Enantioselective Synthesis of 12-Amino Alkylidenecyclopentenone Prostaglandins

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An enantioselective synthesis of new 12-amino alkylidenecyclopentenone prostaglandins is reported. The key step of the synthesis involved a [3.3] sigmatropic rearrangement of an asymmetric allylic cyanate to elaborate an asymmetric 5-amino-1,6-diene which was further transformed into cyclopentenone by successive ring-closing metathesis reaction catalyzed by the Grubbs reagent and one-pot oxidation. A palladium-catalyzed cross-coupling reaction on a 5-iodo-1,5-diene allowed the synthesis of prostanoids with variable Rw side chains. These new compounds exhibit high cytotoxic activities.

Introduction

Biological Activities of Cyclopentenone Prostaglandins. Prostaglandins (PGs), such as Δ^{12}-PGJ$_2$ or Δ^7-PGA$_1$ and its methyl ester (**1**) (Figure 1), bearing a cross-conjugated dienone framework, have been reported to be endowed with potent cytotoxic effects and antitumor activity.[1] It has been shown that they exert their activity, after transport into nuclei, by cell cycle arrest at the G1 phase and that inhibition of the growth of HL-60 human leukemia cells results mainly from the induction of p21, a cyclin-dependent kinase inhibitor regulating the cell cycle progression, via a p53-independent pathway.[2] It has also been demonstrated that these compounds could inhibit topoisomerases I and II.[3] For all these reasons, but also for their potency to inhibit viral replication and to play a role in osteogenesis and adipogenesis,[4] these prostaglandins have received much attention, and **1** is currently evaluated for the treatment of resistant ovarian cancers. However, clinical application of **1** is somewhat hampered by rapid metabolism which occurs in a few minutes, involving methyl ester hydrolysis and intracyclic double bond isomerization, both leading to a decreased activity.[5] Besides these prostaglandins of animal origin, marine prostaglandins such as clavulone II[6] (**2**) and punaglandin III[7] (**3**) (Figure 1) have been isolated from corals. The presence of a C-12 OH and above all substitution at C-10 by an electron-withdrawing chlorine strongly enhance the antiproliferative effects, since the IC$_{50}$ values against L1210 for **2** and **3** are 0.6 μM[8] and 0.03 μM,[9] respectively. Although many syntheses of naturally occurring alkylidenecyclopentenone prostaglandins such as **2** and **3** and their analogues have been reported,[5,10] only limited structure−activity relationship studies have been undertaken concerning simplified analogues despite the potential therapeutic opportunities presented by these compounds. Moreover, there is a growing interest to further understand the biological mechanism of action of cyclopentenone prostaglandins.

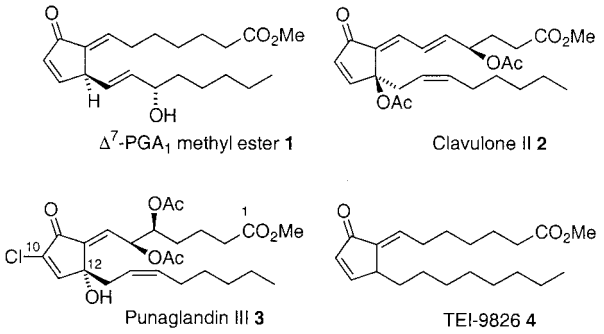

Figure 1. Cytotoxic alkylidenecyclopentenones.

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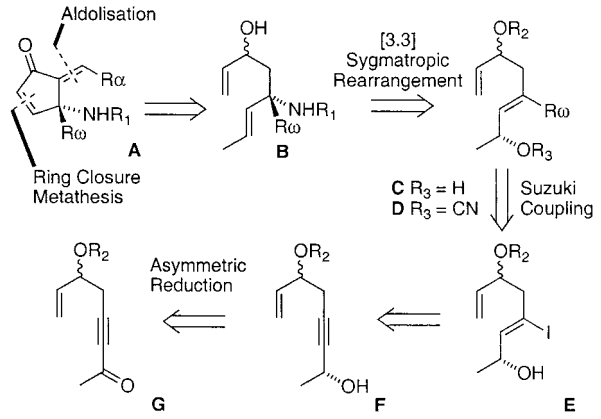
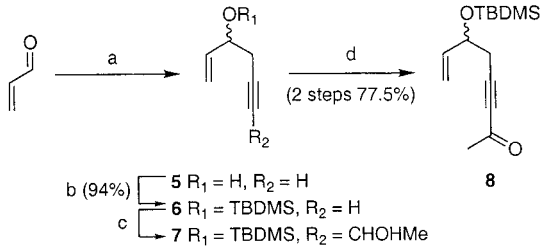


Figure 2. Retrosynthesis.

Recently, a 13,14-dihydro-15-deoxy-Δ^7 prostaglandin A_1 analogue, TEI-9826 (**4**) (Figure 1), has been reported. This compound, which is a very potent analogue active in vivo against cis-platine-resistant tumors, is now under clinical trial.[11] However, its poor water solubility requires the use of lipospheres to enable administration of the drug. The combination of unique molecular architecture and interesting biological properties led us to consider strategies for preparing new analogues that are more water-soluble and metabolically stable.

Retrosynthesis. Our initial interest focused on the synthesis of derivatives such as **A**, with simplified α and *ω* side chains and bearing an amino function at the quaternary position. As depicted in the retrosynthetic scheme (Figure 2), we anticipated that the target cyclopentenone **A** could be obtained by a ring-closing metathesis (RCM) of a suitably functionalized 1,6-diene **B**.[12] Furthermore, the aminated asymmetric quaternary function, as present in **B**, could result from a [3.3] sigmatropic rearrangement of an allylic cyanate **D** which, in turn, could be obtained from the asymmetric allylic alcohol **C**.[13] Allylic alcohol **C** bearing different R*ω* side chains could be elaborated from the iodovinyl compound **E** by palladium-catalyzed Suzuki cross-coupling reaction.[14] The chiral propargylic alcohol **F** has been hypothesized to result from enantioselective reduction of the ynone **G**.

Scheme 1[a]



[a] Reaction conditions: (a) propargyl bromide, Al, $HgCl_2$, THF, −78 °C to rt; (b) TBDMSCl, CH_2Cl_2, imidazole; (c) BuLi, THF, MeCHO, −78 °C; (d) PCC, CH_2Cl_2.

Results and Discussion

Preparation of the 1,5-Diene Framework. The synthesis of ynone **8** began via reaction of acrolein with propargylaluminum, to give the allylic alcohol **5**[15] which was protected as a silyl ether (**6**). Treatment of **6** with BuLi in THF at −78 °C led to a lithium acetylide, which was subsequently reacted with acetaldehyde, affording the racemic propargylic alcohol **7**. The crude alcohol was readily oxidized to ynone **8** by treatment with pyridinium chlorochromate (PCC).

To obtain the single (6(*R*,*S*),2(*R*)) diastereoisomer of propargylic alcohol **7**, a stereoselective reduction of the ynone **8** was attempted using an asymmetric reducing reagent preformed by reaction of the Darvon amino alcohol with $LiAlH_4$ in ether at low temperature (Scheme 2).[16]

The stereochemical outcome of the reduction of ketone **8** was determined by conversion of the alcohol **7** to the corresponding Mosher esters **9** and **10** (Scheme 2). From the ^{1}H NMR study, we deduced that the alcohol **7** was obtained in a 13:2 mixture of 2*R*(6*R*,*S*)/2*S*(6*R*,*S*) diastereoisomers (73% de). It is noteworthy that presence of the second C-6 asymmetric center in both **9** and **10** was not detectable in ^{1}H NMR experiments. No attempt was made to improve the diastereoselectivity of the reduction by using other chiral reducing reagents.[17] The alkyne **7** was next reduced with Red-Al, and the cyclic intermediate alanate was treated with iodine at low temperature, leading to (5*Z*)-5-iodo-1,5-diene **11** in a regioselective manner.[18] The R*ω* side chain was then introduced using palladium-catalyzed cross-coupling reaction between the vinylic iodide **11** and the corresponding 9-alkyl-9-BBN **12** or **13**. This led to the 1,5-dienes **14** and **15**, bearing a 4-fluorobenzyloxypropyl and an octyl linear R*ω* chain, respectively.

Borane **12** was prepared in two steps involving allylation of 4-fluorophenol to give **16** and hydroboration of

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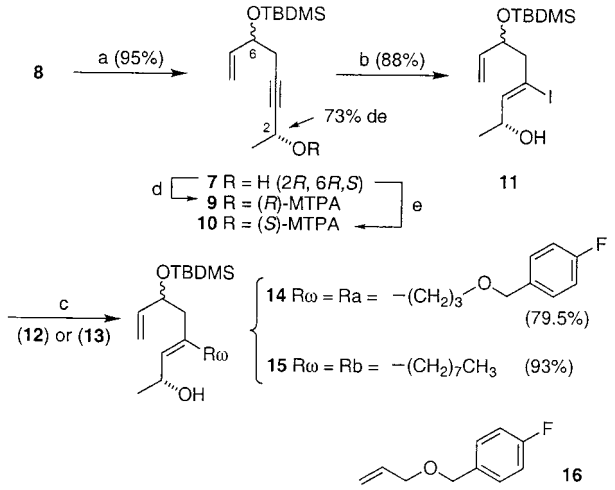
Scheme 2[a]



[a] Reaction conditions: (a) Darvon alcohol, $LiAlH_4$, Et_2O, −78 °C; (b) $(MeO(CH_2)_2O)_2AlH_2Na$, Et_2O, 0 °C, then I_2, THF, −78 to 0 °C; (c) 9-Ra-9-BBN (**12**) or 9-Rb-9-BBN (**13**), $PdCl_2$(dppf), K_3PO_4, DMF, 50 °C; (d) (*R*)-MTPACl, NEt_3, DMAP, CH_2Cl_2; (e) (*S*)-MTPACl, NEt_3, DMAP, CH_2Cl_2.

the latter using 9-BBN-H in THF, giving a solution of the borane **12**. Borane **13** was obtained by 1-octene hydroboration. In both cases, the crude borane solutions were directly used for the next step.

Our trials with the Suzuki cross-coupling between the boranes **12** or **13** and the iodide **11** led us to use an excess of borane (2−3 equiv) to obtain satisfactory yields. Thus, the corresponding compounds **14** and **15** were isolated in 89.5 and 93% yields, respectively.

Formation of the Aminated Quaternary Center. From the allylic alcohols **14** and **15**, the introduction of the nitrogen atom on the quaternary carbon was achieved by using a [3.3] sigmatropic rearrangement of allylic cyanate derivatives.[19] For this purpose, the allylic alcohols were converted into carbamates **17** and **18** (Scheme 3) in near quantitative yields by reaction with trichloroacetyl isocyanate and subsequent hydrolysis. Under dehydrating conditions, allylic carbamate **17** or **18** afforded an allylic cyanate which readily rearranged to give the allylic isocyanate **19** or **20**.

The mechanism of this sigmatropic shift (Figure 3) proceeds by rearrangement of the cyanate **D** to isocyanate **19** or **20** through a transition state (**H**) with a lower activation energy than the transition state **I** where steric hindrance between the axial methyl and the axial Rω chain is present. This is fully consistent with a suprafacial allylic rearrangement as previously reported.[12d,20]

The stereochemistry and the quality of the transfer from the asymmetric allylic cyanate were estimated at a later stage via the Mosher ester derivatives **30a** and **30b** of cyclopentenol intermediate **25b** (vide infra). It is noteworthy that the strongly hindered quaternary isocyanates **19** and **20** are stable enough to allow their chromatographic purification on silica gel.

For completion of this synthesis, we converted the isocyanate to a trimethylsilanylethyloxycarbonyl amino protecting group (Teoc), stable under classical O-desilylating conditions and easily removed under acidic conditions before RCM reaction. Therefore, condensation of the sodium trimethylsilyl ethanolate with the isocyanates **19** and **20** readily afforded the carbamates **21** and **22** in almost quantitative yields. This was followed by a selective desilylation using TBAF to give allylic alcohols **23** and **24**. This deprotection was deemed necessary due to the reported[21] poor reactivity showed by protected allylic alcohols in RCM with ruthenium catalyst **29**.

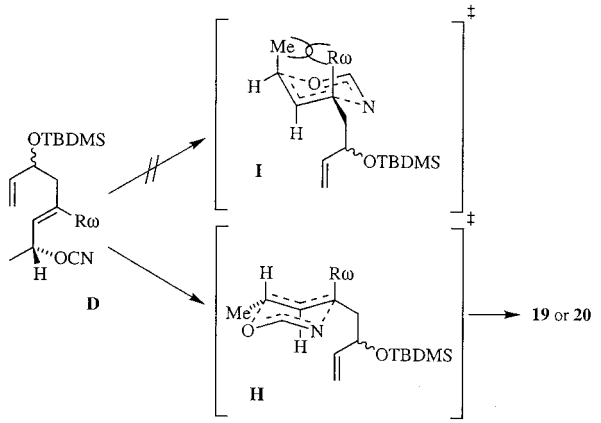


Figure 3. Allylic cyanate [3.3] sigmatropic rearrangement.

Table 1. Torsion Angles and ^{1}H NMR and IR Data for Compounds 25a and 25b

	studied protons[a]	calcd torsion angle (deg), J^3 coupling (Hz)[b]	obsd J^3 coupling constant (Hz)	IR[c]
25a	H_4-H_{5b}	88.4, <0.5	0	3616,[d] 3443[e]
	H_4-H_{5a}	−30.8, 6−7	6.4	
25b	H_4-H_{5b}	35.4, 5−6	6.4	3437[f]
	H_4-H_{5a}	−83.6, <0.5	0	

[a] Proton numbering is shown in Scheme 4. [b] Torsion angle calculations were carried out with the Sibyl package implemented on a silicon graphic station. The minimized energies of compounds **25a** and **25b** were obtained by a random search protocol in a vacuum. [c] Measured in $CHCl_3$ (ν, cm^{-1}). [d] Free O−H. [e] Free N−H. [f] Bound O−H.

Cyclopentenone Ring Formation. Ring-closing metathesis of the 1,6-dienols **23** and **24** with Grubbs catalyst **29** reached completion after 1/2 h (TLC monitoring) to afford the cyclopentenols **25** and **26**, which were then oxidized by in situ addition of NMO, tetrapropylammonium perruthenate, and 4 Å molecular sieves. Such one-pot reaction led to the 4-amino-protected cyclopentenones **27** and **28** in 89 and 90% yields, respectively.

Stereochemistry Determination. To carefully determine the stereochemistry of the aminated stereogenic center as present in **27** and **28**, we isolated the two diastereoisomeric cyclopentenols *trans*-**25a** and *cis*-**25b** obtained by RCM of diene **23** (mixture of 3(*R*,*S*)-diastereoisomers **23a** and **23b**).

Compounds **25a** and **25b** were easily separated by chromatography (R_f = 0.28 and 0.42, respectively; cyclohexane/ethyl acetate, 1:1). The trans configuration of the more polar compound **25a** was unambiguously assigned from IR, and ^{1}H NMR data that are in agreement with the lower energy conformational analysis obtained by molecular modeling employing the MM2 force field (Table 1). The weaker polarity of the compound of cis

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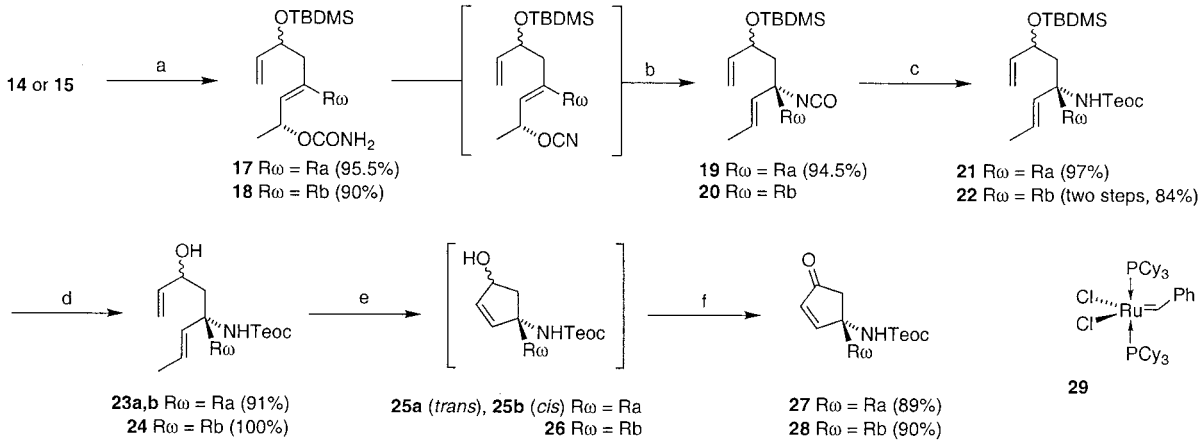
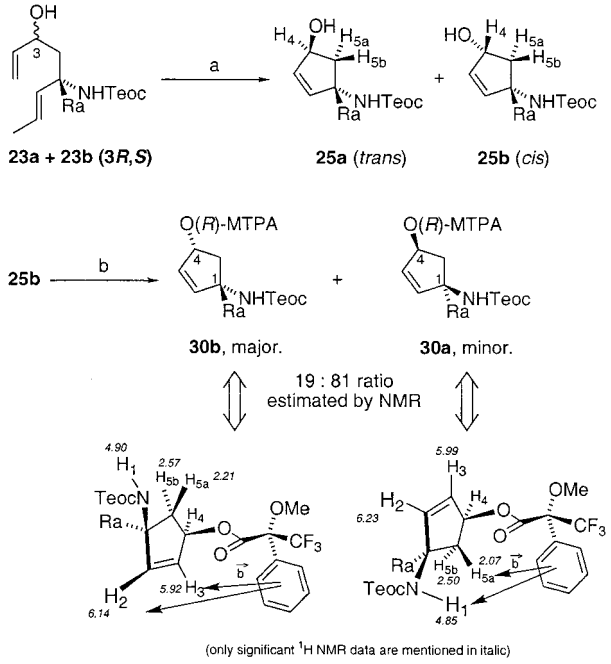
Scheme 3[a]



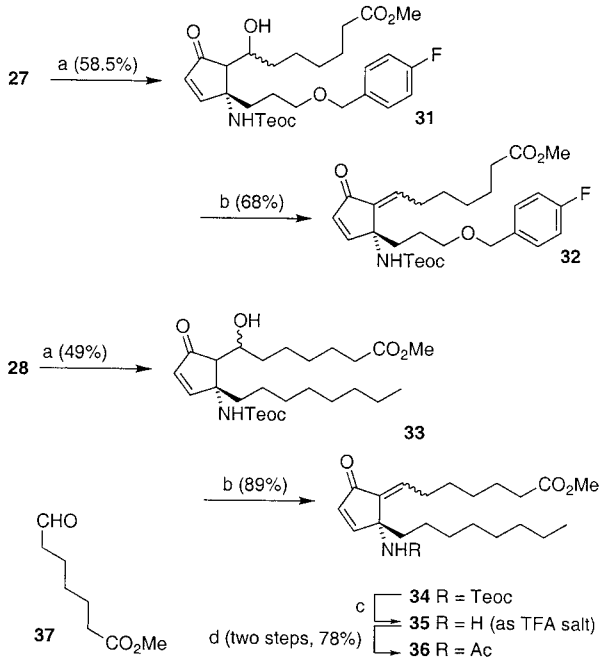
[a] Reaction conditions: (a) $Cl_3CCONCO$, CH_2Cl_2, then K_2CO_3, MeOH/H_2O; (b) PPh_3, CBr_4, NEt_3, CH_2Cl_2, −20 °C; (c) $TMS(CH_2)_2OH$, NaH, THF, 0 °C; (d) TBAF, THF, 0 °C; (e) **29** (1 mol %), CH_2Cl_2; (f) NMO, TPAP, 4 Å molecular sieves.

Scheme 4[a]



[a] Reaction conditions: (a) **29** (1 mol %), CH_2Cl_2, rt; (b) (*R*)-MTPACl, NEt_3, DMAP, CH_2Cl_2.

Scheme 5[a]



[a] Reaction conditions: (a) BuLi, HMDS, **37**, THF, −78 °C; (b) Ac_2O, pyridine, DMAP, 80 °C; (d) TFA, 0 °C to rt; (e) AcCl, NEt_3, CH_2Cl_2, 0 °C to rt.

configuration (**25b**) probably results from intramolecular hydrogen bonding between the hydroxyl and the amino functions. Once the relative configuration of the OH and NH substituents of **25a** and **25b** was established, determination of the absolute configuration for the C−OH of **25b** and its enantiomeric purity was undertaken (Scheme 4).

For this purpose the (*R*)-MTPA ester of the *cis*-cyclopentenol **25b** was synthesized. The ^{1}H NMR revealed the presence of two diastereoisomers (**30a** and **30b**) in a 9:2 or 81:19 (see Scheme 4) ratio. As a consequence we can conclude that the [3.3] sigmatropic rearrangement of allylic cyanates occurred with only negligible loss of chirality at C-2, since the precursor propargylic alcohol **7** was itself a mixture of diastereoisomers at this position, C-2, in a 2:13 ratio. Moreover, the absolute configurations of major (**30b**) and minor (**30a**) cyclopentenols were deduced from the study of the shielding effects induced by the aromatic ring (b vectors, Scheme 4) of the (*R*)-MTPA group upon the hydrogens H_1, H_{5b}, and H_{5a} (**30a**) and H_3 and H_2 (**30b**) as given in italics.

According to the Mosher conformation rule applied on compound **30b**, as depicted in Scheme 4, we can assign the absolute configuration of C-4 as *R*. Since we have a cis configuration for compound **25b**, we can deduce that the major enantiomer of compound **25b** is 1*S* and 4*R*. This confirms that the [3.3] sigmatropic rearrangement took place via the postulated more energetically favorable transition state **H** (Figure 3).

Introduction of the α Side Chains. To achieve the synthesis of the target compounds, introduction of the α side chain was realized using the classical aldol reaction of the enolate obtained from the ketone **27** or **28**, with suitable aldehydes. Ketones **27** and **28** were thus converted into lithium enolates with LiHMDS, and reacted

at −78 °C with the aldehyde **37**.[22] This led to aldols **31** and **33** (Scheme 5) which were eliminated by treatment with acetic anhydride in pyridine in the presence of a catalytic amount of DMAP at 80 °C, to afford the cyclopentadienones **32** and **34** as a 3:1 mixture of *E*/*Z* diastereoisomers. Removal of the Teoc group of **34** with trifluoroacetic acid provided **35** as its trifluoroacetylammonium salt, and then amide **36** after acetyl chloride in pyridine treatment.

Biological Activities. The products **32**, **34**, **35**, and **36**, tested on L1210 leukemia cells, showed IC_{50} values of 2.7, 4.1, 0.7, and 10.7 μM, respectively.

Conclusion

The synthesis of 12-amino prostaglandins was achieved via a novel strategy consisting of the construction of the chiral amino cyclopentenone moiety using a cyanate [3.3] sigmatropic rearrangement followed by an RCM reaction. The latter reaction is currently being generalized to other cyclopentenone prostaglandins in our laboratory. The cytotoxicity of the amino prostanoids was evaluated against L1210 leukemia cells. Their IC_{50} (0.7 μM) compares favorably with the closely related IC_{50} values for the Δ^7-PGA_1 methyl esters and Δ^{12}-PGJ_2. Further biological evaluation of the 12-amino analogue **35** of TEI-9826 is currently in progress.

Experimental Section

General Experimental Procedures. Measurements of NMR spectra (300 or 400 MHz, ^{1}H; 75 MHz, ^{13}C) were made in $CDCl_3$ (which also provided the lock signal at $\delta = 7.26$ ppm, ^{1}H). Mass spectra were determined with CI (NH_3 or CH_4). Melting points are uncorrected. Optical rotations were measured at 25 °C. Silica gel 60 (35−70 μm) was used for flash chromatography, and distilled cyclohexane, ethyl acetate, and dichloromethane were used as eluents. Analytical plates (Merck 60 F_{254} aluminum sheets) were rendered visible by spraying with paranisaldehyde−H_2SO_4−AcOH−EtOH or with phosphomolybdic acid (5% in ethanol), followed by heating. THF and ether were distilled from sodium/benzophenone prior to use. CH_2Cl_2 was distilled from P_2O_5 prior to use. DMF was stored over 4 Å molecular sieves under a dry argon atmosphere. Triethylamine was stored under an argon atmosphere.

***tert*-Butyldimethyl(1-vinylbut-3-ynyloxy)silane (6).** Alcohol **5** (2.73 g, 28.45 mmol) in anhydrous dichloromethane (80 mL) was cooled to 0 °C prior to the addition of imidazole (2.51 g, 37 mmol) and *tert*-butyldimethylchlorosilane (5.14 g, 34.2 mmol). The solution was stirred for 24 h at room temperature and quenched with a saturated solution of sodium hydrogenocarbonate (100 mL). The organic layer was extracted with ether (2 × 100 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/ethyl acetate, 50:1) afforded alcohol **6** as a colorless oil (5.63 g, 94%): IR ($CHCl_3$) 3309, 2957, 2931, 2858, 2121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.98 (t, 1H, J = 2.8, 2.4 Hz), 2.36 (m, 2H, J = 2.8, 6.5 Hz), 4.25 (q, 1H, J = 6.0, 1.0 Hz), 5.10 (dd, 1H, J = 1.4, 10.3 Hz), 5.25 (dd, 1H, J = 17.0 Hz), 5.90 (m, 1H); MS (CI$^+$, NH_3) m/z 228 (M + NH_4)$^+$. Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.51; H, 10.54. Found: C, 68.48; H, 10.60.

(2*R*)-6-(*tert*-Butyldimethylsilanyloxy)oct-7-en-3-yn-2-ol (7). A solution of Darvon alcohol (1.01 g, 3.55 mmol) in ether (7.7 mL) was added, under an argon atmosphere, to a suspension of $LiAlH_4$ (61 mg, 1.61 mmol) in anhydrous ether (40 mL) at 0 °C. After being stirred for 5 min, the solution was cooled to −78 °C, and the ynone **8** (339 mg, 1.34 mmol), dissolved in anhydrous ether (7.7 mL), was slowly introduced over a period of 2.5 h. The resulting solution was stirred for 5 h at −78 °C and was then allowed to reach room temperature. The reaction was quenched by addition of aq 3 N hydrochloric acid and extracted with ether (2 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Purification was conducted by flash chromatography on silica gel (cyclohexane/ethyl acetate, 6:1), yielding alcohol **7** as a colorless oil (324.4 mg, 95%): IR ($CHCl_3$) 3605, 2957, 2931, 2858 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 1.43 (d, 3H, J = 6.5 Hz), 1.65 (br s, 1H), 2.33 (ddd, 1H, J = 2.0, 9.7 Hz), 2.42 (ddd, 1H, J = 2.0, 6.5 Hz), 4.23 (q, 1H, J = 6.5 Hz), 4.51 (q, 1H, J = 6.5 Hz), 5.10 (dt, 1H, J = 10.3, 1.4 Hz), 5.24 (dt, 1H, J = 17.6, 1.4 Hz), 5.90 (m, 1H, J = 10.3 Hz); MS (CI$^+$, NH_3) m/z 272 (M + NH_4)$^+$. Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 66.23; H, 9.97.

6-(*tert*-Butyldimethylsilanyloxy)oct-7-en-3-yn-2-one (8). A 1.6 N solution of BuLi in hexane (3.91 mL, 6.26 mmol) was slowly added to a solution of alkyne **6** (1.07 g, 5.08 mmol) in anhydrous THF (21 mL) under an argon atmosphere at −78 °C. After the resulting solution was stirred for 1 h, freshly distilled acetaldehyde (0.62 mL, 11.17 mmol, kept over 4 Å molecular sieves) was then introduced, and the temperature was allowed to reach room temperature over 15 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride (50 mL) and then extracted with ether (3 × 30 mL). The organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The oily colorless propargylic alcohol **7** (racemic) was dissolved in anhydrous dichloromethane (15 mL), and pyridinium chlorochromate (2.40 g, 11.17 mmol) was added. After the solution was stirred overnight at room temperature, silica gel was added, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate, 40:1) afforded the ynone **8** as a pale yellow oil (1.10 g, 77.5%): IR ($CHCl_3$) 2957, 2931, 2887, 2858, 2213, 1672 cm^{-1}; ^{1}H NMR (300 MHz, CHCl3) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 2.31 (s, 3H), 2.50 (dd, 1H, J = 16.9, 6.3 Hz), 2.57 (dd, 1H, J = 16.9, 6.6 Hz), 4.32 (q, 1H, J = 6.5, 6.0 Hz), 5.13 (dd, 1H, J = 10.3 Hz), 5.25 (dd, 1H, J = 15.6 Hz), 5.85 (m, 1H); MS (CI$^+$, NH_3) m/z 270 (M + NH_4)$^+$. Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 65.82; H, 9.68.

3,3,3-Trifluoro-2(*R*)-methoxy-2-phenylpropionic Acid 5(*R*,*S*)-(*tert*-Butyldimethylsilanyloxy)-1(*R*)-methylhept-6-en-2-ynyl Ester (9). To a solution of propargylic alcohol **7** (25.2 mg, 99.0 μmol) in anhydrous dichloromethane (5 mL) under argon were added DMAP (50 mg, 198 μmol), triethylamine (20 mL, 138 μmol), and (*R*)-MTPACl (30 mg, 119 μmol). After being stirred for 20 min, the reaction was quenched by addition of aq NH_4Cl (10 mL) and extracted with dichloromethane. The organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a solid. Purification by flash column chromatography (cyclohexanes/ethyl acetate, 10:1) gave compound **9** (48 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (m, 6H), 0.89 (s, 9H), 1.49 (d, 0.39H, J = 6.8 Hz), 1.56 (d, 2.61H, J = 6.8 Hz), 2.36 (m, 2H), 3.57 (s, 2.61H), 3.59 (s, 0.39H), 4.20 (m, 1H), 5.06 (m, 1H), 5.20 (m, 1H), 5.65 (m, 1H), 5.82 (m, 1H), 7.40 (m, 3H), 7.54 (m, 2H); MS (CI$^+$, NH_3) m/z 488 (M + NH_4)$^+$.

3,3,3-Trifluoro-2-(*S*)-methoxy-2-phenylpropionic Acid 5(*R*,*S*)-(*tert*-Butyldimethylsilanyloxy)-1(*R*)-methylhept-6-en-2-ynyl Ester (10). The same protocol as above, starting with **7** and (*S*)-MTPACl, led to compound **10**: ^{1}H NMR (400 MHz, CDCl3) δ 0.06 (m, 6H), 0.89 (s, 9H), 1.49 (d, 2.61H, J = 6.8 Hz), 1.56 (d, 0.39H, J = 6.8 Hz), 2.36 (m, 2H, H5), 3.56 (s, 0.39H), 3.58 (s, 2.61H), 4.22 (m, 1H), 5.06 (m, 1H), 5.20 (m, 1H), 5.66 (m, 1H), 5.84 (m, 1H), 7.40 (m, 3H), 7.54 (m, 2H); MS (CI$^+$, NH_3) m/z 488 (M + NH_4)$^+$.

(*Z*)-(2*S*)-6(*R*,*S*)-(*tert*-Butyldimethylsilanyloxy)-4-iodo-octa-3,7-dien-2-ol (11). A 3.5 N solution of Red-Al (1.49 mL, 5.20 mmol) was diluted in anhydrous ether (10 mL) under an argon atmosphere and cooled to 0 °C. Propargylic alcohol **7**

(22) The aldehyde **31** was obtained in three steps from suberone: Robinson, R.; Hart Smith, L. *J. Chem. Soc.* **1937**, 371−374.

(602.0 mg, 2.37 mmol), dissolved in anhydrous ether (5 mL), was introduced. After the resulting solution was stirred for 30 min, the temperature was gradually raised to room temperature and the reaction stirred for an additional 3 h. The solution was quenched with anhydrous ethyl acetate (0.474 mL) at 0 °C. After 30 min, the solution was cooled to −78 °C, and a solution of iodine (0.78 g, 7.28 mmol) in anhydrous THF (4 mL) was slowly added. After 15 min, the reaction mixture was allowed to reach room temperature, and a 10% solution of sodium thiosulfate (20 mL) was added followed by a saturated aq ammonium chloride solution (20 mL). After extraction with ether, the organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (cyclohexane/ethyl acetate, 6:1) led to compound **11** as a colorless oil (798.7 mg, 88.5%): IR ($CHCl_3$) 3605, 2958, 2931, 2897, 2858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 and 0.89 (s, 9H), 1.27 (d, 3H, J = 6.4 Hz), 1.64 and 1.70 (2 br s, 1H), 2.56 (m, 1H), 2.67 (m, 1H), 4.38 (q, 1H), 4.43 (m, 1H), 5.06 (dd, 1H, J = 3.5, 1.4 Hz), 5.27 (dd, 1H, J = 17.2, 9.9 Hz), 5.66 (2 d, 1H, J = 5.4 Hz), 5.79 (m, 1H); MS (CI^+, NH_3) m/z 400 $(M + NH_4)^+$. Anal. Calcd for $C_{14}H_{27}IO_2Si$: C, 43.98; H, 7.12. Found: C, 44.73; H, 7.26.

(*E*)-(2*S*)-6(*R,S*)-(*tert*-Butyldimethylsilanyloxy)-4-[3-(4-fluorobenzyloxy)propyl]octa-3,7-dien-2-ol (14). To the vinyl derivative **16** (798.1 mg, 4.75 mmol) was added a 0.5 M solution of 9-BBN-H in THF (9.61 mL, 4.75 mmol) at 0 °C under an argon atmosphere. The ice bath was removed, and the solution was stirred for 5 h, giving the solution of borane **12**. The vinyl iodide **11** (907.7 mg, 2.37 mmol), K_3PO_4 (1.108 g, 5.22 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (58 mg, 71 mmol) were dissolved in anhydrous DMF (12 mL). The borane solution **12** was then added, and the solution was stirred at 50 °C for 15 h. The reaction was quenched with brine (50 mL), ether (50 mL) was then added, and under strong stirring, a 30% aq H_2O_2 solution (5 mL) was added. After being stirred for 10 min, the reaction was extracted with ether (2 × 50 mL), the organic layer dried over anhydrous $MgSO_4$ and filtered, and the solvent removed under reduced pressure. Purification using flash chromatography over silica gel (cyclohexane/ethyl acetate, 10:1) gave allylic alcohol **14** as a pale yellow oil (795.5 mg, 79.5%): IR ($CHCl_3$) 3610, 3443, 2930, 2859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.88 (s, 9H), 1.22 (dd, 3H, J = 2.1, 6.4 Hz), 1.70 (m, 3H), 2.16 (m, 3H), 2.32 (m, 1H), 3.46 (m, 2H), 4.19 (q, 1H, J = 12.0, 6.0 Hz), 4.46 (s, 2H), 4.56 (m, 1H, J = 6.2 Hz), 5.02 (dt, 1H, J = 1.2, 10.3 Hz), 5.13 (dt, 1H, J = 1.4, 18.8 Hz), 5.31 (d, 1H, J = 8.8 Hz), 5.79 (m, 1H), 7.03 (m, 2H), 7.30 (m); MS (CI^+, NH_3) m/z 423 $(M + H)^+$. Anal. Calcd for $C_{24}H_{39}FO_3Si$: C, 68.20; H, 9.30. Found: C, 68.17; H, 9.37.

(*E*)-(2*R*)-6(*R,S*)-(*tert*-Butyldimethylsilanyloxy)-4-octylocta-3,7-dien-2-ol (15). From 9-octyl-9-BBN **13**, prepared by reaction of 1-octene with 1 equiv of 9-BBN-H in solution in THF, and using the procedure described for compound **14**, compound **15** was obtained (477 mg, 93%): IR ($CHCl_3$) 3609, 2957, 2929, 2857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.89 (m, 12 H), 1.23 (dd, 3H, J = 2.3, 6.1 Hz), 1.28 (s, 12H), 1.58 (s, 1H), 2.08 (t, 2H, J = 8.7 Hz), 2.16 (m, 2H, J = 7.0, 6.0 Hz), 4.19 (q, 1H, J = 6.1 Hz), 4.57 (q, 1H, J = 8.6 Hz), 5.02 (d, 1H, J = 10 Hz), 5.13 (dt, 1H, J = 15.8 Hz), 5.23 (d, 1H, J = 8.8 Hz), 5.78 (m, 1H); MS (CI^+, NH_3) m/z 368 $(M)^+$, 386 $(M + NH_4)^+$. Anal. Calcd for $C_{22}H_{44}O_2Si$: C, 71.67; H, 12.03. Found: C, 71.39; H, 11.95.

(*E*)-Carbamic Acid 5(*R,S*)-(*tert*-Butyldimethylsilanyloxy)-3-[3-(4-fluorobenzyloxy)propyl]-1-methylhepta-2,6-dienyl Ester (17). Trichloroacetyl isocyanate (472 μL, 3.96 mmol) was slowly added to a solution of allylic alcohol **14** (1.115 g, 2.64 mmol) in anhydrous dichloromethane (23 mL) at 0 °C under an argon atmosphere. After 3 h of stirring, the solvent was removed under reduced pressure, and the residue obtained was dissolved in a mixture of methanol (20 mL) and water (8 mL) and cooled to 0 °C. Potassium carbonate (10.9 g, 79 mmol) was added, and the mixture was stirred for 30 min at 0 °C, followed by an additional 2 h at room temperature. The solution was quenched with brine (50 mL) and extracted with ether (3 × 50 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Purification using flash chromatography over silica gel (cyclohexane/ethyl acetate, 5:1) gave allylic carbamate **17** as a colorless oil (1.172 g, 95.5%): IR ($CHCl_3$) 3548, 3434, 2931, 2858, 1723, 1583, 1510, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.88 (s, 9H), 1.27 (m, 3H, J = 6.3 Hz), 1.70 (m, 2H), 2.18 (m, 4H), 3.46 (t, 2H, J = 6.5 Hz), 4.19 (m, 1H), 4.46 (s, 2H), 4.53 (br s, 2H), 5.02 (dd, 1H, J = 1.4, 10.4 Hz), 5.13 (d, 1H, J = 17.5 Hz), 5.22 (dd, 1H, J = 5.0, 8.9 Hz), 5.50 (m, 1H), 5.77 (m, 1H), 7.03 (m, 2H), 7.32 (m, 2H); MS (CI^+, NH_3) m/z 483 $(M + NH_4)^+$. Anal. Calcd for $C_{25}H_{40}FNO_3Si$: C, 64.48; H, 8.66. Found: C, 64.32; H, 8.53.

(*E*)-Carbamic Acid 5(*R,S*)-(*tert*-Butyldimethylsilanyloxy)-1-methyl-3-octylhepta-2,6-dienyl Ester (18). The same procedure used for **17**, but this time from **15**, gave compound **18** as a colorless oil (519 mg, 90%): IR ($CHCl_3$) 3548, 3434, 2930, 2857, 1719, 1372 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.88 (m, 12H), 1.27 (m, 12H), 2.16 (m, 4H, J = 7.2 Hz), 4.19 (q, 1H, J = 1.1, 5.9 Hz), 4.48 (br s, 2H), 5.01 (dd, 1H, J = 1.0, 11.5 Hz), 5.13 (dq, 1H, J = 17.2 Hz), 5.19 (dd, 1H, J = 8.8, 6.8 Hz), 5.50 (m, 1H), 5.79 (m, 1H, J = 1.0 Hz); MS (CI^+, NH_3) m/z 429 $(M + NH_4)^+$. Anal. Calcd for $C_{23}H_{45}NO_3Si$: C, 67.10; H, 11.02; N, 3.40. Found: C, 67.40; H, 10.92; N, 3.39.

(*E*)-{3-(*tert*-Butyldimethylsilanyloxy)-1(*R,S*)-[3-(4-fluorobenzyloxy)propyl]-1-propenylpent-4-enyl}carbamic Acid 2-(Trimethylsilanyl)ethyl Ester (19). A solution of carbamate **17** (172.5 mg, 0.371 mmol), triphenylphosphine (243 mg, 0.93 mmol), and triethylamine (102 μL, 0.742 mmol) in anhydrous CH_2Cl_2 (2.8 mL) was cooled to −20 °C under an argon atmosphere. A solution of carbon tetrabromide (344 mg, 1.039 mmol) in anhydrous CH_2Cl_2 (2 mL) was slowly added. After 55 min of reaction, the temperature was allowed to reach 0 °C. The solvent was then removed under reduced pressure, and purification by flash chromatography over silica gel (cyclohexane/ethyl acetate, 10:1) gave the allylic isocyanate **19** as a colorless oil (156.3 mg, 94.5%): IR (CHCl3) 2930, 2858, 2270, 1510, 1255, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 and 0.03 (s, 6H), 0.88 (2 s, 9H), 1.59−1.96 (br m, 9H), 3.45 (m, 2H), 4.26 (m, 1H), 4.45 (s, 2H), 5.00−5.36 (br m, 3H), 5.63−5.85 (br m, 2H), 7.03 (m, 2H), 7.30 (m, 2H); MS (CI^+, NH_3) m/z 448 $(M + H)^+$, 465 $(M + NH_4)^+$; HMRS (CI^+, NH_4^+) m/z calcd for $C_{25}H_{38}FNO_3Si$ $(M + H^+)$ 448.6783, found 448.6780.

(*Z*)-{1-[3-(4-Fluorobenzyloxy)propyl]-4-oxocyclopent-2-enyl}carbamic Acid 2-(Trimethylsilanyl)ethyl Ester (21). The isocyanate **19** (141.1 mg, 0.315 mmol) and trimethylsilylethanol (452 μL, 3.15 mmol) were dissolved in anhydrous THF (2 mL) under an argon atmosphere. This solution was cooled to 0 °C, and NaH (50% in mineral oil, 18.2 mg, 0.378 mmol) was introduced. After 20 min of reaction at 0 °C, a saturated ammonium chloride solution (10 mL) was added. The reaction was extracted with ether (3 × 10 mL), the organic layer dried over $MgSO_4$ and filtered, and the solvent removed under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate, 20:1) gave the carbamate **21** as a colorless oil (172.6 mg, 97%): IR ($CHCl_3$) 3389, 2957, 2858, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (m, 15 H), 0.90 (m, 11H), 1.56 (m, 2H), 1.70 (m, 3H), 1.95 (m, 1H, J = 4.9 Hz), 3.44 (m, 2H, J = 5.0, 1.9 Hz), 4.03 (m, 2H), 4.29 (m, 1H), 4.44 (d, 2H), 5.00 (d, 1H, J = 10.3 Hz), 5.05 (dd, 1H, J = 17 Hz), 5.48 (m, 2H), 5.60 (br s, 0.6H), 5.75 (m, 1H), 6.16 (br s, 0.4H), 7.02 (m, 2H), 7.28 (m, 2H). MS (CI^+, NH_3) m/z 566 $(M + H)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{30}H_{53}FNO_4Si_2$ $(M + H^+)$ 566.9306, found 566.9304.

[3(*R,S*)-(*tert*-Butyldimethylsilanyloxy)-1-octyl-1-propenylpent-4-enyl]carbamic Acid 2-(Trimethylsilanyl)-ethyl Ester (22). The same procedure for compound **21** was used and gave from compound **20** the compound **22** (510 mg, 84%, from compound **18**): IR ($CHCl_3$) 3389, 2957, 2930, 2857, 1717, 1510, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 0.05 (m, 15H), 0.91 (m, 14H), 1.26 (s, 12H), 1.35−1.98 (m, 7H), 4.06 (m, 2H), 4.30 (m, 1H), 5.00 (d, 1H, J = 10.2 Hz), 5.08 (dd, 1H, J = 17.4, 4.4 Hz), 5.45 (m, 2H), 5.61 (m, 1H), 5.79 (m, 1H, J = 2.2 Hz); MS (CI^+, NH_3) m/z 512 $(M + H)^+$. Anal. Calcd for

$C_{28}H_{57}NO_3Si$: C, 65.69; H, 11.22; N, 2.74. Found: C, 65.95; H, 11.18; N, 2.79.

{1-[3(*R*,*S*)-(4-Fluorobenzyloxy)propyl]-3-hydroxy-1-propenylpent-4-enyl}carbamic Acid 2-(Trimethylsilanyl)-ethyl Ester (23a and 23b). A 1 M solution of tetrabutylammonium fluoride in THF (2.2 mL, 2.2 mmol) was added to a solution of silyl ether **21** (1.017 g, 1.798 mmol) in THF (25 mL) at 0 °C under an argon atmosphere. After being stirred for 1 h at 0 °C, the reaction was quenched by brine (30 mL) and extracted with ether, and the organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Separation by flash chromatography (cyclohexane/ethyl acetate, 5:1 and then 3:1) gave partially separated diastereoisomeric alcohols **23a** and **23b** as colorless oils (total mass 817.7 mg, 100%). Data for diastereoisomer **23a**: IR ($CHCl_3$) 3605, 3384, 2957, 2856, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.95 (m, 2H), 1.62 (m, 3H, J = 6.7 Hz), 1.88 (m, 1H), 1.98 (dd, 1H, J = 6.9 Hz), 2.50 (m, 1H), 3.46 (m, 2H, J = 2.6, 6.5 Hz), 4.09 (m, 2H), 4.34 (m, 1H), 4.45 (s, 2H), 5.07 (dd, 1H, J = 1.3, 10.3 Hz), 5.20 (d, 1H, J = 17.0 Hz), 5.50 (br m, 2H), 5.84 (m, 1H), 5.96 (s, 1H), 7.02 (m, 2H), 7.28 (m, 2H). Data for diastereoisomer **23b**: IR ($CHCl_3$) 3590, 3430, 2957, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9H), 0.95 (m, 2H, J = 3.7, 8.5 Hz), 1.63 (m, 3H), 1.67 (m, 1H), 1.74 (d, 3H, J = 4.7 Hz), 1.83 (m, 1H, J = 8.8, 14.7 Hz), 2.04 (m, 1H), 2.10 (dd, 1H, J = 3.0, 14.7 Hz), 2.20 (m, 1H), 3.44 (m, 2H, J = 7.1 Hz), 4.09 (m, 2H, J = 3.7, 8.5 Hz), 4.30 (m, 1H), 4.45 (s, 2H), 5.07 (d, 1H, J = 10.3 Hz), 5.20 (d, 2H, J = 17.1 Hz), 5.52 (m, 2H), 5.86 (m, 1H), 7.03 (m, 2H), 7.29 (m, 2H). Data for diastereoisomers **23a** and **23b**: MS (CI^+, NH_3) m/z 434 $(M + NH_4)^+$. Anal. Calcd for $C_{24}H_{38}FNO_4Si$: C, 63.82; H, 8.48. Found: C, 63.63; H, 8.48.

(1*S*)-(3(*R*,*S*)-Hydroxy-1-octyl-1-propenylpentyl-4-enyl)-trimethylsilylethyl Carbamate (24). The same procedure described for **23a** and **23b** gave from compound **22** the compound **24** (374 mg, 100%): IR ($CHCl_3$) 3605, 3388, 2957, 2929, 2857, 1718, 1516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.87 (t, 3H, J = 6.5 Hz), 0.96 (m, 2H), 1.25 (s, 12H), 1.58 (s, 1H), 1.60 (m, 1H), 1.73 (d, 3H, J = 5.4 Hz), 1.96 (m, 3H), 4.09 (m, 2H), 4.32 (br m, 1H), 5.07 (dd, 1H, J = 1.1, 10.3 Hz), 5.20 (d, 1H, J = 17.5 Hz), 5.47 (m, 2H), 5.58 (m, 2H); MS (CI^+, NH_3) m/z 398 $(M + H)^+$. Anal. Calcd for $C_{22}H_{43}NO_3Si$: C, 66.45; H, 10.90; N, 3.52. Found: C, 66.26; H, 10.76; N, 3.39.

(1*S*)-(4*S*)-{1-[3-(4-Fluorobenzyloxy)propyl]-4-hydroxycyclopent-2-enyl}carbamic Acid 2-(Trimethylsilanyl)-ethyl Ester (25a) and (1*S*)-(4*R*)-{1-[3-(4-Fluorobenzyloxy)-propyl]-4-hydroxycyclopent-2-enyl}carbamic Acid 2-(Trimethylsilanyl)ethyl Ester (25b). The mixture of dienes **23a** and **23b** (32.5 mg, 72 μmol) was dissolved in dichloromethane (2 mL) under an argon atmosphere. The Grubbs catalyst **29** (1.2 mg, 1.5 μmol) was then introduced into the flask. After the solution was stirred 10 min, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate, 1:1), giving cyclopentenols **25a** (13.2 mg, 45%) and **25b** (13.7 mg, 47%). Data for **25a**: $[\alpha]_D$ −36 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3613, 3443, 2956, 2861, 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.92 (m, 2H), 1.67 (m, 3H), 1.77 (dd, 1H, J = 3.6, 14.2 Hz), 1.86 (m, 2H), 2.51 (q, 1H, J = 7.3, 14.1 Hz), 3.48 (t, 2H), 4.07 (t, 2H), 4.46 (s, 2H), 4.97 (br s, 1H), 5.05 (m, 1H), 5.90 (s, 2H), 7.03 (m, 2H), 7.30 (m, 2H). Data for **25b**: $[\alpha]_D$ −35 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3437, 2955, 2861, 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.91 (m, 2H), 1.66 (m, 5H), 2.03 (d, 1H, J = 15.0 Hz), 2.35 (dd, 1H, J = 6.4, 15.0 Hz), 3.47 (m, 2H), 4.06 (m, 2H), 4.47 (s, 2H), 4.60 (br s, 1H), 5.43 (s, 1H), 5.58 (d, 1H, J = 5.4 Hz), 6.00 (d, 1H, J = 5.4 Hz), 7.04 (m, 2H), 7.30 (m, 2H). Data for **25a** and **25b**: HRMS (CI^+, NH_3) m/z calcd for $C_{21}H_{33}FNO_4Si$ 410.5853, found 410.5850.

{1-[3-(4-Fluorobenzyloxy)propyl]-4-oxocyclopent-2-enyl}carbamic Acid 2-(Trimethylsilanyl)ethyl Ester (27). The diene **23a** and **23b** (764 mg, 1.69 mmol) was dissolved in anhydrous dichloromethane (43 mL) under an argon atmosphere, and the Grubbs catalyst **29** (13 mg, 16 μmol) was added. After 1 h of stirring at room temperature, *N*-methylmorpholine *N*-oxide (297 mg, 2.53 mmol), 4 Å molecular sieves (845 mg), and tetrapropylammonium perruthenate (29 mg, 84 μmol) were introduced, and the mixture was stirred for an additional 1 h and 40 min. The reaction was quenched with a 10% solution of sodium thiosulfate, and the organic layer was washed with brine and a saturated copper sulfate solution. This was dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (cyclohexane/ethyl acetate, 3:1) afforded the cyclopentenone **27** as a colorless oil (661 mg, 89%): $[\alpha]_D$ −23 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3441, 2957, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.92 (m, 2H), 1.66 (m, 2H, J = 7.6 Hz), 1.83 (m, 2H, J = 7.3 Hz), 2.42 (d, 1H, J = 18.0 Hz), 2.77 (d, 1H, J = 18.0 Hz), 3.46 (t, 2H, J = 6.0 Hz), 4.07 (m, 2H), 4.46 (s, 2H), 5.34 (br s, 1H), 6.18 (d, 1H, J = 5.7 Hz), 7.03 (t, 2H), 7.30 (t, 2H), 7.48 (d, 1H, J = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.6, 17.7, 24.5, 36.4, 46.9, 61.5, 63.3, 69.6, 72.5, 115.5, 129.5, 133.6, 133.7, 155.3, 164.0, 165.2, 206.4; HRMS (CI^+, NH_3) m/z calcd for $C_{21}H_{31}O_4NFSi$ 408.2008, found 408.2001. Anal. Calcd for $C_{21}H_{30}O_4NFSi$: C, 61.89; H, 7.42. Found: C, 61.82; H, 7.52.

(1*S*)-(1-Octyl-4-oxocyclopent-2-enyl)carbamic Acid 2-(Trimethylsilanyl)ethyl Ester (28). The diene **24** (347 mg, 0.87 mmol) was dissolved in anhydrous dichloromethane (22 mL) under an argon atmosphere. The Grubbs catalyst **29** was added (7 mg, 9 μmol), and 50 min later, *N*-methylmorpholine *N*-oxide (153 mg, 1.31 mmol), 4 Å molecular sieves (436 mg), and tetrapropylammonium perruthenate (15 mg, 43 μmol) were introduced. After the solution was stirred for 3 h and 20 min, the medium was passed through a short silica gel column (eluent dichloromethane/ethyl acetate, 10:1) to give the cyclopentenone **28** free from ruthenium. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate, 5:1) gave cyclopentenone **28** as a colorless oil (278 mg, 90%): $[\alpha]_D$ −15 (*c* 1.1, $CDCl_3$); IR ($CHCl_3$) 3443, 2957, 2930, 2857, 1718, 1500, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.86 (t, 3H, J = 5.1 Hz), 0.93 (m, 2H), 1.24 (s, 12H), 1.67 (m, 1H), 1.80 (m, 1H), 2.43 (d, 1H, J = 18.5 Hz), 2.71 (d, 1H, J = 18.5 Hz), 4.09 (m, 2H), 4.90 (s, 1H), 6.16 (d, 1H, J = 5.7 Hz), 7.48 (dl, J = 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.6, 14.0, 17.7, 24.5, 28.5, 29.1, 29.3, 29.6, 31.7, 33.6, 47.0, 51.5, 63.2, 133.6, 155.2, 165.7, 206.6; MS (CI^+, NH_3) m/z 371 $(M + NH_4)^+$. Anal. Calcd for $C_{19}H_{35}NO_3Si$: C, 64.54; H, 9.98; N, 3.96. Found: C, 64.89; H, 10.03; N, 3.97.

(1*R*,4*S*)- and (1*S*,4*R*)-4-[3-(4-Fluorobenzyloxy)propyl]-4-[2-(trimethylsilanyl)ethoxycarbonylamino]cyclopent-2-enecarboxylic Acid 2,2,2-Trifluoro-1-methoxy-1-phenylethyl Ester (30a and 30b). To a solution of cyclopentenol **25b** (9.5 mg, 23 μmol) in anhydrous dichloromethane (0.3 mL) were added DMAP (11 mg, 92 μmol) and triethylamine (5 mL, 32 μmol). To this solution was then added, under argon, (*R*)-MTPACl (9 mg, 34.5 μmol) in 0.3 mL of anhydrous dichloromethane. After being stirred for 30 min, the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution. After extraction with dichloromethane, the organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue obtained was purified by flash column chromatography (cyclohexanes/ethyl acetate, 10:1) and gave diastereoisomers esters **30a** and **30b** (11.5 mg, 79%) in an 81:19 ratio (as determined by ^1H NMR spectroscopy): ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.92 (m, 2H), 1.58 (m), 1.86 (m, 2H), 2.07 (dd, 0.81H, J = 4.2, 14.2 Hz), 2.50 (dd, 0.19H, J = 7.2 Hz), 2.57 (dd, 0.81H, J = 7.2, 14.2 Hz), 3.45 (t, 2H, J = 6.4 Hz), 3.54 (s, 3H), 4.06 (m, 2H), 4.44 (s, 2H), 4.85 (s, 0.19H), 4.92 (s, 0.81H), 5.78 (m, 1H), 5.92 (m, 0.81H), 5.99 (m, 0.19H), 6.14 (d, 0.81H), 6.21 (sl, 0.19H), 7.03 (t, 2H), 7.28 (m, 2H), 7.39 (m, 3H), 7.53 (m, 2H).

(7*S*)-7-{2-[3-(4-Fluorobenzyloxy)propyl]-5-oxo-2-[2-(trimethylsilanyl)ethoxycarbonylamino]cyclopent-3-enyl}-7-hydroxyheptanoic Acid Methyl Ester (31). A solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (89 mL, 420 μmol) in anhydrous THF (1 mL) under an argon atmosphere was cooled to 0 °C. Then, a 1.6 M BuLi solution in hexane (262 μL, 420 mmol) was introduced. After 10 min, this solution was cooled to −78 °C, and a solution of the ketone **27** (71.4 mg,

175 μmol) in anhydrous THF (0.5 mL) was then slowly added, followed, 45 min later, by a solution of aldehyde **37** (44.3 mg, 280 μmol) in anhydrous THF (0.5 mL). After 1 h, the reaction was quenched (at −78 °C) by addition of a 10% AcOH solution in THF (0.5 mL), and then a saturated aqueous $NaHCO_3$ solution (10 mL) was added. After extraction by ether, the organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (dichloromethane/methanol, 100:1) gave the aldol **31** (diastereoisomeric mixture) as a colorless oil (58 mg, 58.5%). Another chromatographic fraction gave some starting cyclopentenone **27** (28 mg, 39%): IR ($CHCl_3$) 3607, 3433, 3357, 2954, 2862 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.95 (m, 2H), 1.64 (br m, 8H), 1.85 (m, 2H), 2.11 (m, 1H), 2.32 (m, 2H), 3.48 (m, 2H), 3.68 (s, 3H), 3.94 (m, 0.5H), 4.09 (m, 2H), 4.18 (m, 0.5H), 4.46 (d, 2H), 6.18 (m, 1H), 7.04 (m, 2H), 7.29 (m, 2H), 8.09 (d, <1H); MS (CI^+, NH_3) *m*/*z* 583 $(M + NH_4)^+$.

(*E*,*Z*)-7-{2-[3-(4-Fluorobenzyloxy)propyl]-5-oxo-2-[2-(trimethylsilanyl)ethoxycarbonylamino]cyclopent-3-enylidene}heptanoic Acid Methyl Ester (32). The aldol **31** (86.6 mg, 153 μmol) was dissolved in anhydrous pyridine (6 mL) under an argon atmosphere. A catalytic amount of DMAP (1.8 mg, 15 μmol), DBU (two drops), and acetic anhydride (200 μL, 2.1 mmol) were added, and the solution was heated at 80 °C for 23 h. The solvent was removed under reduced pressure, and purification by flash chromatography over silica gel (dichloromethane/methanol, 100:2) gave alkylidenecyclopentenone **32** (50:50 *E*/*Z* mixture of isomers) as a colorless oil (56.7 mg, 68%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.92 (m, 2H), 1.30−1.69 (m, 6H), 1.75−2.25 (br m, 4H), 2.29 (m, 2.5 H), 2.80 (q, 0.5H, J = 7.2 Hz), 3.42 (m, 2H), 3.66 (s, 3H), 4.07 (m, 2H), 4.44 (s, 2H), 5.19 (s, 0.5H), 5.27 (s, 0.5H), 6.07 (t, 0.5H, J = 7.7 Hz), 6.31 (d, 0.5H, J = 6.1 Hz), 6.38 (d, 0.5H, J = 5.9 Hz), 6.56 (t, 0.5H, J = 7.9 Hz), 7.28 (m, 2H), 7.30 (t, 2H), 7.42 (br s, 1H); MS (CI^+, NH_3) *m*/*z* 565 $(M + NH_4)^+$; HRMS (CI^+, NH_3) *m*/*z* calcd for $C_{29}H_{43}FNO_6Si$ $(M + H)^+$ 548.7530, found 548.7528.

7-Hydroxy-7-{2-octyl-5-oxo-2-[2-(trimethylsilanyl)ethoxycarbonylamino]cyclopent-3-enyl}heptanoic Acid Methyl Ester (33). The same procedure described for **31** gave compound **33** (86.5 mg, 49%) from **28**: IR ($CHCl_3$) 3354, 2930, 2858, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.88 (t, 3H, J = 6.5 Hz), 0.98 (m, 2H), 1.26 (s, 18H), 1.65 (m, 3H), 2.05 (m, 2H), 2.32 (m, 3H), 3.68 (s, 3H), 3.90 (m, 0.5H), 4.11 (m, 2H), 4.20 (m, 0.5H), 6.17 (m, 2H, J = 5.8 Hz), 6.74 (br s, <1H), 7.76 (m, 0.5H), 8.09 (d, 0.5H, J = 5.8 Hz); MS (CI^+, NH_3) *m*/*z* 529 $(M + NH_4)^+$, 511 $(M + NH_4 - H_2O)^+$.

7-[2-Octyl-5-oxo-2-(2-trimethylsilanyl)ethoxycarbonylamino)cyclopent-3-enylidene]heptanoic Acid Methyl Ester (34). The procedure described for compound **32** gave compound **34** (79 mg, 89%) as a 3:2 *E*/*Z* mixture. Data for (*Z*)-**34**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.86 (t, 3H, J = 4.4 Hz), 0.95 (m, 2H), 1.05 (m, 18H), 1.64 (m, 2H, J = 7.5 Hz), 2.30 (m, 2H), 2.78 (m, 2H), 4.91 (s, 1H), 6.05 (t, 1H, J = 7.7 Hz), 6.30 (d, 1H, J = 6.04 Hz), 7.42 (br s, 1H). Data for (*E*)-**34**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.90 (m, 5H), 1.05−1.95 (m, 20H), 2.30 (m, 4H), 3.67 (s, 3H), 4.08 (m, 2H), 4.94 (s, 1H), 6.37 (d, 1H, J = 6.0 Hz), 6.55 (t, 1H, J = 7.8 Hz), 7.40 (br s, 1H). Data for (*Z*)-**34** and (*E*)-**34**: MS (CI^+, NH_3) *m*/*z* 511 $(M + NH_4)^+$, 494 $(M + H)^+$; HRMS (CI^+, CH_4) *m*/*z* calcd for $C_{27}H_{47}NO_5Si$ $(M + H)^+$ 494.3302, found 494.3293.

5-(6-Methoxycarbonylhexylidene)-1-octyl-4-oxocyclopent-2-enylammonium Trifluoroacetate (35). The cyclopentenone **34** (12.5 mg, 25 μmol) was dissolved in trifluoroacetic acid (1 mL) under an argon atmosphere. After 40 min, the solvent was removed under reduced pressure, giving the trifluoroacetate salt **35** as a pale yellow oil (12.2 mg, 100%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (br s, H_20), 1.26 (br s, 18H), 1.65 (m, 2H), 2.20−2.40 (m, 4H), 3.66 (s, 3H), 6.15 (t), 6.21 (d), 6.25 (d), 6.54 (t), 7.17 (d), 7.21 (d); MS (CI^+, NH_3) *m*/*z* 350 $(M + H)^+$; HRMS (CI^+, CH_4) *m*/*z* calcd for $C_{21}H_{36}NO_3$ $(M + H)^+$ 350.2695, found 350.2692.

7-(2-Acetylamino-2-octyl-5-oxocyclopent-3-enylidene)-heptanoic Acid Methyl Ester (36). The cyclopentenone **34** (19.9 mg, 40 μmol) was dissolved in trifluoroacetic acid (1 mL) under an argon atmosphere. After 1 h, the solvent was removed under reduced pressure, and the residue was then dissolved in a mixture of anhydrous dichloromethane (1 mL) and anhydrous pyridine (1 mL). To this solution were added triethylamine (2 drops) and acetyl chloride (2 drops). After 25 min of reaction, the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (dichloromethane/methanol, 98:2) gave **36** as a colorless oil (12.3 mg, 78%): $[\alpha]_D$ −4.5 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 3441, 2929, 2857, 1729, 1704, 1681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, H_20), 1.20−1.85 (m, 22H), 1.95 (s, 3H), 2.30 (m, <3H), 2.81 (m, 0.7H, J = 7.4 Hz), 3.66 (s, 3H), 5.71 (br s, 0.3H), 5.77 (br s, 0.7H), 6.09 (t, 0.3H, J = 7.6 Hz), 6.28 (d, 0.3H, J = 6.0 Hz), 6.36 (d, 0.7H, J = 6.2 Hz), 6.54 (t, 0.7H, J = 7.8 Hz), 7.59 (d, 0.7H, J = 6.0 Hz), 7.67 (d, 0.3H, J = 6.0 Hz); MS (CI^+, NH_3) *m*/*z* 409 $(M + NH_4)^+$, 392 $(M + H)^+$; HRMS (CI^+, NH_3) *m*/*z* calcd for $C_{23}H_{38}NO_4$ 392.5636, found 392.5633.

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Supporting Information Available: ^1H NMR spectra of **6**−**8**, **10**, **11**, **14**, **15**, **17**−**24**, **25a**, **25b**, **27**, **28**, **30b**, **31**−**34**, and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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