alcohol **15b** (851 mg, 94%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.42−5.32 (m, 2H), 4.63(d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.19−4.14 (m, 1H), 3.80−3.75 (m, 1H), 3.63 (dd, J = 10.4, 5.1 Hz, 1H), 3.51 (dd, J = 10.4, 6.2 Hz, 1H), 3.36 (s, 3H), 2.50 (quintet, J = 9.1 Hz, 1H), 2.21 (ddd, J = 13.4, 7.3, 7.3 Hz, 1H), 2.05−1.98 (m, 3H), 1.96−1.90 (m, 1H), 1.69−1.62 (m, 1H), 1.53−1.50 (m, 1H), 1.49−1.30 (m, 5H), 1.12 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.6, 130.2, 95.2, 77.0, 68.4, 65.3, 55.2, 46.7, 40.6, 39.2, 38.8, 36.0, 27.5, 25.9, 25.8, 23.7, 18.1, −4.5, −4.8; IR (neat) 3444, 1042 cm^{-1}; $[\alpha]^{22}_D$ =

−15.4 (c = 1.0, CH_3OH); HRMS (EI) calcd for $C_{20}H_{39}O_3Si$ (M^+ − OMe) 355.2669, found 355.2670.

***tert*-Butyl{(1*S*,5*Z*)-6-[(1*S*,2*R*,4*S*)-(4-(methoxymethoxy)-2-(nitromethyl)cyclopentyl)]-1-methylhex-5-enyloxy}-dimethylsilane (16b). 1. Iodination.** To a solution of alcohol **15b** (850 mg, 2.20 mmol) in THF (22 mL) were added imidazole (419 mg, 6.15 mmol), Ph_3P (807 mg, 3.08 mmol), and iodine (781 mg, 3.08 mmol) at 0 °C. After 30 min at room temperature, the mixture was diluted with hexane and filtered through a short pad of silica gel. Concentration of the filtrate in vacuo and purification of the residue by column chromatography on silica gel (EtOAc/hexane, 1:20) gave the iodo compound (1.08 g, 99%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.43 (ddd, J = 10.0, 7.4, 7.4 Hz, 1H), 5.22 (t, J = 10.3 Hz, 1H), 4.62 (s, 2H), 4.20−4.15 (m, 1H), 3.81−3.76 (m, 1H), 3.38−3.35 (m, 1H), 3.36 (s, 3H), 3.11 (dd, J = 9.5, 7.1 Hz, 1H), 2.43 (quintet, J = 9.1 Hz, 1H), 2.30 (ddd, J = 13.5, 7.0, 7.0 Hz, 1H), 2.08−2.03 (m, 2H), 2.01−1.96 (m, 1H), 1.83−1.76 (m, 1H), 1.67−1.60 (m, 1H), 1.58−1.52 (m, 1H), 1.48−1.31 (m, 4H), 1.12 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.1, 131.4, 95.2, 76.1, 68.4, 55.2, 45.8, 42.3, 41.0, 40.1, 39.3, 27.8, 26.1, 25.9, 23.8, 18.1, 12.9, −4.4, −4.7; IR (neat) 1045 cm^{-1}; $[\alpha]^{23}_D$ = −19.5 (c = 1.1, CH_3OH); HRMS (EI) calcd for $C_{21}H_{40}IO_3Si$ (M^+ − H) 495.1792, found 495.1808.

2. Conversion to Nitro Compound. To a solution of the above iodo compound (1.08 g, 2.18 mmol) in DMF (22 mL) were added sodium nitrite (300 mg, 4.35 mmol) and urea (392 mg, 6.53 mmol). The reaction mixture was stirred for 12 h at room temperature, poured into ice water, and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:13) to give nitro compound **16b** (654 mg, 72%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46 (ddd, J = 10.6, 7.4, 7.4 Hz, 1H), 5.28 (dd, J = 10.6, 9.7 Hz, 1H), 4.61 (s, 2H), 4.42 (dd, J = 12.0, 4.4 Hz, 1H), 4.23−4.18 (m, 1H), 4.19 (dd, J = 12.0, 9.0 Hz, 1H), 3.80−3.74 (m, 1H), 3.35 (s, 3H), 2.57−2.42 (m, 2H), 2.27 (ddd, J = 14.1, 7.1, 7.1 Hz, 1H), 2.09 (ddd, J = 13.5, 7.1, 2.2 Hz, 1H), 2.01−1.95 (m, 2H), 1.65 (ddd, J = 13.7, 10.2, 7.1 Hz, 1H), 1.54−1.49 (m, 1H), 1.47−1.30 (m, 4H), 1.11 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.0, 131.1, 95.2, 78.5, 76.1, 68.3, 55.2, 42.9, 40.3, 39.9, 39.2, 37.4, 27.5, 25.9, 25.8, 23.8, 18.0, −4.4, −4.8; IR (neat) 1555 cm^{-1}; $[\alpha]^{19}_D$ = −7.4 (c = 1.0, CH_3OH); HRMS (EI) calcd for $C_{21}H_{40}NO_5Si$ (M^+ − H) 414.2676, found 414.2671.

Acrylic Acid (1*S*,5*Z*)-6-[(1*S*,2*R*,4*S*)-(4-(Methoxymethoxy)-2-(nitromethyl)cyclopentyl)]-1-methylhex-5-enyl Ester (4b). 1. Removal of Silyl Group. To a solution of silyl ether **16b** (652 mg, 1.57 mmol) in ethanol (78 mL) was added PPTS (788 mg, 3.14 mmol). The mixture was stirred for 12 h at 50 °C, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give the alcohol (400 mg, 85%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.47 (ddd, J = 10.8, 7.4, 7.4 Hz, 1H), 5.30 (dd, J = 10.8, 9.5 Hz, 1H), 4.62 (s, 2H), 4.42 (dd, J = 12.0, 4.6 Hz, 1H), 4.22 (dd, J = 12.0, 8.5 Hz, 1H), 4.23−4.18 (m, 1H), 3.84−3.77 (m, 1H), 3.36 (s, 3H), 2.58−2.46 (m, 2H), 2.28 (ddd, J = 13.4, 6.7, 6.7 Hz, 1H), 2.12−2.08 (m, 1H), 2.05−2.01 (m, 2H), 1.69−1.62 (m, 1H), 1.60−1.41 (m, 5H), 1.40−1.35 (m, 1H), 1.20 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.7, 131.3, 95.2, 78.5, 76.1, 67.9, 55.3, 42.9, 40.3, 39.9, 38.7, 37.3, 27.4, 25.8, 23.5; IR (neat) 3443, 1555 cm^{-1}; $[\alpha]^{25}_D$ = −18.2 (c = 0.40, CH_3OH); HRMS (EI) calcd for (M^+ − OMe) 270.1705, found 270.1691.

2. Acryloylation. The above alcohol (186 mg, 0.94 mmol) and *N*,*N*-dimethylaniline (0.80 mL, 6.32 mmol) were dissolved in CH_2Cl_2 (4.6 mL) and cooled to 0 °C. To the solution was added dropwise acryloyl chloride (0.40 mL, 4.92 mmol), and the resulting mixture was stirred at 0 °C for 30 min. After saturated aqueous NH_4Cl was added, the mixture was diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give acrylate **4b** (185 mg, 89%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.39 (dd, J = 17.2, 1.2 Hz, 1H), 6.10 (dd, J = 17.2, 10.4 Hz, 1H), 5.81 (dd, J = 10.4, 1.2 Hz, 1H), 5.44 (ddd, J = 10.8, 7.4, 7.4 Hz, 1H), 5.30 (t, J = 10.1 Hz, 1H), 5.02−4.97 (m, 1H), 4.61 (s, 2H), 4.40 (dd, J = 11.9, 4.5 Hz, 1H), 4.20 (dd, J = 11.9, 8.8 Hz, 1H), 4.23−4.18 (m, 1H), 3.35 (s, 3H), 2.58−2.44 (m, 2H), 2.27 (ddd, J = 13.5, 7.4, 7.4 Hz, 1H), 2.09 (ddd, J = 13.4, 6.9, 2.3 Hz, 1H), 2.06−1.96 (m, 2H), 1.70−1.47 (m, 4H), 1.46−1.28 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8, 131.5, 131.4, 130.3, 128.9, 95.2, 78.5, 76.1, 70.7, 55.3, 42.8, 40.3, 39.9, 37.4, 35.4, 27.1, 25.4, 19.9; IR (neat) 1715, 1556 cm^{-1}; $[\alpha]^{13}_D$ = −17.0 (c = 0.40, CH_3OH); HRMS (EI) calcd for $C_{17}H_{26}NO_5$ (M^+ − OMe) 324.1811, found 324.1801.

Intramolecular Nitrile Oxide Cycloaddition of Acrylate 4b. A mixture of acrylate **4b** (190.0 mg, 0.54 mmol), *p*-chlorophenyl isocyanate (821 mg, 5.35 mmol), and Et_3N (0.75 mL, 0.54 mmol) in benzene (160 mL) was refluxed for 20 h. The reaction mixture was filtered through a short pad of Celite and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4). The first fraction was collected and rechromatographed (EtOAc/hexane, 1:6) to give C2-(*R*) fused isomer **6b** (2.3 mg, 1%) as a white solid: ^{1} H NMR ($CDCl_3$, 500 MHz) δ 5.75 (t, J = 11.2 Hz, 1H), 5.29 (ddd, J = 11.2, 11.2, 3.4 Hz, 1H), 5.20−5.13 (m, 1H), 4.63 (s, 2H), 4.59 (dd, J = 11.0, 8.4 Hz, 1H), 4.57 (dd, J = 11.0, 8.4 Hz, 1H), 4.48−4.43 (m, 1H), 4.22 (t, J = 10.9 Hz, 1H), 3.36 (s, 3H), 3.12 (t, J = 8.3 Hz, 1H), 2.75−2.64 (m, 3H), 2.04 (ddd, J = 14.3, 7.7, 7.7 Hz, 1H), 1.98−1.83 (m, 4H), 1.62 (d, J = 14.5 Hz, 1H), 1.55−1.47 (m, 1H), 1.33−1.22 (m, 1H), 1.28 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 157.1, 134.0, 129.5, 95.9, 77.9, 74.2, 72.3, 55.4, 54.4, 45.2, 39.1, 36.9, 35.2, 31.3, 27.0, 24.0, 18.1; IR (neat) 1732, 1651 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1884.

The second fraction was collected and rechromatographed ($MeOH/CH_2Cl_2$, 1:40) to give C2-(*S*) fused isomer **6b** (2.5 mg, 1%) and C2-(*R*) bridged isomer **5b** (28.1 mg, 16%) as white solids. C2-(*S*) fused isomer **6b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.40−5.35 (m, 2H), 5.04−4.97 (m, 1H), 4.64 (d, J = 6.7 Hz, 1H), 4.62 (d, J = 6.7 Hz, 1H), 4.56 (dd, J = 8.7, 6.0 Hz, 1H), 4.44 (dd, J = 10.9, 8.7 Hz, 1H), 4.26−4.21 (m, 1H), 3.90 (dd, J = 10.9, 6.0 Hz, 1H), 3.36 (s, 3H), 3.21−3.14 (m, 1H), 2.72 (q, J = 7.7 Hz, 1H), 2.36 (ddd, J = 13.5, 8.8, 6.1 Hz, 1H), 2.32−2.22 (m, 1H), 2.11−2.07 (m, 2H), 1.97−1.85 (m, 1H), 1.80−1.70 (m, 2H), 1.58−1.51 (m, 1H), 1.40−1.31 (m, 1H), 1.28−1.18 (m, 1H), 1.22 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0, 159.5, 135.2, 130.4, 95.3, 77.2, 73.6, 72.6, 58.5, 55.3, 42.9, 41.6, 40.3, 39.1, 33.9, 27.7, 25.3, 20.2; IR (neat) 1731 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1877. C2-(*R*)-bridged isomer **5b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.45−5.33 (m, 2H), 5.18−5.11 (m, 1H), 4.99 (dd, J = 12.1, 4.7 Hz, 1H), 4.62 (s, 2H), 4.31−4.26 (m, 1H), 3.35 (s, 3H), 3.35 (dd, J = 17.6, 12.1 Hz, 1H), 3.17 (dd, J = 17.6, 4.7 Hz, 1H), 2.86 (dddd, J = 9.7, 9.7, 9.7, 8.8 Hz, 1H), 2.56 (ddd, J = 10.8, 10.8, 3.9 Hz, 1H), 2.40−2.20 (m, 3H), 2.10−2.05 (m, 1H), 1.93−1.88 (m, 1H), 1.84−1.78 (m, 1H), 1.68−1.60 (m, 1H), 1.53−1.41 (m, 2H), 1.28 (d, J = 6.4 Hz, 3H), 1.27−1.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 160.2, 133.2, 130.9, 95.2, 76.9, 76.4, 72.8, 55.4, 45.1, 45.1, 42.2, 40.7, 38.2, 32.7, 26.8, 24.7, 19.0; IR (neat) 1747, 1652 cm^{-1}; $[\alpha]^{18}_D$ = −148.7 (c = 0.45, CH_3OH); HRMS (EI) calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1885.

The third fraction was collected and rechromatographed (EtOAc/hexane, 1:2) to give C2-(*S*)-bridged isomer **5b** (110.0 mg, 61%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.42 (ddd, J = 10.3, 10.3, 4.7 Hz, 1H), 5.23 (t, J = 10.3 Hz, 1H), 5.16−5.09 (m, 1H), 5.03 (dd, J = 11.1, 2.8 Hz, 1H), 4.62 (s, 2H), 4.26−4.21 (m, 1H), 3.35 (s, 3H), 3.31 (dd, J = 16.9, 2.8 Hz, 1H), 3.18 (dd, J = 16.9, 11.1 Hz, 1H), 3.19−3.11 (m, 1H), 2.77 (quintet, J = 9.6 Hz, 1H), 2.35−2.29 (m, 1H), 2.12−2.00 (m, 2H), 1.92−1.82 (m, 2H), 1.78 (ddd, J = 13.4, 11.5, 6.9 Hz, 1H), 1.68−1.53 (m, 2H), 1.43−1.38 (m, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.06−0.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 159.5, 131.8, 130.4, 95.2, 76.9, 76.5, 73.1, 55.2, 42.2, 41.1, 40.3, 37.0, 36.1, 33.8, 27.5, 25.7, 19.5; IR (neat) 1747 cm^{-1}; $[\alpha]^{19}_D$ =

+39.1 (c = 2.0, CH_3OH); HRMS (EI) calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1875.

Isomerization of Cis-Bridged Isomers 5b to Trans-Bridged Isomers 5a. A mixture of C2-(*R*)-bridged isomer **5b** (10.2 mg, 0.027 mmol), thiophenol (0.014 mL, 0.14 mmol), and AIBN (22 mg, 0.13 mmol) in benzene (0.9 mL) was refluxed for 6 h. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give C2-(*R*)-bridged isomer **5a** (4.6 mg, 82% based on 55% conversion). The conversion of C2-(*S*)-bridged isomer **5b** to C2-(*S*)-bridged isomer **5a** was also carried out under the same conditions (81% based on 56% conversion).

(1*R*,2*S*,4*S*)-4-(Methoxymethoxy)-1-(nitromethyl)-2-vinylcyclopentane (17). 1. Iodination. To a solution of alcohol **12** (78.2 mg, 0.42 mmol) in THF (1.4 mL) were added imidazole (86 mg, 1.26 mmol), triphenylphosphine (220 mg, 0.84 mmol), and iodine (320 mg, 1.26 mmol) at 0 °C. After 5 min at the same temperature, the reaction mixture was stirred for 4 h at room temperature. The mixture was filtered through a short pad of silica gel, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to afford the iodo compound (116.2 mg) in 93% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.70 (ddd, J = 17.1, 9.8, 8.6 Hz, 1H), 5.06 (d, J = 16.7 Hz, 1H), 5.01 (dd, J = 10.1, 1.4 Hz, 1H), 4.62 (s, 2H), 4.19−4.14 (m, 1H), 3.40 (dd, J = 9.8, 3.5 Hz, 1H), 3.36 (s, 3H), 3.12 (dd, J = 9.8, 7.3 Hz, 1H), 2.34 (ddd, J = 14.1, 7.6, 6.5 Hz, 1H), 2.12 (quintet, J = 9.0 Hz, 1H), 2.01 (ddd, J = 13.4, 7.5, 2.7 Hz, 1H), 1.86 (dddd, J = 17.1, 10.1, 7.1, 3.1 Hz, 1H), 1.69−1.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.5, 115.4, 95.3, 75.9, 55.3, 48.8, 44.8, 40.4, 40.1, 12.4; IR (neat) 1044 cm^{-1}; $[\alpha]^{20}_D$ = −51.1 (c = 1.1, $CHCl_3$); HRMS (EI) calcd for $C_{10}H_{17}IO_2$ (M^+) 296.0273, found 296.0271.

2. Conversion to Nitro Compound. To a solution of the above iodo compound (98.0 mg, 0.33 mmol) in DMSO (1.7 mL) was added urea (139 mg, 2.31 mmol). After 5 min, $NaNO_2$ was added to the mixture, which was stirred for 6 h at room temperature. The mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to afford nitro compound **17** (53.8 mg) in 76% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.73 (ddd, J = 17.0, 9.9, 8.9 Hz, 1H), 5.05 (d, J = 17.5 Hz, 1H), 5.04 (d, J = 9.9 Hz, 1H), 4.61 (s, 2H), 4.47 (dd, J = 12.2, 4.8 Hz, 1H), 4.22 (dd, J = 12.1, 9.2 Hz, 1H), 4.22−4.18 (m, 1H), 3.35 (s, 3H), 2.63−2.54 (m, 1H), 2.32 (ddd, J = 14.0, 8.0, 6.3 Hz, 1H), 2.16 (quintet, J = 9.3 Hz, 1H), 2.10 (ddd, J = 13.5, 7.4, 2.4 Hz, 1H), 1.67−1.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.7, 116.2, 95.3, 78.5, 76.1, 55.4, 46.6, 41.8, 39.8, 37.5; IR (neat) 1556, 1383, 1041 cm^{-1}; $[\alpha]^{20}_D$ = −32.9 (c = 0.32, $CHCl_3$); HRMS (CI) calcd for $C_{10}H_{18}O_4N$ (MH^+) 216.1236, found 216.1239.

Acrylic Acid (1*S*)-1-Methylhex-5-enyl Ester (19). To a solution of (*S*)-heptenol (**18**) (1.759 g, 15.41 mmol) in CH_2Cl_2 (22.0 mL) were added *N*,*N*-dimethylaniline (5.9 mL, 46.55 mmol) and acryloyl chloride (1.9 mL, 23.39 mmol) at 0 °C. After 3 h at this temperature, the mixture was diluted with ether and washed with 1 N HCl solution. The organic layer was concentrated at reduced pressure, and the resulting residue was purified by column chromatography on silica gel (hexane/ether, 20:1) to afford acrylate **19** (2.155 g) in 83% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.39 (dd, J = 17.4, 1.3 Hz, 1H), 6.11 (dd, J = 17.4, 10.4 Hz, 1H), 5.83−5.75 (m, 2H), 5.03−4.95 (m, 3H), 2.07 (q, J = 7.1 Hz, 2H), 1.65 (dddd, J = 13.1, 10.5, 7.5, 5.2 Hz, 1H), 1.58−1.51 (m, 1H), 1.50−1.36 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.8, 138.3, 130.2, 128.9, 114.7, 70.9, 35.2, 33.4, 24.5, 19.9; IR 1723, 1199 (neat) cm^{-1}; $[\alpha]^{20}_D$ = +8.7 (c = 1.5, $CHCl_3$).

3-[(1*R*,2*S*,4*S*)-4-(Methoxymethoxy)-2-vinylcyclopentyl]-4,5-dihydroisoxazole-5-carboxylic Acid (1*S*)-1-Methylhex-5-enyl Esters 20 and 21. A mixture of nitro compound **17** (128.0 mg, 0.60 mmol), acrylate 19 (110.5 mg, 0.66 mmol), *p*-chlorophenyl isocyanate (547 mg, 3.56 mmol), and triethylamine (0.1 mL, 0.72 mmol) in benzene (6.0 mL) was refluxed for 24 h. After the mixture was filtered through a short pad of Celite, the filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:1) to afford C2-(*S*) isomer **20** (91.7 mg, 42%) and C2-(*R*) isomer **21** (92.3 mg, 43%). C2-(*S*) isomer **20**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.83−5.74 (m, 2H), 5.06 (d, J = 17.1 Hz, 1H), 5.02−4.95 (m, 4H), 4.92 (dd, J = 11.3, 6.4 Hz, 1H), 4.62 (s, 2H), 4.26−4.22 (m, 1H), 3.36 (s, 3H), 3.24 (dd, J = 17.1, 11.4 Hz, 1H), 3.12 (dd, J = 17.1, 6.3 Hz, 1H), 2.88 (ddd, J = 10.2, 10.2, 7.8 Hz, 1H), 2.54 (quintet, J = 8.9, 1H), 2.34 (ddd, J = 14.1, 8.1, 6.2 Hz, 1H), 2.13−2.07 (m, 1H), 2.06 (q, J = 7.1 Hz, 2H), 1.96 (ddd, J = 13.6, 10.9, 6.5 Hz, 1H), 1.68−1.61 (m, 2H), 1.57−1.49 (m, 1H), 1.48−1.34 (m, 2H), 1.24 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 159.4, 140.4, 138.2, 115.3, 114.9, 95.2, 77.2, 76.5, 72.7, 55.3, 47.0, 42.0, 39.8, 39.7, 37.3, 35.1, 33.3, 24.6, 19.8; IR (neat) 1733, 1041 cm^{-1}; $[\alpha]^{20}_D$ = +78.8 (c = 1.7, $CHCl_3$); HRMS (FAB) calcd for $C_{20}H_{32}O_5N$ (MH^+) 366.2280, found 366.2277. C2-(*R*) isomer **21**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.85−5.73 (m, 2H), 5.06 (d, J = 17.1 Hz, 1H), 5.02−4.95 (m, 4H), 4.93 (dd, J = 11.3, 6.2 Hz, 1H), 4.62 (s, 2H), 4.25−4.21 (m, 1H), 3.36 (s, 3H), 3.24 (dd, J = 17.1, 6.2 Hz, 1H), 3.12 (dd, J = 17.1, 11.4 Hz, 1H), 2.87 (ddd, 10.2, 10.2, 7.8 Hz, 1H), 2.52 (quintet, J = 8.9, 1H), 2.33 (ddd, J = 14.0, 8.1, 6.2 Hz, 1H), 2.11−1.97 (m, 4H), 1.68−1.60 (m, 2H), 1.57−1.50 (m, 1H), 1.48−1.33 (m, 2H), 1.25 (d, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 159.6, 140.6, 138.2, 115.4, 114.9, 95.2, 77.2, 76.5, 72.7, 55.4, 47.2, 41.9, 39.9, 39.8, 37.4, 35.1, 33.4, 24.5, 19.8; IR (neat) 1733, 1041 cm^{-1}; $[\alpha]^{20}_D$ = −122.8 (c = 1.9, $CHCl_3$); HRMS (FAB) calcd for $C_{20}H_{32}O_5N$ (MH^+) 366.2280, found 366.2277.

(2*R*,4*S*,6*S*,12*S*)-4-(Methoxymethoxy)-12-methyl-13,16-dioxa-17-azatricyclo[13.2.1.02,6]octadeca-1(17),7-dien-14-one (23). A mixture of olefin **21** (36.5 mg, 0.10 mmol) and $Cl_2(Cy_3P)_2RuCHC_6H_5$ (74.0 mg, 0.090 mmol) in degassed CH_2Cl_2 (100 mL) was refluxed for 30 h. The mixture was filtered through a pad of silica gel, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to afford a mixture of macrolides **23** (E/Z = 2.2:1, 500 MHz ^{1}H NMR analysis, 14.2 mg) in 42% total yield. The two isomers were then separated by column chromatography on silica gel (EtOAc/hexane, 1:10) to afford *E*-isomer **23** (9.5 mg) and *Z*-isomer **23** (4.4 mg). The spectral data for both of the isomers were in good agreement with our data obtained by INOC reactions.

Preparation of Acryl Amide 25. A mixture of nitro compound **17** (10.7 mg, 0.050 mmol) and acrylate derivative **24** of Oppolzer's camphor sultam (17 mg, 0.063 mmol), *p*-chlorophenyl isocyanate (53 mg, 0.35 mmol), and Et_3N (0.05 mL) in benzene (1.7 mL) was refluxed for 14 h. The mixture was filtered through a short pad of Celite, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to afford a mixture of isoxazoline **25** and its C2-(*S*) epimer (94:6, 500 MHz ^{1}H NMR analysis, 18.8 mg) in 81% yield. The two isomers were then separated by column chromatography on silica gel (EtOAc/hexane, 1:10) to give isoxazoline **25** (17.3 mg) and its C2-(*S*) epimer (0.9 mg). Isoxazoline **25**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80 (ddd, J = 17.4, 9.8, 7.9 Hz, 1H), 5.48 (dd, J = 10.9, 6.5 Hz, 1H), 5.08 (d, J = 17.1 Hz, 1H), 5.01 (d, J = 9.9 Hz, 1H), 4.62 (s, 2H), 4.25−4.21 (m, 1H), 3.92 (dd, J = 7.2, 5.0 Hz, 1H), 3.54 (d, J = 13.7 Hz, 1H), 3.44 (d, J = 13.7 Hz, 1H), 3.35 (s, 3H), 3.39−3.34 (m, 1H), 3.14 (dd, J = 17.3, 11.1 Hz, 1H), 2.89 (ddd, J = 10.1, 10.1, 7.9 Hz, 1H), 2.54 (quintet, J = 8.9 Hz, 1H), 2.32 (ddd, J = 14.0, 8.1, 6.2 Hz, 1H), 2.20−2.14 (m, 1H), 2.12−2.06 (m, 2H), 2.03−1.88 (m, 4H), 1.65−1.61 (m, 1H), 1.60−1.32 (m, 2H), 1.19 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 159.6, 140.4, 115.4, 95.2, 76.5, 65.2, 53.3, 52.9, 49.0, 47.9, 46.8, 44.6, 41.8, 39.7, 39.6, 38.1, 37.3, 32.9, 26.4, 20.9, 19.9; IR (neat) 1698, 1040 cm^{-1}; $[\alpha]^{20}_D$ = −221.6 (c = 0.70, $CHCl_3$); HRMS (EI) calcd for $C_{23}H_{34}O_6N_2S$ (M^+) 466.2138, found 466.2156. C2-(*S*) epimer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.79 (ddd, J = 17.5, 9.7, 7.5 Hz, 1H), 5.52 (dd, J = 11.7, 6.3 Hz, 1H), 5.04 (d, J = 17.2 Hz, 1H), 5.00 (d, J = 10.5 Hz, 1H), 4.61 (s, 2H), 4.25−

4.20 (m, 1H), 3.92 (t, J = 6.3 Hz, 1H), 3.48 (d, J = 3.5 Hz, 2H), 3.41 (dd, J = 17.3, 11.6 Hz, 1H), 3.35 (s, 3H), 2.95 (dd, J = 17.5, 6.2 Hz, 1H), 2.88−2.82 (m, 1H), 2.52 (quintet, J = 9.0 Hz, 1H), 2.32 (ddd, J = 14.3, 7.3, 6.4 Hz, 1H), 2.10−2.07 (m, 3H), 2.00−1.89 (m, 4H), 1.65−1.55 (m, 1H), 1.46−1.33 (m, 2H), 1.18 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 158.9, 140.4, 115.5, 95.2, 76.4, 65.1, 55.4, 52.8, 49.1, 47.9, 47.2, 44.5, 41.9, 41.8, 39.8, 38.0, 37.4, 32.7, 26.3, 20.8, 19.8; IR (neat) 1698, 1041 cm^{-1}; $[\alpha]^{20}_D = -49.8$ (c = 0.24, $CHCl_3$); HRMS (EI) calcd for $C_{21}H_{29}O_4N_2S$ (M^+ − OMOM) 405.1848, found 405.1856.

Preparation of Olefin 21 from Amide 25. A mixture of amide **25** (10.0 mg, 0.021 mmol) and $LiOH\cdot H_2O$ (9 mg, 0.21 mmol) in THF/H_2O (2:1, 1.5 mL) was stirred for 12 h. The mixture was neutralized with saturated NH_4Cl solution, diluted with EtOAc, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 3:1) to afford the crude acid. Without further purification, a mixture of the crude acid, Et_3N (0.15 mL, 1.08 mmol), DMAP (3 mg, 0.025 mmol), and 2,4,6-trichlorobenzoyl chloride (0.05 mL, 0.32 mmol) in THF (1.0 mL) was stirred for 4 h at room temperature. To the mixture was added a solution of (*S*)-heptenol (**18)** (35 mg, 0.31 mmol) in toluene (2 mL). The reaction mixture was refluxed for 18 h and filtered through a short pad of silica gel. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to afford olefin **21** (5.8 mg) in 72% yield.

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Supporting Information Available: Data for the structure elucidation of **5a**−**d** and **6a**−**d**, results of MM2 calculations, experimental procedures and spectral characterization of **15c,d**, **16c,d**, **4c,d**, **5c,d**, and **6c,d**, and copies of the ^{1}H and ^{13}C NMR spectra for **1**, **5a**−**d**, **6a**−**d**, **12**, **20**, and **21** and the ^{1}H−^{1}H COSY and NOESY spectra of **5a,b** and **6a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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