DIPOLAR CYCLOADDITION ROUTE TO THE SYNTHESIS OF 1α,25-DIHYDROXY-26-NORVITAMIN D_2 DERIVATIVES†

Peter M. Wovkulich,* Enrico G. Baggiolini,[1] Bernard M. Hennessy, and Milan R. Uskoković

Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey 07110, USA

Abstract -The intramolecular dipolar cycloadditions of nitrones derived from aldehydes (**8**) and (**14**) were found to proceed with a high degree of diastereoselectivity. By taking advantage of the functionality and stereochemical features residing in the cycloadducts (**10**) and (**11**), respectively, the two novel vitamin D_2 derivatives (**1c**) and (**1d**) were synthesized.

Vitamin D_3 and particularly its metabolites possess a diverse array of biological activities. In addition to their more established roles in the regulation of calcium and phosphate metabolism, compounds in the vitamin D family have, more recently, been found to affect basic cellular processes such as proliferation and differentiation. Indeed, a major driving force behind this rapidly expanding field is the therapeutic application to disease states characterized by abnormal cell proliferation and/or differentiation.[2]

A pattern of exquisite sensitivity to modifications on the side chain has emerged from the assay of numerous analogs and metabolites. As part of a continuing program designed to probe the influence of side chain substituents on the biological activity of 1α,25-dihydroxy vitamin D_3 (**1a**), we have undertaken the synthesis of side chain modifications in the 1α,25-dihydroxy vitamin D_2 series (**1b**). In this report we describe the synthesis of the 25R-norvitamin D_2 derivative (**1c**) and the 24-epi-25S-norvitamin D_2 derivative (**1d**).

Relying on the high efficiency of the coupling reaction between the ring A synthon (**2**) and CD units for the construction of the triene system,[3] attention was directed at the preparation of the CD unit (**3**) (Scheme 1).

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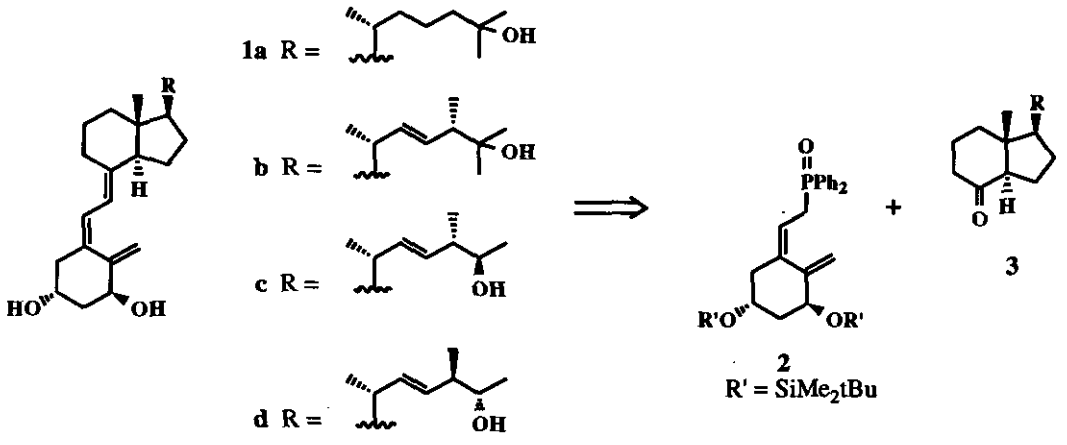
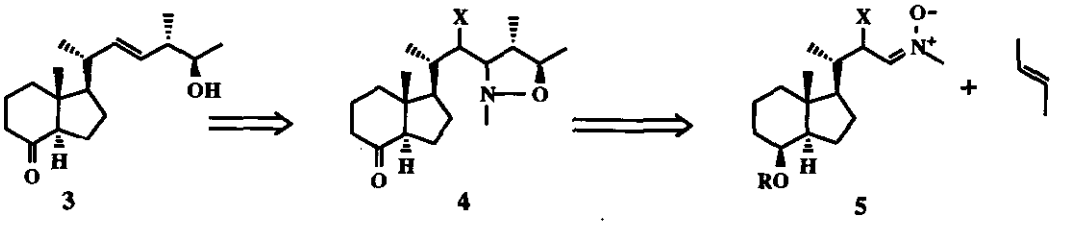
†Dedicated to Professor E. C. Taylor of Princeton University on the occasion of his 70th birthday.

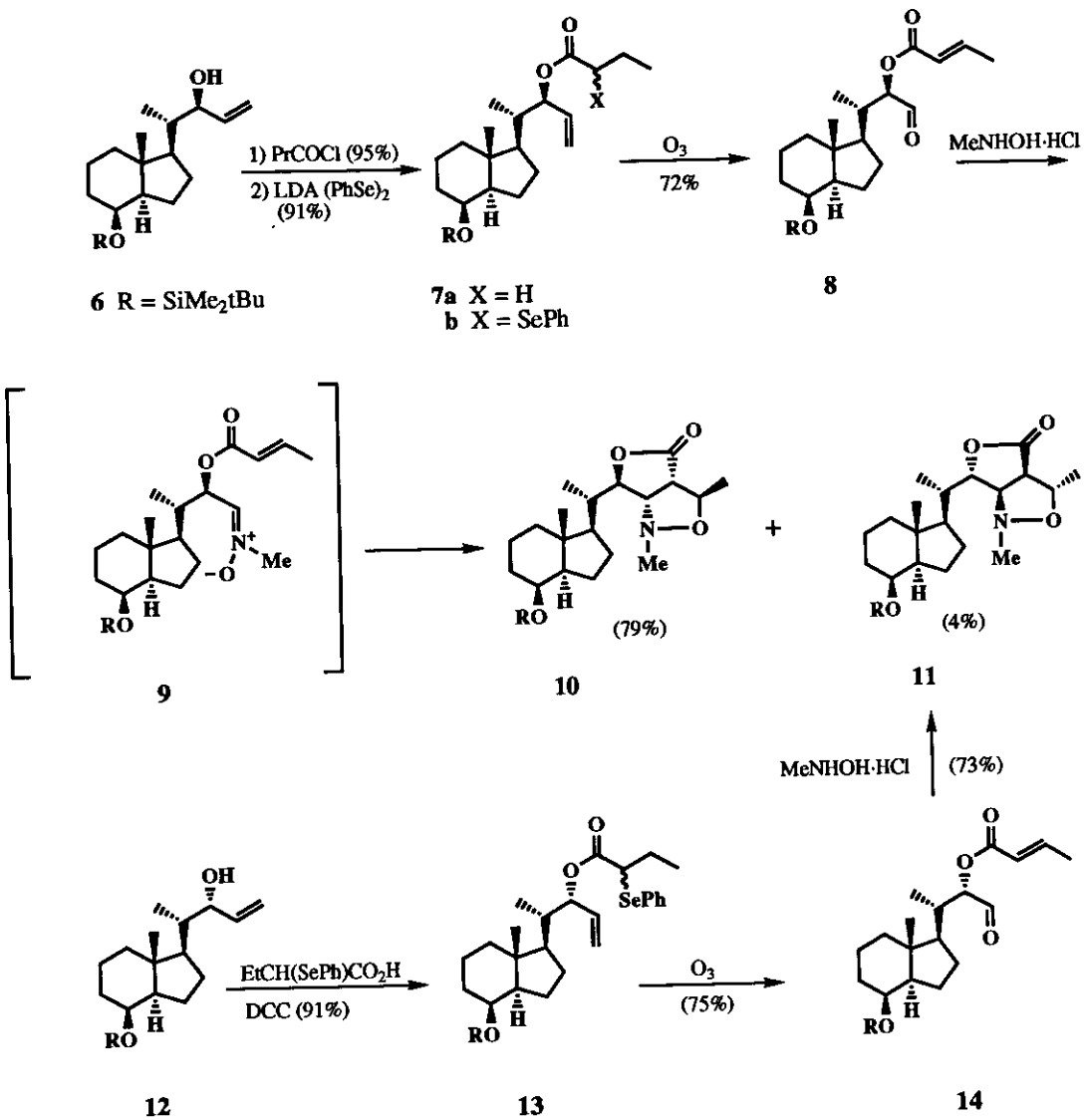


Scheme 1

Our previous studies, directed toward the synthesis of 1α,25S,26-trihydroxycholecalciferol, demonstrated the feasibility of utilizing a [3+2] dipolar cycloaddition reaction to deliver the functional and stereochemical features necessary to build the steroid side chain from a preexisting CD unit.[3e] In that work, nitrone (5) (with X = OAc, Scheme 2) was reacted with methacrylate esters to form cycloadducts which were subsequently transformed to 25,26-dihydroxy side chain . Although the diasteroselectivity of the cycloaddition was useful (i. e. 81:19), application of that methodology to the current problem would require the use of *trans*-2-butene, a relatively unreactive and volatile dipolarophile (Scheme 2). Alternatively, a crotonate ester could function as a reasonable *trans*-2-butene substitute, however, the level of diastereoselection observed previously in the reaction of crotonate esters with other nitrones had been relatively low.[4] We have now found that very high levels of diastereoselection may be obtained with the intramolecular version of this reaction and report on the application of this methodology to the synthesis of **1c** and **1d.**



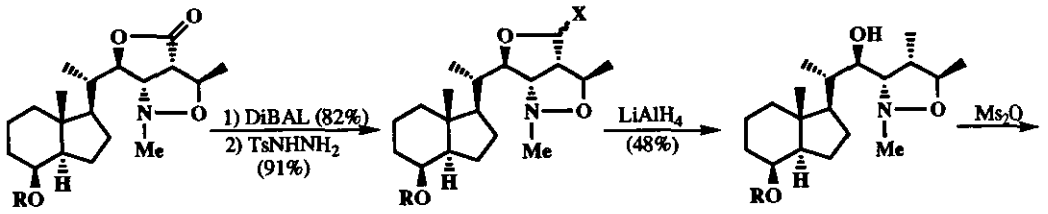
Scheme 2


OH
RO
H
1) PrCOCl (95%)
2) LDA (PhSe)2
(91%)
O
X
O3
72%
MeNHOH·HCl
6 R = SiMe2tBu
7a X = H
b X = SePh
8
N+
Me
-O
9
N
Me
(79%)
10
(4%)
11
MeNHOH·HCl
(73%)
SePh
EtCH(SePh)CO2H
DCC (91%)
12
13
14

Scheme 3

The synthesis began with allylic alcohol (**6**), a readily available intermediate prepared during our previous investigations.[3e] Esterification of **6** with butyryl chloride produced ester (**7a**), which was then α-phenylselenated using PhSeSePh and LDA to give **7b** as an epimeric mixture (91%, Scheme 3). It was subsequently established that esterification to **7b** could be carried out directly from **6** using 2-phenylselenobutyric acid[5] and DCC. On exposure of **7b** to ozone (CH_2Cl_2, -78 °C), double bond cleavage, selenide to selenoxide oxidation, and selenoxide elimination occurred to give the E-butenoate ester (**8**) in 72% yield. After examining a variety of conditions for nitrone formation, the best results were obtained simply by heating aldehyde (**8**) with methylhydroxyl amine hydrochloride. These conditions produced nitrone (**9**), which gradually underwent the intramolecular cycloaddition to form cycloadduct (**10**) in 79% yield. The structure of **10** was established by an X-ray crystallographic analysis at a later stage in the synthesis. Accompanying **10** was a minor product (4% yield), which was identified as diastereomer (**11**) by an X-ray crystallographic analysis. The formation of **11** results from the epimerization of nitrone (**9**) or its precursor aldehyde (**8**) prior to cycloaddition. It is noteworthy that the same *relative* sense of cycloaddition produced exclusively **10** from **8** and **11** from **14**. To further corroborate this point, alcohol (**12**)[3e] was esterified with 2-phenylselenobutyric acid to give the ester mixture (**13**) in 91% yield. Treatment of **13** with ozone as above generated the crotonate aldehyde (**14**) in 75% yield, which on exposure to methylhydroxyl amine hydrochloride in refluxing dichloroethane produced cycloadduct (**11**) in 73% yield, accompanied by a few percent of **10**. The structure of the cycloadduct (**11**) generated in this manner was again verified by an X-ray crystallographic analysis. The high diastereoselectivity of this cycloaddition reaction reflects the preference for the less congested transition state leading to the lower energy cycloadduct which has the C20 substituent (steroid numbering) in the exo position on the newly formed bicyclic system. It is of interest to note that this intramolecular variation generates the syn relationship for the oxygen and nitrogen substituents at C22 (steroid numbering) and C23 respectively. This outcome is complementary to the *inter*molecular reaction (i.e. nitrone (**5**),X = OAc[3e]) which produces the anti relationship. With this highly diastereoselective process in hand, the conversion of each cycloadduct to its respective homoallylic alcohol was investigated.

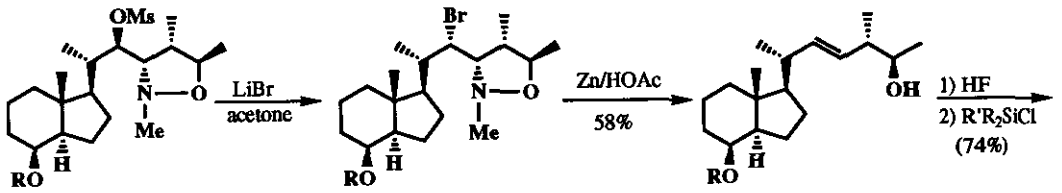
The strategy for generating the homoallylic alcohols was envisioned as a two stage process. The first stage would entail the conversion of the lactone carbonyl to a methyl group and the second stage would require the reductive elimination of the vicinally situated nitrogen and oxygen atoms.



10 R = $SiMe_2tBu$

15a X = OH
b X = NHNHTs
c X = H

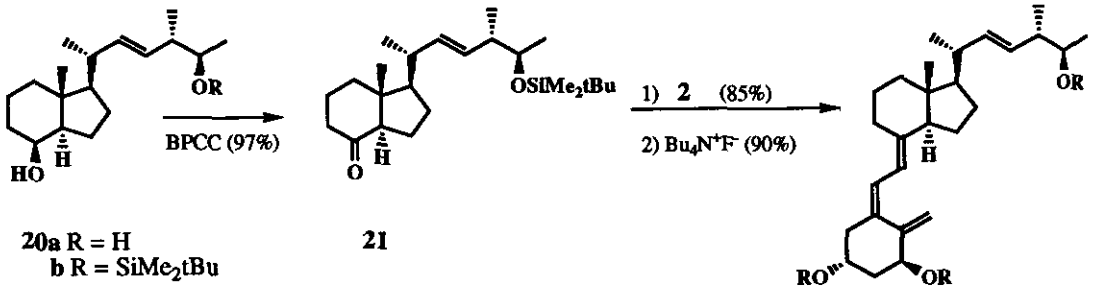
16



17

18

19



20a R = H
b R = $SiMe_2tBu$

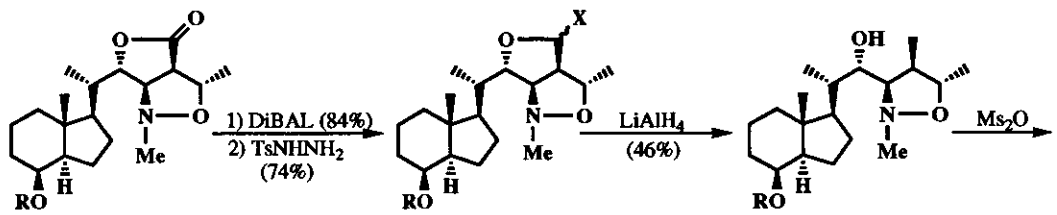
21

22 R = $SiMe_2tBu$
1c R = H

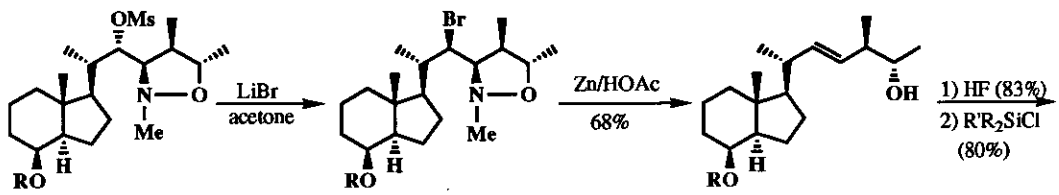
Scheme 4

While a variety of methods were examined to effect the carbonyl to methyl conversion, a novel variation of the Caglioti reduction was eventually employed for the first stage in the sequence.[6] Reduction of **10** with DiBAL produced the hemiacetal (**15a**) (82%) which on exposure to tosylhydrazine gave the hydrazide (**15b**) in 91% yield (Scheme 4). Reduction of **15b** with $LiAlH_4$ in THF produced the alcohol (**16**) in 48% yield. Despite the modest yield encountered in this reduction, other methods for the conversion of carbonyl to methyl were far less effective. For example, reduction of the lactone (**10**) with $LiAlH_4$ generated the corresponding diol (not shown) in excellent yield. Attempts to convert the primary alcohol to a functionality (e.g. halide, sulfonate ester, thiocarbonates) which could be further reduced to a methyl group were complicated by the formation of tetrahydrofuran (**15c**). Remarkably, even treatment of the diol with thiocarbonyldiimidazole at room temperature produced **15c**. Further insight into this outcome was gained from the X-ray crystallographic analysis of **16**, which shows the hydroxyl group in close proximity to the newly formed methyl group. Such a conformation in the aforementioned diol would explain the exceptionally facile ring closure to **15c** whenever the primary hydroxyl was converted to a leaving group. The success of the tosylhydrazide reduction is due to the initial reduction of **15b** to the ring opened tosyl hydrazide which does not suffer intramolecular displacement by alkoxide.[7] To our knowledge the conversion of **15b** to **16** is the first example of a reductive ring opening for cyclic hemiacetal-hydrazide systems.

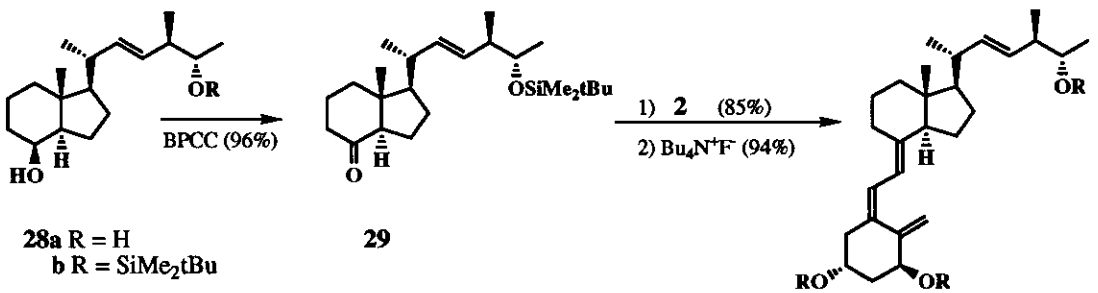
For the second stage, the reductive elimination step, the alcohol moiety of **16** was first converted to the corresponding mesylate (**17**) using methansulfonic anhydride in pyridine and then, without purification, transformed to bromide (**18**) using LiBr in acetone. Although bromide (**18**) could be purified by silica gel chromatography, it suffered partial rearrangement to two other isomeric bromides. It was therefore preferable to carry the crude bromide (**18**) directly through the reductive elimination step using zinc in acetic acid/THF to give olefin (**19**) in 58% overall yield for the three step process, accompanied by 10% of the cis olefin. A readjustment of the protecting group in **19** was required for the final ring A + CD coupling step. Treatment of **19** with aqueous HF produced diol (**20a**), which on monosilylation ($tBuMe_2SiCl$, DMF) gave silyl ether (**20b**) in 74% yield for the two steps. Oxidation of **20b** with bipyridinium chlorochromate gave ketone (**21**) (97%) which, on treatment with the anion of the ring A unit (**2**)[8], generated the protected triene (**22**) in 85% yield. Desilylation of **22** with $Bu_4N^+F^-$ gave the vitamin D_2 analog (**1c**) (90%).



11 R = $SiMe_2tBu$ **23a** X = OH, **b** X = NHNHTs **24**



25 **26** **27**



28a R = H, **b** R = $SiMe_2tBu$ **29** **30** R = $SiMe_2tBu$, **1d** R = H

Scheme 5

The transformation of cycloadduct (**11**) to its corresponding homoallylic alcohol (**27**) and the final conversion to the vitamin D_2 analog (**1d**) was carried out using the same sequence of reactions as described above with similar yields (Scheme 5).

The analog (**1c**) was active as 1α,25-dihydroxy vitamin D_3 (**1a**) in respect to the competitive binding to specific nuclear receptors and differentiation of the human HL-60 leukemic cell line. In contrast, the 24-epi-25S analog (**1d**) had diminished binding affinity (i. e. 30% of **1a**) and was an order of magnitude weaker in the cell differentiation assay.

ACKNOWLEDGMENTS

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EXPERIMENTAL

General Procedure. Unless otherwise noted all reactions were run under an argon atmosphere. THF was distilled from sodium-benzophenone; CH_2Cl_2 was stored over 4Å molecular sieves. Chromatography was performed on 230-400 mesh silica gel 60. Extracted reaction mixtures were dried over anhydrous Na_2SO_4, filtered, and solvent removed under reduced pressure. Rotations were carried out at 25 °C. ^1H Nmr spectra were obtained in $CDCl_3$ at 200 or 400 MHz (50 MHz for ^{13}C), significant chemical shifts are reported in ppm (δ units) downfield from TMS, and J values are given in Hertz.

Compound **7a**. Prepared in 95% yield by esterification of **6** with butyryl chloride in pyridine, in the presence of a catalytic amount of *N*,*N*-dimethyl-4-aminopyridine (DMAP). ^1H Nmr δ -0.02 (s, 3 H), 0.01 (s, 3 H), 0.87 (s, 9 H), 0.90 (s, 3 H), 0.93 (d, J = 7.4 Hz, 3 H), 0.95 (t, J = 7.6 Hz, 3 H), 2.32 (t, J = 7.6 Hz, 1 H), 3.97 (m, 1 H), 5.06, (d, J = 17.1 Hz, 1 H), 5.13 (d, J = 10.7 Hz, 1 H), 5.39 (dd, J = 1.8, 4.5 Hz, 1 H), 5.74 (ddd, J = 4.5, 10.7, 17.1 Hz, 1 H).

Compound **7b**. To a solution of LDA (prepared from 13 ml of dry THF, 0.449 ml (3.2 mmol) of diisopropyl amine and 2.56 ml of 1.2 M BuLi in hexanes) at -78 °C was added a solution of 0.50 g (1.18 mmol) of **7a** in 3 ml of THF. After 30 min 0.49 g (1.57 mmol) of diphenyldiselenide in 6 ml of THF was added. The mixture was stirred at -20 °C for 30 min and then quenched by the addition of 1M HCl and extracted with EtOAc.

Chromatography of the crude product, eluting with hexane/CH_2Cl_2 (50:40), gave 0.620 g (91%) of **7b** as a mixture of epimers. ^{1}H Nmr δ -0.012 (s, 3 H), -0.001 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 1.01 (t, J = 7.7 Hz, 3 H), 3.55 plus 3.56 (t, J = 6.3 Hz, 1 H), 3.96 (br s, 1 H), 5.09-5.25 (m, 2 H), 5.84 (m, 1 H), 5.61-5.84 (m, 1 H), 7.35 (m, 3 H), 7.59 (m, 2 H).

Compound **8**. Ozone was passed through a solution of 1.089 g (1.89 mmol) of **7b** in 150 ml of CH_2Cl_2/MeOH (5:1) at -78 °C until a blue color persisted. The mixture was purged with a stream of argon (10 min) and then 6.7 ml of dimethyl sulfide was added. The mixture was stirred overnight during which time the temperature was allowed to warm to ambient. Volatiles were removed under reduced pressure and the residue chromatographed, eluting with hexane/CH_2Cl_2/EtOAc (90:10:2.5), to give 0.57 g (72%) of **8** (amorphous solid). $[\alpha]_D^{25}$ = +9.5° (c = 0.768, $CHCl_3$). ^{1}H Nmr δ 0.01 (s, 6 H), 0.90 (s, 9 H), 0.98 (d, J = 6.0, Hz, 3 H), 0.99 (s, 3 H), 1.96 (dd, J = 2.0, 7.9 Hz, 3 H), 4.02 (br s, 1 H), 5.17 (d, J = 3.1 Hz, 1 H), 5.99 (dq, J = 16.4, 2.0 Hz, 1 H), 7.11 (dq, J = 16.4, 7.9 Hz, 3 H), 9.55 (s, 1 H). Ir ($CHCl_3$) 1738, 1718 cm^{-1}. Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20: H, 10.02. Found: C, 68.32; H, 10.10.

Compound **10**. A mixture of 6.04 g (14.29 mmol) of **8**, 600 ml of dichloroethane (dried by passage through basic alumina) and 2.384 g (28.56 mmol) of methylhydroxylamine hydrochloride was refluxed for 19 h. The cooled mixture was washed successively with saturated $NaHCO_3$ and brine. Chromatography of the crude product, eluting with hexane/EtOAc (88:12), gave 5.100 g (79%) of **10** (amorphous solid). $[\alpha]_D^{25}$ = -4.8° (c = 0.31, $CHCl_3$). ^{1}H Nmr δ 0.01 (s, 6 H), 0.88 (s, 9 H), 0.88 (d, J = 6.0 Hz, 3 H), 0.92 (s, 3 H), 1.43 (d, J = 7.2 Hz, 3 H), 2.71 (s, 3 H), 3.11 (br s, 2 H), 4.02 (m, 1 H), 4.21 (m, 1 H), 4.48 (br s, 1 H). Ir ($CHCl_3$) 1768 cm^{-1}. Anal. Calcd for $C_{25}H_{45}NO_4Si$: C, 66.47: H, 10.04; N, 3.10. Found: C, 66.38; H, 10.30; N, 3.11. Also isolated was 0.276 g (4%) of **11**. mp 157-158 °C (from isopropanol). $[\alpha]_D^{25}$ = +108.1° (c = 0.932, $CHCl_3$). ^{1}H Nmr δ 0.005 (s, 3 H), 0.01 (s, 3 H), 0.84 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.97 (s, 3 H), 1.43 (d, J = 6.8 Hz, 3 H), 2.75 (s, 3 H), 3.06 (dd, J = 5.2, 8.0 Hz, 1 H), 3.19 (d, J = 8.0 Hz, 1 H), 4.03 (br s, 1 H), 4.22 (dq, J = 6.8, 6.8 Hz, 1 H), 4.43 (d, J = 2.8 Hz, 1 H). Ir ($CHCl_3$) 1762 cm^{-1}. Anal. Calcd for $C_{25}H_{45}NO_4Si$: C, 66.47: H, 10.04; N, 3.10. Found: C, 66.47; H, 9.99; N, 3.02.

Compound **13**. Alcohol(**12**)(0.240 g, 0.681 mmol) was stirred with 5 ml of THF, 0.25 g (1.03 mmol) of 2-phenylselenobutanoic acid, 0.055 g of pyridine, 0.55 g of DMAP and 0.216 g (1.05 mmol) of dicyclohexylcarbodiimide (DCC) for 2.5 h, after which time an additional 0.042 g of DMAP and 0.072 g of DCC was added. The mixture was stirred another 1 h, 4 drops of H_2O were added. Stirring was continued for

30 min after which time the mixture was taken up in EtOAc and washed successively with 1M HCl, brine and saturated $NaHCO_3$. Chromatography of the crude product, eluting with hexane/CH_2Cl_2/EtOAc (50:50:3), gave 0.359 g (91%) of **13** as a mixture of epimers. ^{1}H Nmr δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.83 (d, J = 7.2 Hz, 3 H), 0.91 (s, 9 H), 0.94 (s, 3 H), 1.01 (t, J = 7.1 Hz, 3 H), 3.55 plus 3.56 (t, J = 6.0 Hz, 1 H), 4.01 (br s, 1 H), 5.10-5.22 (m, 3 H), 5.60-5.90 (m, 1 H), 7.25-7.41 (m, 3 H), 7.62 (m, 2 H).

Compound **14**. Prepared from **13** in 75% yield by the same procedure as described for **8**. **14** (oil): $[\alpha]_D^5$ = +59.7° (c = 0.424, $CHCl_3$). ^{1}H Nmr δ 0.00 (s, 6 H), 0.88 (s, 9 H), 0.93 (s, 3 H), 1.05 (d, J = 6.4 Hz, 3 H), 1.93 (dd, J = 2.0, 7.6 Hz, 3 H), 4.02 (br s, 1 H), 5.04 (d, J = 2.0 Hz, 1 H), 5.96 (dq, J = 15.6, 2.0 Hz, 1 H), 7.09 (dq, J = 15.6, 7.6 Hz, 1 H), 9.61 (s, 1 H). ^{13}C Nmr (C) 165.9, 42.4, 18.0; (CH) 199.7, 146.2, 121.9, 81.0, 69.2, 52.7, 52.4, 38.8; (CH_2) 40.5, 34.3, 27.5, 23.1, 17.6; (CH_3) 25.8(3), 18.1, 15.5, 13.5, -5.5(2). IR ($CHCl_3$) 1738, 1718 cm^{-1}. Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20: H, 10.02. Found: C, 68.12; H, 10.05.

Compound **11**. Aldehyde(**14**)(0.260 g, 0.615 mmol) was refluxed with 0.102 g (1.22 mmol) of methylhydroxylamine hydrochloride in 28 ml of dichloroethane for 8 h. The cooled mixture was taken up in CH_2Cl_2 and washed successively with H_2O, saturated $NaHCO_3$ and then brine. Chromatography of the crude product, eluting with hexane/EtOAc (5:1), gave 0.203 g (73%) of **11** (nmr and mp was the same as **11** generated from **8**, the structure confirmed by an X-ray crystallographic analysis) and 0.011 g (4%) of **10**.

Compound **15a**. To a solution of 3.50 g (7.75 mmol) of lactone(**10**)in 100 ml of THF at -78 °C was added 15.4 ml of 1.0M diisobutylaluminum hydride in hexanes solution. The mixture was stirred 1 h at -78 °C, and then 1 h at 0 °C. The reaction mixture was recooled to -78 °C and 20 ml of MeOH added. The mixture was then stirred at room temperature for 15 min and then diluted with 500 ml of EtOAc. After stirring 2 h, the mixture was filtered through a pad of anhydrous $MgSO_4$. Chromatography of the crude product, eluting with hexane/EtOAc (2:1), gave 2.90 g (82%) of **15a** as a 60:40 mixture of anomers. ^{1}H Nmr δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.89 (s, 9 H), 0.92 (s, 3 H), 0.86 plus 0.98 (d, J = 5.2 Hz, 3 H), 2.62 plus 2.67 (s, 3 H, NMe), 4.02 (br s, 1 H), 4.06-4.50 (m, 2 H), 5.29 plus 5.47 (m, 1 H). Anal. Calcd for $C_{25}H_{47}NO_4Si$: C, 66.18: H, 10.44. Found: C, 66.36; H, 10.80.

Compound **15b**. A mixture of 2.90 g (6.39 mmol) of **15a**, 3.57 g (19.2 mmol) of *p*-toluenesulfonyl hydrazide, 1.20 g (6.4 mmol) of *p*-toluenesulfonic acid monohydrate and 20 ml of THF was refluxed for 15 h. The cooled mixture was taken up in EtOAc and washed successively with saturated $NaHCO_3$ and brine. Chromatography of the crude product, eluting with hexane/EtOAc (1:1), gave 3.60 g (91%) of **15b** as a single

isomer (amorphous solid). ^{1}H Nmr δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 0.90 (s, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 2.44 (s, 3 H), 2.56 (s, 3 H), 2.97 (br d, J = 8.3 Hz, 1 H), 3.83 (m, 1 H), 3.92 (br s, 1 H), 4.01 (br s, 1 H), 4.16 (d, J = 8.3 Hz, 1 H), 4.49 (d, J = 8.3 Hz, 1 H), 6.11 (br s, 1 H), 7.42 (d, J = 8.8 Hz, 2 H), 7.79 (d, J = 8.8 Hz, 2 H).

Compound **16**. To a mixture of 0.55 g (14.51 mmol) of $LiAlH_4$ and 9 ml of THF at -78 °C was added 0.30 g (0.48 mmol) of **15b** in 6 ml of THF. The mixture was placed in an oil bath at 45 °C and stirred for 3 h, then cooled to -78 °C and 34 ml of EtOAc added. The mixture was stirred at 0 °C 30 min and then saturated NH_4Cl was added. The mixture was taken up in CH_2Cl_2 and washed with brine. Chromatography of the crude product, eluting with hexane/EtOAc (3:1), gave 0.101 g (48%) of **16**. mp 137-138 °C (from MeCN). $[\alpha]_D^{25}$ = +30.4° (c = 0.345, $CHCl_3$). ^{1}H Nmr δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.92 (s, 9 H), 0.93 (d, J = 6.1 Hz, 3 H), 1.19 (d, J = 7.4 Hz, 3 H), 1.31 (d, J = 6.2 Hz, 3 H), 2.38 (m, 1 H), 2.78 (s, 3 H), 2.86 (m, 1 H), 3.66 (m, 1 H), 3.78 (m, 1 H), 4.03 (br s, 1 H). ^{13}C Nmr (C) 42.2, 18.0; (CH) 80.0, 71.8, 70.7, 69.3, 53.3, 53.1, 45.7, 36.4; (CH_2) 40.8, 34.4, 26.7, 22.9, 17.7; (CH_3) 47.6(broad), 25.8(3), 19.2, 13.8, 12.5(broad), 11.9, -5.4(2). Anal. Calcd for $C_{25}H_{49}NO_3Si$: C, 68.28: H, 11.23; N, 3.19. Found: C, 68.11; H, 11.21; N, 3.27.

Compound **19**. To a mixture of 7.2 ml of pyridine and 0.120 g (0.273 mmol) of **16** at 0 °C was added 0.38 g (2.18 mmol) of methanesulfonic anhydride followed by 0.024 g of DMAP. The cooling bath was removed for 15 min and replaced. The mixture was quenched by the addition of 2.7 ml of H_2O and then taken up in EtOAc and washed successively with 0.5 M H_2SO_4, saturated Na_2SO_4, saturated $NaHCO_3$ and brine. The crude mesylate (**17**) was refluxed for 3 h in 20 ml of acetone with 0.384 g (4.42 mmol) of LiBr. The cooled mixture was taken up in EtOAc and washed successively with H_2O and saturated $NaHCO_3$. In a separate experiment the bromide (**18**) was purified by chromatography (elution solvent = hexane/EtOAc (97.5:2.5)). **18** (amorphous solid): $[\alpha]_D^{25}$ = +23.6° (c = 0.161, dioxane). ^{1}H Nmr δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.88 (s, 9 H), 0.96 (s, 3 H), 0.97 (d, J = 6.0 Hz, 3 H), 1.21 (d, J = 7.3 Hz, 3 H), 1.29 (d, J = 7.0 Hz, 3 H), 2.48 (m, 1 H), 2.78 (s, 3 H), 3.44 (m, 1 H), 3.79 (m, 1 H), 4.01 (br s, 1 H), 4.13 (d, J = 11.6 Hz, 1 H). Anal. Calcd for $C_{25}H_{48}NO_2BrSi$: C, 59.74: H, 9.63. Found: C, 59.75; H, 9.52. The crude bromide (**18**) from above was stirred overnight with 5 ml of acetic acid and 0.44 g (6.7 mmol) of Zn dust after which time an additional 0.44 g of Zn dust was added. After stirring 4 h the mixture was taken up in hexane/Et_2O (1:1) and washed successively with 7M NH_4OH and brine. Chromatography of the crude product, eluting with hexane/EtOAc (10:1), gave 0.063 g (58%) of **19**. ^{1}H Nmr δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 0.91 (s, 3 H), 0.95

(d, J = 7.5 Hz, 3 H), 0.99 (d, J = 7.5 Hz, 3 H), 1.16 (d, J = 7.5 Hz, 3 H), 3.48 (dq, J = 7.5, 7.5 Hz, 1 H), 4.00 (br s, 1 H), 5.19 (dd, J = 7.0, 15.6 Hz, 1 H), 5.39 (dd, J = 8.0, 15.6 Hz, 1 H). ^{13}C Nmr (C) 42.1, 18.0; (CH) 139.8, 129.0, 71.0, 69.4, 56.4, 53.1, 45.0, 39.8; (CH_2) 40.6, 34.4, 27.8, 23.0, 17.7; (CH_3) 25.8(3), 20.7, 20.0, 16.6, 13.9, -5.3(2). Anal. Calcd for $C_{24}H_{46}O_2Si$: C, 73.03; H, 11.75. Found: C, 73.05; H, 11.58. Also obtained was 0.011 g (10%) of the corresponding *cis*-olefin. ^{1}H Nmr δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.90 (s, 9 H), 0.92 (d, J = 6.0 Hz, 3 H), 0.93 (s, 3 H), 0.94 (d, J = 6.0 Hz, 3 H), 1.23 (d, J = 6.4 Hz, 3 H), 2.45 (m, 2 H), 3.49 (dq, J = 6.4 Hz, 3 H), 4.01 (br s, 1 H), 5.08 (dd, J = 8.2, 8.2 Hz, 1 H), 5.35 (dd, J = 8.2, 8.2 Hz, 1 H). ^{13}C Nmr (C) 42.1, 18.0; (CH) 139.7, 128.6, 71.8, 69.3, 56.7, 53.1, 40.3, 34.7; (CH_2) 40.7, 34.4, 27.7, 23.1, 17.7; (CH_3) 25.8(3), 20.9, 20.0, 17.3, 14.1, -5.3(2).

Compound **20a**. Olefin **19** (0.091, 0.23 mmol) was stirred with 5.4 ml of MeCN, 3.9 ml of THF and 5.7 ml of 50% HF for 50 min and then poured onto ice. The mixture was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed successively with saturated $NaHCO_3$ and H_2O. Chromatography of the crude product, eluting with hexane/EtOAc (2:1), gave 0.063 g (99%) of **20a**. mp 84 °C (from MeCN). ^{1}H Nmr δ 0.97 (s, 3 H), 0.99 (d, J = 7.8 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.17 (d, J = 6.6 Hz, 3 H), 2.03 (m, 2 H), 3.50 (dq, J = 6.6, 6.6 Hz, 1 H), 4.09 (br s, 1 H), 5.23 (dd, J = 7.9, 15.6 Hz, 1 H), 5.39 (dd, J = 8.0, 15.6 Hz, 1 H). Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.02; H, 11.31.

Compound **20b**. A mixture of 0.058 g (0.207 mmol) of **20a**, 2.5 ml of DMF, 0.28 g (4.1 mmol) of imidazole and 0.31 g (2.06 mmol) of *tert*-butyldimethylchlorosilane was stirred at room temperature for 2 h and then quenched by the addition of ice. The mixture was taken up in hexane/Et_2O (1:1) and washed successively H_2O and brine. Chromatography of the crude product, eluting with hexane/EtOAc (5:1), gave 0.061 g (75%) of **20b** (oil). ^{1}H Nmr δ 0.04 (s, 6 H), 0.90 (s, 9 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.93 (s, 3 H), 0.98 (d, J = 6.6 Hz,, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 3.68 (dq, J = 4.0, 6.6 Hz, 1 H), 4.09 (br s, 1 H), 5.18 (dd, J = 8.0, 14.4 Hz, 1 H), 5.30 (dd, J = 6.2, 14.4 Hz, 1 H). Also isolated was 0.025 g (24%) of the bis-silylated material which was reconverted to **20a** with the aqueous HF procedure above.

Compound **21**. Alcohol(**20b**)(0.056 g, 0.142 mmol) was stirred in 4 ml of CH_2Cl_2 with 0.17 g (0.581 mmol) of 2,2'-bipyridinium chlorochromate (BPPC) and 0.085 g of anhydrous sodium acetate for 2.5 h. An additional 0.085 g of BPPC and 2 ml of CH_2Cl_2 was added and the mixture stirred for an additional 3 h. Isopropanol (0.5 ml) was added, the mixture was stirred for 15 min and then H_2O was added. The mixture was extracted with Et_2O/EtOAc (1:1) and the extracts washed successively with H_2O, ice cold 1M HCl, H_2O and then brine.

Chromatography of the crude product, eluting with hexane/EtOAc (7:1), gave 0.054 g (97%) of **21** (oil). ^{1}H Nmr δ 0.04 (s, 6 H), 0.65 (s, 3 H), 0.89 (s, 9 H), 0.94 (d, J = 6.2 Hz, 3 H), 1.02 (d, J = 6.4 Hz, 3 H), 1.05 (d, J = 6.4 Hz, 3 H), 3.68 (dq, J = 4.0, 6.4 Hz, 1 H), 5.19 (dd, J = 7.6, 15.5 Hz, 1 H), 5.29 (dd, J = 8.0, 15.5 Hz, 1 H). Ir (KBr) 1715 cm^{-1}.

Compound **1c**. To a solution of the lithium anion of **2** (prepared from 0.211 mmol of **2**, 128 ml of 1.6 M BuLi in hexane solution and 6 ml of THF)[8] at -78 °C was added 0.052 g (0.132 mmol) of **21** in 1 ml of THF. After 1.5 h, the mixture was quenched by addition of a 2M Rochelle salt/1M $KHCO_3$ (1:1, v/v) solution. The mixture was allowed to warm to room temperature and was then extracted with EtOAc. The extract was washed with brine. Chromatography of the crude product, eluting with hexane/EtOAc (30:1), gave 0.085 g (85%) of **22** which was used directly in the next step. Also isolated was 0.005 g (10%) of the starting material **21**. A solution of 0.085 g (0.112 mmol) of **22** and 6.85 ml of 0.12 M tetrabutylammonium fluoride in THF solution was stirred for 21 h at room temperature. The mixture was diluted with H_2O and extracted with EtOAc. The extract was washed successively with H_2O and brine. Chromatography of the crude product, eluting with hexane/EtOAc (1:2), gave 0.042 g (90%) of **1c** (amorphous solid). ^{1}H Nmr (CD_3OD) δ 0.62 (s, 3 H), 1.01 (d, J = 6.2 Hz, 3 H), 1.07 (d, J = 6.4 Hz, 3 H), 1.10 (d, J = 6.4 Hz, 3 H), 2.27 (m, 1 H), 2.54 (bd, J = 13.6 Hz, 1 H), 2.89 (bd, J = 14.6 Hz, 1 H), 3.64 (dq, J = 6.4, 6.4 Hz, 1 H), 4.14 (m, 1 H), 4.37 (t, J = 5.2 Hz, 1 H), 5.31 (m, 3 H), 6.10 (d, J = 10.4 Hz, 1 H), 6.35 (d, J = 10.4 Hz, 1 H). HRms calcd for $C_{27}H_{42}O_3$: 414.3134. Found: 414.3126.

Compound **23a**. Prepared as a 2:1 mixture of anomers in 84% by reduction of **11** with diisobutylaluminum hydride using the procedure described for **15a**. **23a**: mp 106-107 °C (from MeCN). ^{1}H Nmr (major) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 0.96 (s, 3 H), 1.02 (d, J = 7.5 Hz, 3 H), 1.36 (d, J = 7.5 Hz, 3 H), 2.69 (s, 3 H), 4.02 (br s, 1 H), 5.42-5.48 (m, 1 H). ^{1}H Nmr (minor) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.86 (d, J = 7.4 Hz, 3 H), 0.89 (s, 9 H), 0.96 (s, 3 H), 1.29 (d, J = 7.5 Hz, 3 H), 2.66 (s, 3 H), 4.02 (br s, 1 H), 5.22-5.37 (m, 1 H). Anal. Calcd for $C_{25}H_{47}NO_4Si$: C, 66.18; H, 10.44. Found: C, 66.31; H, 10.36.

Compound **23b**. Prepared as a single isomer in 74% yield by the reaction of **23a** with toluenesulfonyl hydrazide using the procedure described for **15b**. **23b**: mp 100-101 °C (from hexane/Et_2O). $[\alpha]_D^{25}$ = +71.0° (c = 0.358, $CHCl_3$). ^{1}H Nmr δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.90 (s, 9 H), 0.96 (s, 3 H), 0.97 (d, J = 6.0 Hz, 3 H), 1.19 (d, J = 7.4 Hz, 3 H), 2.46 (s, 3 H), 2.64 (s, 3 H), 3.08 (dd, J = 2.0, 8.1 Hz, 1 H), 3.88 (m, 2 H), 4.01 (br s, 1 H), 4.15 (d, J = 7.9 Hz, 1 H), 4.53 (t, J = 6.6 Hz, 1 H), 6.16 (br s, 1 H), 7.35 (d, J = 7.9 Hz, 2

H), 7.81 (d, J = 7.9 Hz, 2 H). Anal. Calcd for $C_{32}H_{55}N_3O_5SSi$: C, 61.80: H, 8.91; N, 6.76. Found: C, 61.57; H, 8.94; N, 6.76.

Compound **24**. Prepared in 46% yield from **23b** using the same procedure described for **16**. **24** (oil): $[\alpha]_D^{25}$ = +80.8° (c = 0.332, $CHCl_3$). ^1H Nmr δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.87 (s, 9 H), 0.95 (s, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 1.20 (d, J = 6.9 Hz, 3 H), 1.24 (d, J = 5.8 Hz, 3 H), 2.20 (ddq, J = 6.9, 6.9, 6.9 Hz, 1 H), 2.47 (br s, 1 H), 2.65 (dd, J = 4.0, 6.9 Hz, 1 H), 2.69 (s, 3 H), 3.58 (m, 2 H), 3.98 (br s, 1 H). ^{13}C Nmr (C) 42.8, 18.0; (CH) 80.9, 74.4, 72.0, 69.4, 56.2, 52.6, 46.1, 39.2; (CH_2) 40.9, 34.5, 27.0, 23.2, 17.7; (CH_3) 44.6, 25.8(3), 18.9, 15.4, 14.2, 13.8, -5.3(2). Anal. Calcd for $C_{25}H_{49}NO_3Si$: C, 68.28: H, 11.23; N, 3.19. Found: C, 68.38; H, 11.39; N, 3.15.

Compound **27**. Prepared in 68% overall yield from **24** via mesylate(**25**)and bromide(**26**)using the procedure described for **19**. Bromide **26** (oil): ^1H Nmr δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.87 (s, 9 H), 0.92 (s, 3 H), 1.04 (d, J = 7.3 Hz, 3 H), 1.11 (d, J = 7.2 Hz, 3 H), 1.26 (d, J = 6.2 Hz, 3 H), 2.68 (s, 3 H), 3.15 (dd, J = 2.3, 4.1 Hz, 1 H), 3.66 (dq, J = 6.2, 6.2 Hz, 1 H), 3.98 (br s, 1 H), 4.35 (dd, J = 4.1, 4.1 Hz, 1 H). **27** (oil): ^1H Nmr δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.87 (s, 9H), 0.92 (s, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 1.15 (d, J = 6.2 Hz, 3 H), 3.43 (dq, J = 6.2, 6.2 Hz, 1 H), 3.97 (br s, 1 H), 5.14 (dd, J = 8.8, 15.4 Hz, 1 H), 5.36 (dd, J = 8.8, 15.4 Hz, 1 H). **27** was accompanied by 10% of the corresponding *cis*-olefin isomer (amorphous solid). ^1H Nmr δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.87 (s, 9H), 0.95 (s, 3 H), 0.95 (d, J = 6.5 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 1.19 (d, J = 6.5 Hz, 3 H), 2.42 (m, 2 H), 3.46 (dq, J = 6.5, 6.5 Hz, 1 H), 4.00 (br s, 1 H), 5.01 (dd, J = 9.9, 9.9 Hz, 1 H), 5.32 (dd, J = 9.9, 9.9 Hz, 1 H).

Compound **28a**. Prepared in 83% yield by desilylation of **27** using the procedure described for **20a**. **28a**: mp 84-85 °C (from hexane/EtOAc). ^1H Nmr δ 0.95 (s, 3 H), 0.97 (d, J = 7.6 Hz, 3 H), 1.01 (d, J = 6.4 Hz, 3 H), 1.16 (d, J = 6.4 Hz, 3 H), 3.44 (m, 1 H), 4.07 (br s, 1 H), 5.19 (dd, J = 7.6, 14.8 Hz, 1 H), 5.36 (dd, J = 8.0, 14.8 Hz, 1 H). Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09: H, 11.50. Found: C, 76.79; H, 11.50.

Compound **28b**. Prepared in 80% yield from **28a** using the procedure described for **20b**. **28b** (oil): $[\alpha]_D^{25}$ = +30.2° (c = 0.288, $CHCl_3$). ^1H Nmr δ 0.04 (s, 6 H), 0.90 (s, 9 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.96 (s, 3 H), 0.99 (d, J = 7.6 Hz, 3 H), 1.02 (d, J = 7.7 Hz, 3 H), 3.69 (m, 1 H), 4.07 (br s, 1 H), 5.19 (dd, J = 7.9, 15.2 Hz, 1 H), 5.28 (dd, J = 7.9, 15.2 Hz, 1 H). Anal. Calcd for $C_{24}H_{46}O_2Si$: C, 73.03: H, 11.75. Found: C, 73.12; H, 11.44.

Compound **29**. Prepared in 96% yield from **28b** using the procedure described for **21**. **29**: ^{1}H Nmr δ 0.04 (s, 6 H), 0.65 (s, 3 H), 0.89 (s, 9 H), 0.94 (d, J = 6.2 Hz, 3 H), 1.01 (d, J = 6.4 Hz, 3 H), 1.03 (d, J = 6.4 Hz, 3), 2.44 (m, 1 H), 3.68 (m, 1 H), 5.20 (dd, J = 8.0, 15.6 Hz, 1 H), 5.31 (dd, J = 7.6, 15.6 Hz, 1 H). Ir ($CHCl_3$) 1708 cm^{-1}.

Compound **1d**. Prepared from **29** via the two stage process (**29** → **30**, 85%, and **30** → **1d**, 94%) as described for **1c**. **1d** (amorphous solid): ^{1}H Nmr δ 0.58 (s, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.03 (d, J = 6.4 Hz, 3 H), 1.08 (d, J = 6.4 Hz, 3 H), 2.24 (m, 1 H), 2.51 (bd, J = 14.4 Hz, 1 H), 2.86 (bd, J = 13.6 Hz, 1 H), 3.61 (dq, J = 4.0, 6.4 Hz, 3 H), 4.12 (m, 1 H), 4.36 (t, J = 6.4 Hz, 1 H), 4.88 (br s, 1 H), 5.29 (m, 3 H), 6.08 (d, J = 10.4 Hz, 1 H), 6.33 (d, J = 10.4 Hz, 1 H). HRms calcd for $C_{27}H_{42}O_3$: 414.3134. Found: 414.3167.

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