Studies Directed Toward the Synthesis of Taxanes: Evaluation of the B-Ring Formation By an Intramolecular Nitrile Oxide Cycloaddition

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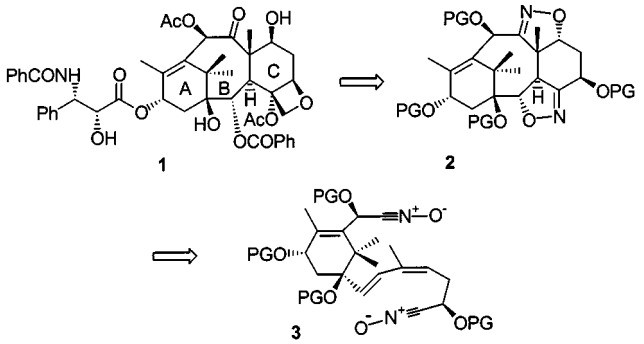
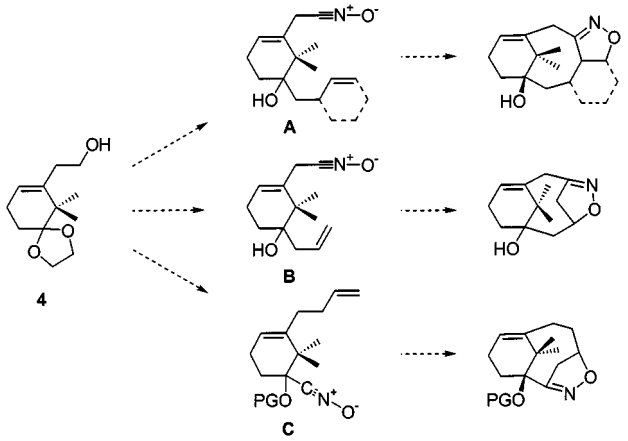
Several models for the formation of the 8-membered B-ring of taxanes by an intramolecular nitrile oxide [3+2] cycloaddition were prepared from the monoacetal of 2,2-dimethylcyclohexane-1,3-dione **(5)**. The nitrile oxides were then generated under high-dilution conditions. In most cases only oligomers were obtained. The isoxazoline **19**, containing a 9-membered ring, was formed from the nitrile oxide **17**, and a bis(isoxazoline) **21** was isolated from the reaction of the nitro compound **16c**.

The considerable interest in the synthesis of taxane diterpenes stems from the antitumor activity of paclitaxel (taxol® **1**), and its analogue docetaxel (taxotere®), which are now both used in the treatment of certain cancers, and also from their synthetically challenging structures.[1] Among the various strategies employed to construct the taxane skeleton, approaches that rely on the formation of the central B-ring from a precursor which already contains the A and C rings are particularly appealing since they are supposed to be more convergent. Our recently disclosed strategy,[2] depicted in Scheme 1, was based on the formation of the C and B rings by two consecutive intramolecular [3+2] cycloadditions involving nitrile oxides. Thus, taxol (**1**) would derive from the bis(isoxazoline) **2**, generated from compound **3**, containing two nitrile oxide moieties and two double bonds acting as dipolarophiles.



Scheme 1. Retrosynthetic analysis (PG = protecting group)

This approach was successful for the construction of the 6-membered C-ring. However, it remained to be seen whether it would also allow the cyclization to the 8-membered B-ring, which was thought to be the more challenging task.[3] We thus carried out the synthesis of several model nitrile oxide precursors and tested their ability to give an intramolecular [3+2] cycloaddition.[4] Several types of cyclizations were envisioned as described in the Scheme 2. The nitrile oxides **A** (in which the olefin could be included in a cyclohexene ring or not), **B** and **C** would be generated either from the corresponding primary nitroalkanes or oximes, which could all be derived from a single synthetic intermediate, alcohol **4**.



Scheme 2. Strategies for the formation of the ring B of taxanes by intramolecular nitrile oxide cycloaddition (PG = protecting group)

Two methods were applied to gain access to alcohol **4** (Scheme 3), both from the monoacetal of 2,2-dimethylcyclohexane-1,3-dione **(5)**. Reaction of the potassium enolate of **5** with *N*-phenyltrifluoromethanesulfonimide yielded the enol triflate **6**, which was converted into diene **7** by a palladium-mediated cross-coupling reaction with vinyltributylstannane. A regioselective hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by alkaline oxidation then afforded **4** (81% overall yield from **5**). An analogous sequence has been previously published by the Danishefsky

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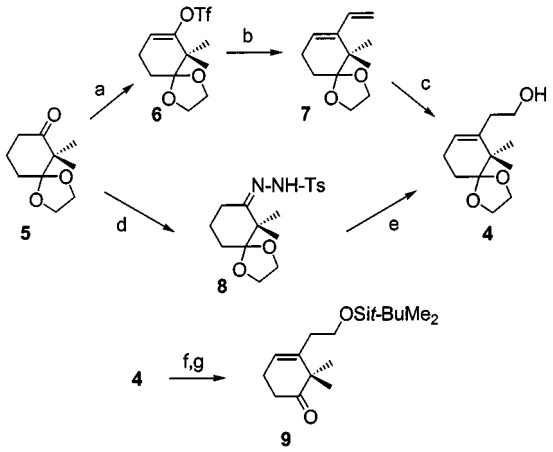
  1434–193X/99/1212–3241 $ 17.50+.50/0

group.[5] The second method was found to be more convenient to prepare large amounts of **4**, and also cheaper. Thus, treatment of **5** with *para*-toluenesulfonyl hydrazide afforded the tosyl hydrazone **8** in 95% yield.[6] Conversion of **8** to the corresponding cycloalkenyllithium compound by reaction with excess *tert*-butyllithium was followed by addition of ethylene oxide, giving rise to alcohol **4**. Ketone **9** was then prepared from **4** in two high-yield steps: firstly, an acid-catalyzed cleavage of the dioxolane ring and, secondly, the protection of the primary hydroxyl function as its *tert*-butyldimethylsilyl ether (Scheme 3).



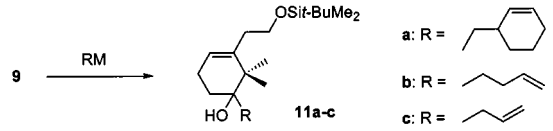
Scheme 3. Synthesis of ketone **9**; reagents and conditions: (a) $KN(SiMe_3)_2$, $PhNTf_2$, THF, 0°C, 85%; (b) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$ cat., LiCl, THF, reflux, 95%; (c) 9-BBN, THF, reflux, then H_2O_2, NaOH, THF/EtOH, 100%; (d) ref.[6]; (e) *t*BuLi (4 equiv.), THF, −78 to 5°C, then ethylene oxide, THF, −78°C to room temp., 5 h, 67%; (f) TsOH, THF/H_2O, reflux, 15 h, 99%; (g) $tBuMe_2SiCl$, Et_3N, DMAP cat., CH_2Cl_2, room temp., 1 h, 99%

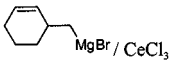
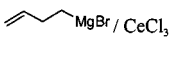
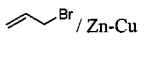
Ketone **9** was used as a precursor to the series of nitrile oxides **A** and **B**. The first step to be implemented at this stage was the introduction, by the addition of an organometallic reagent to the ketone function, of a chain containing the olefin which would later serve as the dipolarophile in the [3+2] cycloaddition. Preliminary tests for such an addition showed that the Grignard reagent made from 3-(bromomethyl)cyclohexene **(10)**[7] reacted with ketones to yield the corresponding reduction products. In contrast, the desired alkylated tertiary alcohol was obtained when the Grignard reagent was added to a preformed suspension of the ketone **5** and thoroughly dried cerium(III) chloride in THF.[8] Such conditions were applied to the preparation of compounds **11a** and **11b**, from the ketone **9** and the Grignard reagents derived from **10** or from 4-bromobutene, respectively (Table 1). A Barbier-type coupling with allyl bromide and a zinc/copper couple[6] was used to prepare the adduct **11c**. All these reactions proceeded with satisfactory yields.

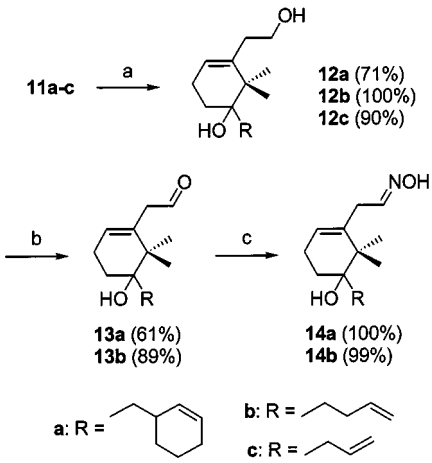
The oximes **14a,b** were prepared from the corresponding silyl ethers **11a,b** in three steps (Scheme 4): fluoride-induced desilylation to the primary alcohols, Swern oxidation, and conversion of the aldehydes **13a,b** to the corresponding oximes **14a,b**.

Other precursors of nitrile oxides, the nitro compounds **16a−c** were synthesized in two steps from the diols **12a−c**

Table 1. Alkylation of ketone **9**



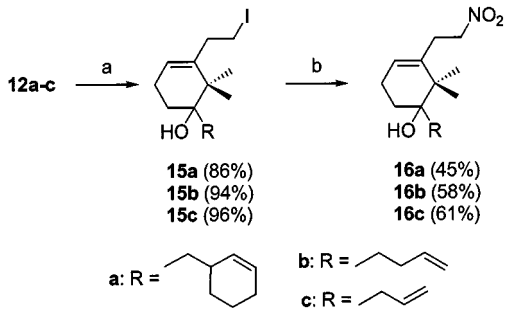
RM	Conditions	Product	Yield (%)
	THF, 0 °C to room temp.	**11a**	83
	15 h		
	THF, 0 °C to room temp.	**11b**	90
	15 h		
	THF, reflux	**11c**	96
	35 min		



Scheme 4. Preparation of oximes **14a−b**; reagents and conditions: (a) Bu_4NF, THF, 0°C to room temp., 15 h; (b) $(ClCO)_2$, DMSO, CH_2Cl_2, −60°C, 15 min, then Et_3N, −60°C to room temp.; (c) NH_2OH/HCl, Na_2CO_3, CH_2Cl_2/H_2O, 5 h, room temp.

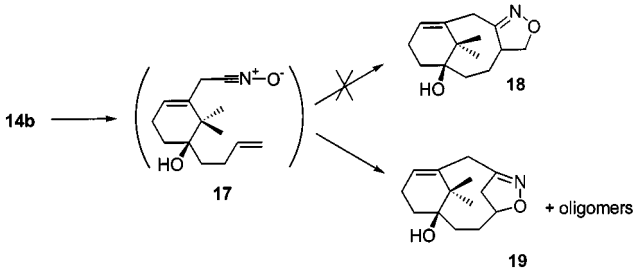
(Scheme 5). Treatment of **12a−c** with the reagent formed from triphenylphosphane, imidazole and iodine afforded the iodides **15a−c**.[9] These were then reacted with sodium nitrite in DMF. The nitro compounds **16a−c** were obtained in 45−61% yield, along with some isomeric nitrites.

Cycloaddition reactions were then performed using oximes **14a,b** and nitro compounds **16a−c** as substrates. In order to favor an intramolecular reaction, high dilution conditions (2×10^{-3} M) were employed in all cases. Thus, solutions of oximes **14a** or **14b** in dichloromethane were treated with aqueous sodium hypochlorite[10] (commercial bleach, 3−20 equiv.), at room temperature, in the presence of a catalytic quantity of tetrabutylammonium hydroxide. No adduct resulting from the expected intramolecular



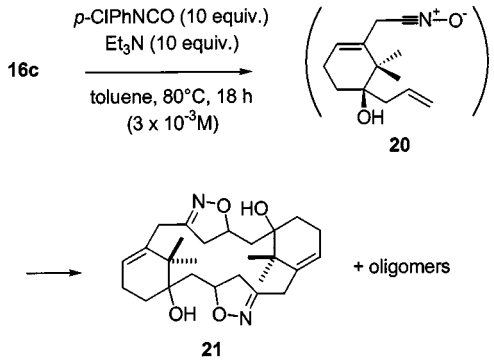
Scheme 5. Preparation of nitro compounds **16a–c**; reagents and conditions: (a) PPh_3, imidazole, I_2, Et_2O/CH_3CN, 0°C to room temp., 4 h; (b) $NaNO_2$, DMF, room temp.

cycloaddition was formed from oxime **14a** – only oligomers and furoxanes were obtained, as confirmed by ^1H NMR and mass spectroscopy. Under similar conditions oxime **14b** was consumed more rapidly and afforded, along with oligomers, an intramolecular cycloadduct, the isoxazoline **19** (Scheme 6). This compound could not be obtained as a pure material despite several chromatographic separations. The chemical shift values in the ^1H NMR spectrum and an HRMS exact mass determination are in agreement with the proposed structure (see experimental section). The regioselectivity of the cycloaddition leading to **19** is analogous to that which predominates in intermolecular reactions of nitrile oxides with monosubstituted alkenes. Also, **19** contains a nine-membered ring instead of an eight-membered ring. These factors may explain why this compound is formed, rather than the isoxazoline **18**.



Scheme 6. Cycloaddition from oxime **14b**

Reactions were then carried out with the nitro compounds **16a–c** under Mukaiyama conditions,[11] with phenyl or 4-chlorophenyl isocyanate as dehydrating agent and triethylamine as the base catalyst. High dilution conditions were also employed, and the solutions (in benzene or toluene) were refluxed until the substrate had disappeared. The reactions with **16a** and **16b** led essentially to the same outcome as the reactions with oximes **14a** and **14b**: mixtures of oligomers were obtained. The isoxazoline **19** was also obtained from **16b** although the reaction was not as clean. The alkenyl chain of **16c** contains one carbon less than in **14b**, and therefore an intramolecular cycloaddition proceeding with the same regioselectivity that led to **19** should have yielded an isoxazoline with an eight-membered ring. However, no such product was observed in this reaction which afforded mainly oligomeric compounds; the bis(isoxazoline) **21** was also isolated, in 10% yield, under the conditions described in Scheme 7. The relative configuration of this compound, which derives from two successive cycloadditions, one intermolecular and the second one intramolecular, was not established, but the molecule must be C_2- or C_i-symmetric since only half of the expected signals are found in the ^1H NMR spectrum. Mass spectrometry (CI/NH_3) indicated that the mass of this compound was twice that of the expected isoxazoline.

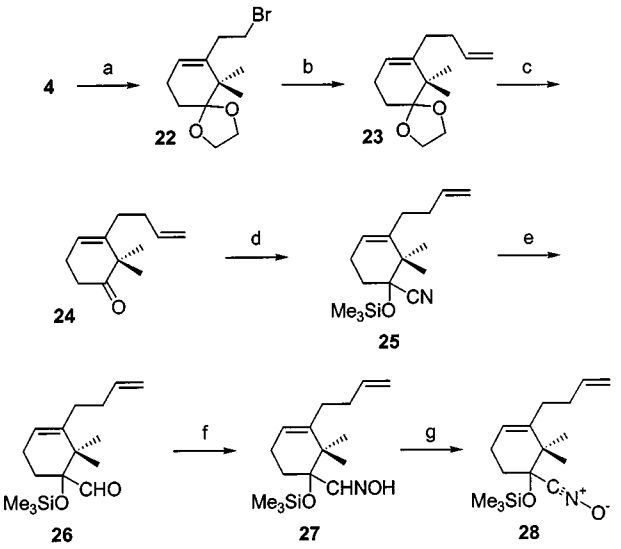


Scheme 7. Cycloaddition from nitro compound **16c**

The nitrile oxide **28** was also tested as substrate for intramolecular cycloaddition. Its preparation is depicted in Scheme 8. Alcohol **4** was converted into the bromide **22**, which was coupled with a vinyl Grignard reagent in the presence of copper iodide[12] to afford diene **23**. Acid treatment then yielded ketone **24**. Treatment of **24** with cyanotrimethylsilane in the presence of zinc(II) iodide[13] led to the protected cyanohydrin **25**, which was converted into the oxime **27** in two steps. This series of synthetic steps proceeded efficiently in high yields. Oxidation of oxime **27** with bleach in dichloromethane gave the nitrile oxide **28**, which was found to be stable in solution at room temperature; it was even possible to purify it by chromatography.[14] This stability is probably due to the very hindered environment around the nitrile oxide function. Concentration of a solution of **28** in vacuo afforded an oil, which after three days at room temperature did not contain terminal alkene, as seen from its ^1H NMR spectrum: signals typical of 3,5-disubstituted isoxazoline rings were observed at $\delta = 4.5$, 3.1 and 2.7 as unresolved multiplets.

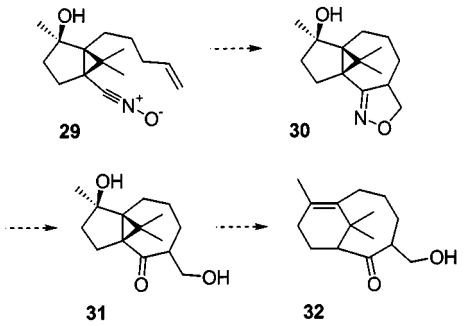
Highly diluted solutions of **28** were heated at reflux in various solvents (dichloromethane, chloroform, benzene, toluene). However, intractable mixtures of oligomers were obtained in each case. It was not possible to isolate a compound having the correct ^1H NMR and mass spectra corresponding to the desired intramolecular cycloadduct. Thus it was concluded that cycloaddition occurred only in an intermolecular fashion.

In conclusion, as part of a program aimed at the synthesis of taxanes, we have studied the possibility of constructing the B-ring using an intramolecular [3+2] cycloaddition. Several model nitrile oxide precursors were prepared and tested in the cycloaddition step. However, no cycloadduct containing the expected eight-membered ring was obtained using this strategy.[15] Its principal weaknesses lie probably in the presence of the two methyl groups in the



Scheme 8. Preparation of nitrile oxide **28**; reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, room temp., 100%; (b) vinylMgBr, CuI, THF, 0°C to room temp., 95%; (c) TsOH, THF, H_2O, 100%; (d) Me_3SiCN, ZnI_2, CH_2Cl_2, 0°C to room temp., 85%; (e) DIBAL-H, Et_2O, 0°C, 70%; (f) $NH_2OH.HCl$, pyridine/EtOH, 100%; (g) NaOCl, H_2O/CH_2Cl_2, 95%

space between the two components of the cycloaddition, i. e. the nitrile oxide and alkene moieties, and also in the lack of flexibility of the alkene chain, which is bonded to the sp^2 carbon of the cyclohexene mimicking the A ring of taxanes. Modification of the initial strategy to gain access to the A/B ring system was clearly needed. Taking these elements into account, a modified approach, involving a presumably more facile intramolecular cycloaddition of nitrile oxide **29** that would lead to the formation of a seven-membered ring isoxazoline **30**, and then the fragmentation of the cyclopropylketone **31** to generate bicyclic ketone **32** was then studied, as described in the following paper in this journal (Scheme 9).



Scheme 9. Modification of the strategy planned

Experimental Section

General: All reactions were performed under an atmosphere of argon. − THF was freshly distilled from sodium benzophenone ketyl. − TLC: Silica Gel $60F_{254}$ plates (Merck), with detection by UV light or with a solution of phosphomolybdic acid in EtOH. − Column chromatography: 40−63 μm Merck Silica Gel. − IR: Perkin−Elmer 2000. − Melting points (uncorrected): Büchi 535. − NMR: Bruker AM 300 (300.13 and 75.47 MHz for ^1H and ^{13}C, respectively). − MS: Finnegan-Mat 4600 (70 eV).

5,5-Ethylenedioxy-6,6-dimethylcyclohex-1-enyl Trifluoromethanesulfonate (6): A solution of LiHMDS (32.6 mL, 1 M in THF) was diluted in THF (100 mL) and cooled to 0°C. Ketone **5** (4 g, 21.7 mmol) was then added dropwise. After 2.5 h, *N*-phenyltrifluoromethanesulfonimide (12.6 g, 35.2 mmol) was added. After stirring for 30 min at 0°C, ether (100 mL) was added, the organic phase was washed with brine (2 × 50 mL), the aqueous phases were back extracted with ether (2 × 100 mL), and the combined organic phases were dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/dichloromethane, 9:1), afforded 5.82 g (85%) of triflate **6**. − IR (film): $\tilde{\nu}$ = 2980, 2950, 2882, 1670, 1460, 1350, 1240, 1160, 1175, 1050, 1025, 1175, 980, 870 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.17 (s, 6 H), 1.76 (t, *J* = 6.6 Hz, 2 H), 2.24 (dt, *J* = 6.6, 3.8 Hz, 2 H), 3.96 (s, 4 H), 5.68 (t, *J* = 3.8 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 20.51, 20.65, 26.20, 44.12, 65.02, 110.59, 114.79, 118.11 (q, *J* = 315.4 Hz. *C*F_3), 152.63. − $C_{11}H_{15}F_3O_5S$: calcd. 316.0592; found 316.0581 (HRMS).

Diene 7: A mixture of triflate **6** (3.01 g, 9.53 mmol), tributylvinyltin (4.2 mL, 14.3 mmol), lithium chloride (0.55 g, 0.48 mmol) and tetrakis(triphenylphosphane)palladium(0) in THF (60 mL) was heated at reflux for 20 h. Then the mixture was allowed to cool to room temperature and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.13 mL, 14.3 mmol) was added. Ether (250 mL) was added, the organic phase was washed successively with 1 N NaOH (3 × 60 mL) and brine (80 mL), and then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/AcOEt, 97:3), afforded 1.74 g (95%) of diene **7**. − IR (film): $\tilde{\nu}$ = 2960, 2876 (br, CH), 1650−1600 (C=C), 1460, 1380, 1160, 1138, 1094, 1040, 990 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.10 (s, 6 H), 1.75 (t, *J* = 6.7 Hz, 2 H), 2.22 (dt, *J* = 6.7, 3.8 Hz, 2 H), 3.99 (s, 4 H), 4.94 (dd, *J* = 2.1, 10.9 Hz, 1 H), 5.30 (dd, *J* = 2.1, 17.1 Hz, 1 H), 5.74 (t, *J* = 3.8 Hz, 1 H), 6.28 (dd, *J* = 10.9, 17.1 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.53, 23.81, 26.15, 41.79, 64.77, 111.80, 113.78, 120.73, 135.87, 143.96. − $C_{12}H_{18}O_2$: calcd. 194.1307; found 194.1311 (HRMS).

Alcohol 4. − Method Starting From Diene 7: A solution of 9-borabicyclo[3.3.1]nonane (9-BBN, 132 mL, 0.5 M in THF) was added to a solution of diene **7** (4.3 g, 22.2 mmol) in THF (40 mL). The mixture was refluxed for 3 h, and then cooled to room temperature. Ethanol (45 mL), 6 N NaOH (16 mL), and dropwise 30% H_2O_2 (14.7 mL) were successively added. The mixture was refluxed for 1 h, and then cooled to room temperature. Ether (400 mL) was added and the organic phase was washed with brine (2 × 200 mL), the aqueous phases were back extracted with ether (3 × 100 mL), and the combined organic phases were dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/AcOEt, 1:1), afforded 4.7 g (100%) of alcohol **4**.

Method Starting From Tosylhydrazone 8: To a solution of tosylhydrazone **8**[6] (2 g, 5.68 mmol) in THF (120 mL) cooled to −78°C was added a solution of *tert*-butyllithium (1.7 M in pentane, 13.4 mL, 22.7 mmol). After stirring for 15 min at −78°C, the solution was placed in a bath at 0°C for 5 min, then again cooled to −78°C. Ethylene oxide (1.14 mL, 22.8 mmol) was added. The reaction mixture was allowed to warm to room temperature over 5 h. Water (200 mL) and then brine (200 mL) were added, The organic phase was separated and the aqueous phase was extracted with ether (4 × 200 mL). The combined organic phases were successively

washed with water (3 × 200 mL) and brine (200 mL), and then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/AcOEt, 1:1), afforded 0.81 g (67%) of alcohol **4**. − IR (film): $\tilde{\nu}$ = 3400 (br, OH), 2936 (CH), 1460, 1380, 1130, 1082, 1040, 1020, 840 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.06 (s, 6 H), 1.74 (t, *J* = 6.9 Hz, 2 H), 1.85 (broad s, 1 H, OH), 2.16 (dt, *J* = 3.3, 6.9 Hz, 2 H), 2.26 (t, *J* = 7.2 Hz, 2 H), 3.72 (t, *J* = 7.2 Hz, 2 H), 3.98 (s, 4 H), 5.37 (t, *J* = 3.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.12, 23.56, 26.02, 34.00, 42.57, 61.47, 64.64, 111.94, 120.66, 139.90. − $C_{12}H_{20}O_3$: calcd. 212.1412; found 212.1419 (HRMS).

3-(2-Hydroxyethyl)-2,2-dimethylcyclohex-3-en-1-one: A solution of ketal **4** (5.9 g, 27.8 mmol) and *para*-toluenesulfonic acid (266 mg, 1.4 mmol) in 1:1 THF/water (400 mL) was refluxed for 18 h. After cooling to room temperature, ether (400 mL) was added and the organic phase was successively washed with saturated aqueous $NaHCO_3$ (100 mL), water (2 × 100 mL) and brine (200 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, 4.6 g (99%) of the title compound were obtained; it was used in the next reaction without further purification. − IR (film): $\tilde{\nu}$ = 3360 (broad, OH), 2920, 1670 (CO), 1010 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.17 (s, 6 H), 2.29 (t, *J* = 7.2 Hz, 2 H), 2.39 (m, 2 H), 2.44 (t, *J* = 7.1 Hz, 2 H), 2.51 (s, 1 H, OH), 3.76 (t, *J* = 7.2 Hz, 2 H), 5.61 (t, *J* = 3.9 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 23.87, 24.66, 33.45, 35.40, 47.76, 61.72, 121.38, 140.66, 214.99. − $C_{10}H_{16}O_2$ [M^+]: calcd. 168.1150, found 168.1163 (HRMS).

Ketone 9: To a solution of 3-(2-hydroxyethyl)-2,2-dimethylcyclohex-3-en-1-one (3 g, 17.9 mmol), triethylamine (3 mL, 21.5 mmol) and DMAP (0.22 g, 1.8 mmol) in dichloromethane (90 mL) at 0°C was added dropwise a solution of *tert*-butyldimethylsilyl chloride (2.97 g, 19.7 mmol) in dichloromethane (50 mL). The reaction mixture was then allowed to warm to room temperature. After stirring for 15 h, the organic phase was successively washed with 5% aqueous $NaHCO_3$ (250 mL) and brine (250 mL). The combined aqueous washings were extracted with dichloromethane (3 × 250 mL). The combined organic phases were then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/AcOEt, 97:3), afforded 5.0 g (99%) of ketone **9**. − IR (film): $\tilde{\nu}$ = 2840, 1690 (CO), 1397,1370, 1240, 1060, 810 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.05 (s, 6 H), 0.89 (s, 9 H), 1.17 (s, 6 H), 2.23 (t, *J* = 7.3 Hz, 2 H), 2.37 (m, 2 H), 2.51 (t, *J* = 6.7 Hz, 2 H), 3.70 (t, *J* = 7.3 Hz, 2 H), 5.55 (t, *J* = 4.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 0.13 (*C*H_3Si), 16.06 (Me_3*C*Si), 23.66, 24.78, 25.68 {(*C*H_3)$_3$CSi}, 33.80, 35.48, 47.67, 63.22, 121.38, 141.02, 214.57. − $C_{16}H_{30}O_2Si$ (282.5): calcd. C 68.03, H 10.70; found C 67.86, H 10.54. − $C_{15}H_{27}O_2Si$ [M^+ − CH_3]: calcd. 267.1780; found 267.1790 (HRMS).

General Procedure for the Addition of a Grignard Reagent to a Ketone in the Presence of Cerium(III) Chloride.

7-(Cyclohex-2-enylmethyl)-6,6-dimethyl-1,4-dioxaspiro[4.5]decan-7-ol: To a suspension of magnesium turnings (27.7 mg, 1.14 × 10^{-3} mol) in ether (0.7 mL) was added dropwise a solution of 3-(bromomethyl)cyclohexene **(10)** in ether (0.7 mL), so as to maintain a gentle reflux. The reaction mixture was then refluxed for 15 min. In another vessel, cerium(III) chloride heptahydrate (320 mg, 0.86 mmol) was heated at 160°C under vacuum for 6 h. After cooling to room temperature, THF (3 mL) was added, and the suspension was sonicated for 2 h. A solution of ketone **5** (105 mg, 0.57 mmol) in THF (0.5 mL) was then added. After stirring for 1 h and cooling to 0°C, the previously prepared solution of Grignard reagent was added dropwise through a cannula. The reaction mixture was allowed to warm to room temperature. After stirring for 15 h, a 5% aqueous AcOH solution (5 mL) was added. The organic phase was separated and the aqueous phase was extracted with ether (5 × 2 mL). The combined organic phases were successively washed with brine (2 mL), saturated aqueous $NaHCO_3$ (5 × 2 mL) and brine (2 mL), and then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/AcOEt, 99:1), afforded 210 mg (73%) of the expected alcohol as a mixture of two diastereomers. − ^1H NMR ($CDCl_3$): δ = 0.93 (s, 3 H), 1.01 (s, 3 H), 1.19−1.77 (m, 13 H), 1.97−2.00 (m, 2 H), 2.36−2.42 (m, 1 H), 3.95−4.02 (m, 4 H), 5.50−5.90 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 14.81, 17.93, 21.16, 21.43, 24.85, 29.84, 30.57, 31.20, 31.55, 41.91, 45.87, 63.93, 65.36, 73.69, 113.56, 125.63, 133.72. − MS (CI, NH_3); *m*/*z* (%): 263 (100) [M^+ − OH], 280 (6) [M^+], 298 (33) [M^+ + NH_4].

Alcohol 11a: Prepared as described above from ketone **9** (237.5 mg, 0.84 mmol) and 3-(bromomethyl)cyclohexene **(10)** (294 mg, 1.68 mmol). Chromatography on silica gel (petroleum ether/AcOEt, 98:2), afforded 375 mg (83%) of alcohol **11a** as a 6:4 mixture of two diastereomers. − IR (film): $\tilde{\nu}$ = 3500 (broad, OH), 2950, 2924, 2860, 1640, 1380, 1358, 1250 (δSi−CH_3), 1090, 830 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.05 (s, 6 H), 0.89 (s, 9 H), 0.97 (s, 3 H), 1.05 (s, 3 H), 1.25−2.07 (m, 13 H), 2.19 (t, *J* = 7.7 Hz, 2 H), 2.33 (m, 1 H), 3.66 (t, *J* = 3.0 Hz, 1 H), 5.32 (t, *J* = 7.7 Hz, 2 H), 5.50 (dd, *J* = 1.6, 9.9 Hz, 1 H_{major}), 5.58−5.71 (m, 1 H), 5.92 (dd, *J* = 1.85, 11.1 Hz, 1 H_{minor}). − ^{13}C NMR ($CDCl_3$): δ = 0.14 (*C*H_3Si), 18.12 (*C*Me_3Si), 21.15, 21.66, 22.54, 24.85, 25.75 ((*C*H_3)$_3$CSi), 27.37, 30.78 (minor), 30.80 (major), 30.93 (major), 31.46 (minor), 34.74, 40.44 (major), 40.63 (minor), 42.70, 63.48, 75.16, 121.05, 125.90 (minor), 126.49 (major), 133.14 (minor), 133.60 (major), 140.34. − $C_{23}H_{42}O_2Si$ (378.67): calcd. C 72.95, H 11.18; found C 72.94, H 11.07. − $C_{19}H_{33}O_2Si$ [M^+ − *t*Bu]: calcd. 321.2250; found 321.2248 (HRMS).

Alcohol 11b: Prepared as described above from ketone **9** (667 mg, 2.37 mmol) and 1-bromobut-3-ene (640 mg, 4.74 mmol). Chromatography on silica gel (pentane/AcOEt, 93:7), afforded 721 mg (90%) of alcohol **11b** as a 6:4 mixture of two diastereomers. − IR (film): $\tilde{\nu}$ = 3486 (broad, OH), 2958, 1641 (C=C), 1472, 1387, 1361, 1255, 1098, 837 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.03 (s, 6 H), 0.87 (s, 9 H), 0.96 (s, 3 H), 1.04 (s, 3 H), 1.37 (s, 1 H, OH), 1.43−2.09 (m, 9 H), 2.17 (t, *J* = 7.4 Hz, 2 H), 3.64 (t, *J* = 7.4 Hz, 2 H), 4.92 (d, *J* = 9.9 Hz, 1 H), 5.02 (d, *J* = 17.1 Hz, 1 H), 5.30 (t, *J* = 3.0 Hz, 1 H), 5.77−5.89 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 0.12 (*C*H_3Si), 16.11 (*C*Me_3Si), 22.01, 22.11, 22.65, 25.74 ((*C*H_3)$_3$CSi), 26.98, 27.96, 33.32, 34.61, 42.56, 63.47, 74.47, 114.00, 120.98, 139.36, 140.33. − MS (CI, NH_3); *m*/*z* (%): 338 (19) [M^+], 356 (100) [M^+ + NH_4]. − $C_{16}H_{29}O_2Si$ [M^+ − *t*Bu]: calcd. 281.1937; found 281.1932 (HRMS).

Alcohol 11c: To a suspension of zinc/copper couple (16 g) in THF (240 mL) was added ketone **9** (2.77 g, 9.8 mmol). The reaction mixture was refluxed, then allyl bromide (1.25 mL, 14.4 mmol) was added. After 25 min a further portion of allyl bromide (0.24 mL, 2.8 mmol) was added and the reaction mixture was refluxed for 10 min, then cooled to room temperature. Saturated aqueous $NaHCO_3$ (200 mL) was added, then the solid was filtered off. and washed with ethyl acetate (2 × 200 mL). The aqueous phase was extracted with ethyl acetate (2 × 200 mL). The combined organic phases were washed with water (200 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (heptane/AcOEt, 95:5), afforded 3.1 g (97%) of alcohol **11c** as a mixture of two diastereomers. − IR (film): $\tilde{\nu}$ = 3492 (broad, OH), 3075, 1639, 1255, 1190, 1097, 1004 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 5.95 (dddd, *J* = 17.1, 10.2,

7.8, 6.9 Hz, 1 H), 5.55 (t, J = 3.6 Hz, 1 H), 5.12 (d, J = 10.2 Hz, 1 H), 5.10 (d, J = 17.1 Hz, 1 H), 3.65 (t, J = 7.8 Hz, 2 H), 2.33 (dd, J = 14.1, 6.9 Hz, 1 H), 2.22 (t, J = 7.8 Hz, 2 H), 2.15−2.2 (m, 1 H), 2.0−2.1 (m, 2 H), 1.7 (dt, J = 13.2, 6.6 Hz, 1 H), 1.6 (dt, J = 13.2, 6.6 Hz, 1 H), 1.56 (broad s, 1 H, OH), 1.00 (s, 3 H), 1.08 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 140.3, 134.8, 121.1, 117.9, 74.3, 63.6, 42.2, 39.1, 34.6, 27.9, 25.8, 22.5, 22.2, 18.4, 5.4. − MS (CI, NH_3); *m/z* (%): 307 (94) [M^+ − OH], 325 (38) [M^+ + H], 342 (90) [M^+ + NH_4]. − $C_{16}H_{31}O_2Si$ [M^+ − $CH_2CH{=}CH_2$]: calcd. 283.2093; found 283.2089 (HRMS).

General Procedure for the Cleavage of *tert*-Butyldimethylsilyl Ethers 11a−c.

Diol 12a: A solution of tetrabutylammonium fluoride (1.85 mL, 1 M in THF) was added dropwise to a solution of *tert*-butyldimethylsilyl ether **11a** (350 mg, 0.93 mmol) in THF (1.4 mL) at 0°C. The reaction mixture was allowed to warm to room temperature. After stirring for 15 h, dichloromethane (10 mL) was added and the organic phase washed with water (5 mL). The aqueous phase was then extracted with dichloromethane (2 × 5 mL). The combined organic phases were washed with water (2 × 5 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/AcOEt, 8:2), afforded 174 mg (71%) of diol **12a** as a 6:4 mixture of two diastereomers. − IR (film): $\tilde{\nu}$ = 3380 (broad, OH), 2920, 1640 (C=C), 1030 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.98 (s, 3 H), 1.24 (s, 3 H), 1.19−2.10 (m, 14 H), 2.25 (t, J = 6.8 Hz, 2 H), 2.33 (m, 1 H), 3.72 (t, J = 6.8 Hz, 2 H), 5.39 (m, 1 H,), 5.50 (d, J = 11.6 Hz, 1 H_{major}), 5.62−5.70 (m, 1 H), 5.91 (dd, J = 10.0, 2.0 Hz, 1 H_{minor}). − ^{13}C NMR ($CDCl_3$): δ = 21.20, 21.75, 22.40, 22.59, 24.84, 27.31, 30.61 (minor), 30.81 (major), 30.92 (major), 31.44 (minor), 34.55, 40.50 (major), 40.70 (minor), 42.89, 61.70 (Cp), 75.25, 121.25, 126.09 (minor), 126.55 (major), 132.97 (minor), 133.47 (major), 139.88. − $C_{17}H_{28}O_2$ [M^+]: calcd. 264.2089; found 264.2082 (HRMS).

Diol 12b: Prepared as described above from *tert*-butyldimethylsilyl ether **11b** (1.77 g, 5.24 mmol) and tetrabutylammonium fluoride (10.5 mL, 1 M in THF). Chromatography on silica gel (pentane/AcOEt, 6:4), afforded 1.19 g (quantitative) of diol **12b**. − IR (film): $\tilde{\nu}$ = 3291 (broad, OH), 2951, 1640 (C=C), 1470, 1447, 1135, 1039 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.93 (s, 3 H), 1.01 (s, 3 H), 1.41−2.09 (m, 9 H), 2.17 (t, J = 7.0 Hz, 2 H), 2.61 (s, 1 H, OH), 3.62 (t, J = 7.0 Hz, 2 H), 4.88 (d, J = 9.8 Hz, 1 H), 4.98 (d, J = 17.1 Hz, 1 H), 5.30 (t, J = 3.1 Hz, 1 H), 5.73−5.85 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.05, 22.65, 26.91, 27.89, 33.32, 34.36, 42.59, 61.62, 74.58, 114.06, 121.17, 139.22, 139.88. − $C_{14}H_{24}O_2$ [M^+]: calcd. 224.1776; found 224.1774 (HRMS).

Diol 12c: Prepared as described above from *tert*-butyldimethylsilyl ether **11c** (78 mg, 0.24 mmol) and tetrabutylammonium fluoride (0.42 mL, 1 M in THF). Chromatography on silica gel (pentane/ether, 2:8), afforded 38 mg (90%) of diol **12c**. − IR (film): $\tilde{\nu}$ = 3380 (broad, OH), 3070, 2970, 2950, 2900, 2850, 1640, 1470, 1440, 1360, 1200, 1050, 1000 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 5.95 (dddd, J = 17.1, 10.2, 8.1, 6.6 Hz, 1 H), 5.4 (t, J = 3 Hz, 1 H), 5.15 (d, J = 10.2 Hz, 1 H), 5.1 (d, J = 17.1 Hz, 1 H), 3.75 (t, J = 6.6 Hz, 2 H), 2.30 (dd, J = 6.9, 14.1 Hz, 1 H), 2.25 (t, J = 6.6 Hz, 2 H), 2.15 (dd, J = 8.1, 14.1 Hz, 1 H), 1.75 (dt, J = 13.5, 6.9 Hz, 1 H), 1.70 (br. s, 1 H, OH), 1.60 (J = 13.5, 6.6 Hz, 1 H), 1.01 (s, 3 H), 1.09 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 140.2, 135.0, 120.8, 117.6, 74.1, 61.7, 42.2, 39.04, 34.4, 27.76, 22.4, 21.9, 22.3. − MS (CI, NH_3); *m/z* (%): 193 (100) [M^+ − OH], 228 (31) [M^+ + NH_4].

Aldehyde 13a: Dimethyl sulfoxide (160 μL, 2.25 mmol) was added to a solution of oxalyl chloride (114 mg, 0.9 mmol) in dichloromethane (3 mL) cooled to −60°C. After stirring for 15 min at −60°C, a solution of diol **12a** (120 mg, 0.45 mmol) in dichloromethane (1 mL) was added dropwise. After stirring for 15 min, triethylamine (1.4 mL) was added and the reaction mixture allowed to warm to room temperature. Water (5 mL) was added and the aqueous phase was extracted with ether (3 × 5 mL), then the combined organic phases were successively washed with 0.1 M HCl (5 mL) and brine (5 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/AcOEt, 98:2), afforded 72 mg (61%) of aldehyde **13a**. − IR (film): $\tilde{\nu}$ = 3491 (broad, OH), 2926, 1722 (CO), 1658 (C=C) cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.94 (s, 3 H), 1.02 (s, 3 H), 1.15−2.23 (m, 13 H), 2.27−2.42 (m, 1 H), 3.01 (s, 2 H), 5.47 (s, 1 H), 5.51−5.54 (m, 1 H_{major}), 5.59−5.73 (m, 1 H), 5.90 (dd, J = 1.9, 8.1 Hz, 1 H_{minor}), 9.57 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.10, 21.80, 22.32, 22.87, 24.84, 27.30, 29.43 (minor), 30.72 (major), 30.92 (major), 31.39 (minor), 40.58 (major), 40.76 (minor), 42.89, 47.49, 75.13, 126.34, 126.75 (major), 127.00 (minor), 132.76 (major), 133.32 (minor), 135.49, 200.97. − MS (CI, NH_3); *m/z* (%): 245 (18) [M^+ − OH], 280 (100) [M^+ + NH_4]. − $C_{17}H_{26}NO_2$ [M^+]: calcd. 262.1933; found 262.1917 (HRMS).

Aldehyde 13b: Prepared by oxidation of diol **12b** (212 mg, 0.95 mmol) by the procedure described above. Chromatography on silica gel (pentane/AcOEt, 9:1), afforded 187 mg (89%) of aldehyde **13b**. − IR (film): $\tilde{\nu}$ = 3451 (broad, OH), 2973, 1721 (CO), 1641 (C=C), 1470 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 3 H), 0.98 (s, 3 H), 1.40 (s, 1 H, OH), 1.43−2.24 (m, 8 H), 2.96 (s, 2 H), 4.90 (d, J = 10.8 Hz, 1 H), 5.00 (d, J = 17.1 Hz, 1 H), 5.42 (t, J = 3.4 Hz, 1 H), 5.74−5.85 (m, 1 H), 9.53 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.67, 22.13, 22.95, 26.92, 27.87, 33.39, 42.59, 47.36, 74.28, 114.20, 126.30, 135.48, 139.10, 201.01. − MS (CI, NH_3); *m/z* (%): 240 (100) [M^+ + NH_4]. − $C_{14}H_{22}O_2$ [M^+]: calcd. 222.1620; found 222.1614 (HRMS).

Oxime 14a: To a solution of hydroxylamine hydrochloride (34.2 mg, 0.49 mmol) in water were successively added sodium carbonate (26.1 mg, 0.25 mmol) and a solution of aldehyde **13a** (58.7 mg, 0.22 mmol) in dichloromethane (2 mL). After vigorously stirring for 5 h, dichloromethane (20 mL) was added. The organic phase was washed successively with water (2 × 5 mL) and brine (5 mL), and then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (petroleum ether/AcOEt, 85:15), afforded 62 mg (quantitative) of oxime **14a** as a 1:1 mixture of *syn* and *anti* isomers. − IR (film): $\tilde{\nu}$ = 3280 (broad, OH), 2930, 1700 (C=N), 1640 (C=C), 905 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.96 (s, 3 H), 1.04 (s, 3 H), 1.15−2.14 (m, 13 H), 2.25−2.40 (m, 1 H), 2.83 (d, J = 6.2 Hz, 2 H_{syn}), 3.05 (d, J = 5.4 Hz, 2 H_{anti}), 5.33 (t, J = 3.0 Hz, 1 H_{syn}), 5.38 (t, J = 3.0 Hz, 1 H_{anti}), 5.54 (d, J = 10.0 Hz, 1 H_{major}), 5.55−5.67 (m, 1 H), 5.89 (dd, J = 1.6, 9.3 Hz, 1 H_{minor}), 6.70 (t, J = 5.4 Hz, 1 H_{anti}), 7.37 (t, J = 6.2 Hz, 1 H_{syn}), 9.06 (broad s, 1 H, OH_{anti}), 9.50 (broad s, 1 H, OH_{syn}). − ^{13}C NMR ($CDCl_3$): δ = 21.19, 21.75, 22.14, 22.71, 24.85, 27.43, 28.08 (*syn*), 30.61 (major), 30.73 (major), 30.93 (minor), 31.40 (minor), 31.96 (*anti*), 40.45 (major), 40.63 (minor), 42.91, 75.38, 122.73 (*syn*), 123.19 (*anti*), 126.10 (minor), 126.62 (major), 132.99 (minor), 133.42 (major), 138.97, 151.01 (*anti*), 151.52 (*syn*). − MS (CI, NH_3); *m/z* (%): 260 (36) [M^+ − OH], 278 (58) [M^+ + H], 295 (100) [M^+ + NH_4]. − $C_{17}H_{27}NO_2$ [M^+]: calcd. 277.2042; found 277.2041 (HRMS).

Oxime 14b: Prepared from aldehyde **13b** (284 mg, 1.28 mmol) by the procedure described above. Chromatography on silica gel (pentane/AcOEt, 8:2), afforded 299 mg (99%) of oxime **14b**. − IR (film): $\tilde{\nu}$ = 3267 (broad, OH), 2952, 1641 (C=C), 1470, 1450, 914 cm^{-1}.

– ^{1}H NMR ($CDCl_3$): δ = 0.97 (s, 3 H), 1.06 (s, 3 H), 1.42–2.22 (m, 9 H), 2.84 (d, *J* = 6.0 Hz, 2 H_{syn}), 3.05 (d, *J* = 5.1 Hz, 2 H_{anti}), 4.92 (d, *J* = 10.1 Hz, 1 H), 5.02 (d, *J* = 17.1 Hz, 1 H), 5.32 (t, *J* = 3.0 Hz, 1 H_{syn}), 5.38 (t, *J* = 3.0 Hz, 1 H_{anti}), 5.76–5.90 (m, 1 H), 6.69 (t, *J* = 5.1 Hz, 1 H_{anti}), 7.37 (t, *J* = 6.0 Hz, 1 H_{syn}), 9.28 (broad s, 1 H, OH_{anti}), 9.72 (broad s, 1 H, OH_{syn}). – ^{13}C NMR ($CDCl_3$): δ = 21.82, 22.00, 22.72, 26.92, 27.69, 31.84, 33.34, 42.65, 74.73, 114.17, 122.76 (*syn*), 123.25 (*anti*), 138.98, 139.17, 151.03 (*anti*), 151.51 (*syn*). – MS (CI, NH_3); *m/z* (%): 220 (16) [M^+ – OH], 238 (56) [M^+ + H], 255 (100) [M^+ + NH_4]. – $C_{14}H_{23}NO_2$ [M^+]: calcd. 237.1729; found 237.1725 (HRMS).

General Procedure for the Preparation of Iodides 15a–c From the Corresponding Alcohols.

Iodide 15a: Iodine (290 mg, 1.14 mmol) was added portionwise to a solution of triphenylphosphane (299 mg, 1.14 mmol) and imidazole (77 mg, 1.14 mmol) in ether/acetonitrile (4:1, 5 mL) at 0 °C. After vigorously stirring for 20 min at 0 °C, the reaction mixture was stirred for 20 min at room temperature, then cooled to 0 °C. A solution of diol **12a** (100 mg, 0.38 mmol) in ether/acetonitrile (4:1, 2 mL) was added dropwise over 10 min. The reaction mixture was vigorously stirred for 4 h at room temperature, and then filtered. The solid residue was washed with ether (20 mL), and the filtrate concentrated in vacuo. Ether (40 mL) was added, and the organic phase successively washed with brine (10 mL), saturated aqueous $NaHCO_3$ (3 × 10 mL) and brine (10 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (pentane/AcOEt, 95:5), afforded 122 mg (86%) of iodide **15a**. – IR (film): $\tilde{\nu}$ = 3261 (broad, OH), 2924, 1650 (C=C), 1170 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.97 (s, 3 H), 1.05 (s, 3 H), 1.18–2.10 (m, 13 H), 2.33–2.45 (m, 1 H), 2.56 (t, *J* = 7.9 Hz, 2 H), 3.21 (t, *J* = 7.9 Hz, 2 H), 5.38 (s,1 H), 5.49 (dd, *J* = 1.7, 9.8 Hz, 1 H_{major}), 5.60–5.65 (m, 1 H), 5.91 (dd, *J* = 1.8, 9.8 Hz, 1 H_{minor}). – ^{13}C NMR ($CDCl_3$): δ = 5.05, 21.18, 21.91, 22.40, 22.58, 24.86, 27.31, 30.60 (minor), 30.74 (major), 30.94 (major), 31.40 (minor), 36.50, 40.42 (major), 40.62 (minor), 42.89, 75.18, 121.63, 126.22 (minor), 126.66 (major), 132.88 (minor), 133.45 (major), 142.98. – MS (CI, NH_3); *m/z* (%): 357 (7) [M^+ – OH], 392 (100) [M^+ + NH_4].

Iodide 15b: Prepared as described above from diol **12b** (500 mg, 2.23 mmol). Chromatography on silica gel (pentane/AcOEt, 95:5), afforded 700 mg (94%) of iodide **15b**. – IR (film): $\tilde{\nu}$ = 3397 (broad, OH), 2954, 1639 (C=C), 1470, 1446, 1168, 1032 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.99 (s, 3 H), 1.07 (s, 3 H), 1.36 (s, 1 H, OH), 1.45–2.30 (m, 8 H), 2.53 (t, *J* = 8.0 Hz, 2 H), 3.22 (t, *J* = 8.0 Hz, 2 H), 4.95 (d, *J* = 11.0 Hz, 1 H), 5.08 (d, *J* = 17.1 Hz, 1 H), 5.38 (s, 1 H), 5.80–5.93 (m, 1 H). – ^{13}C NMR ($CDCl_3$): δ = 4.92, 21.91, 22.07, 22.65, 27.04, 27.89, 33.33, 36.44, 42.58, 74.41, 114.14, 121.64, 139.25, 142.98. – MS (CI, NH_3); *m/z* (%): 317 (27) [M^+ – OH], 352 (100) [M^+ + NH_4]. – $C_{14}H_{23}O$ [M^+ – I]: calcd. 207.1749; found 207.1746 (HRMS).

Iodide 15c: Prepared as described above from diol **12c** (246 mg, 1.17 mmol). Chromatography on silica gel (pentane/ether, 4:6), afforded 370 mg (99%) of iodide **15c**. – IR (film): $\tilde{\nu}$ = 3580 (broad, OH), 3460, 3075, 2980, 1638, 1470, 1440, 1360, 1170 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 5.85 (dddd, *J* = 17.1, 10.2, 8.4, 6.6 Hz, 1 H), 5.3 (t, *J* = 3.6 Hz, 1 H), 5.06 (d, *J* = 10.2 Hz, 1 H), 5.03 (d, *J* = 17.1 Hz, 1 H), 3.15 (t, *J* = 8.1 Hz, 2 H), 2.45 (t, *J* = 8.1 Hz, 2 H), 2.25 (dd, *J* = 14.1, 6.6 Hz, 1 H), 2.11 (dd, *J* = 14, 8.4 Hz, 1 H), 1.9–2.0 (m, 2 H), 1.6 (m, 1 H), 1.5 (m, 1 H), 0.93 (s, 3 H), 1.0 (s, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 142.9, 134.6, 121.8, 118.2, 74.1, 42.1, 38.9, 36.3, 27.8, 22.4, 21.9, 5.0. – MS (CI, NH_3); *m/z* (%): 303 (28) [M^+ – OH], 338 (100) [M^+ + NH_4].

General Procedure for the Preparation of Nitro Compounds 16a–c From the Corresponding Iodides.

Nitro Compound 16a: A solution of iodide **15a** (1.4 g, 3.74 mmol) in DMF (100 mL) was added to a mixture of sodium nitrite (577 mg, 8.36 mmol) and urea (638 mg, 10.5 mmol) in DMF (50 mL). After vigorously stirring for 6 h at –78 °C in the dark ether (150 mL) and water (250 mL) were added. The organic layer was separated and the aqueous phase extracted with ether (4 × 150 mL). The combined organic phases were successively washed with water (2 × 100 mL), 20% aqueous sodium thiosulfate (100 mL) and brine (100 mL), and then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (pentane/ether, 2:1), afforded 489 mg (45%) of **16a**. – ^{1}H NMR ($CDCl_3$): δ = 1.01 (s, 3 H), 1.08 (s, 3 H), 1.21–2.32 (m, 13 H), 2.31 (m, 1 H), 2.66 (t, *J* = 7.4 Hz, 2 H), 4.48 (t, *J* = 7.4 Hz, 2 H), 5.32 (s,1 H), 5.47 (dd, *J* = 1.7, 9.8 Hz, 1 H_{major}), 5.61–5.73 (m, 1 H), 5.90 (dd, *J* = 1.9, 9.5 Hz, 1 H_{minor}). – ^{13}C NMR ($CDCl_3$): δ = 21.14, 21.87, 22.20, 22.65, 24.85, 27.37, 29.05, 30.60 (minor), 30.75 (major), 30.92 (major), 31.39 (minor), 40.44 (major), 40.64 (minor), 43.03, 74.86, 75.04, 122.03, 126.34 (minor), 126.75 (major), 133.28, 138.25. – MS (CI, NH_3); *m/z* (%): 311 (100) [M^+ + NH_4].

Nitro Compound 16b: Prepared as described above from iodide **15b** (805 mg, 2.41 mmol). Chromatography on silica gel (pentane/AcOEt, 97:3), afforded 352 mg (58%) of **16b**. – IR (film): $\tilde{\nu}$ = 3451 (broad, OH), 2956, 1640 (C=C), 1554, 1473, 1447, 1380 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.02 (s, 3 H), 1.10 (s, 3 H), 1.38 (s, 1H, OH), 1.50–2.10 (m, 8 H), 2.68 (t, *J* = 7.2 Hz, 2 H), 4.48 (t, *J* = 7.2 Hz, 2 H), 4.95 (d, *J* = 9.8 Hz, 1 H), 5.04 (d, *J* = 17.1 Hz, 1 H), 5.32 (t, *J* = 3.0 Hz, 1 H), 5.78–5.84 (m, 1 H). – ^{13}C NMR ($CDCl_3$): δ = 21.87, 22.13, 22.65, 26.85, 27.89, 28.92, 33.27, 42.71, 74.34, 74.81, 114.29, 122.03, 138.26, 139.11. – MS (CI, NH_3); *m/z* (%): 271 (100) [M^+ + NH_4]. – $C_{13}H_{20}NO_3$ [M^+ – CH_3]: calcd. 238.1443; found 238.1464 (HRMS).

Nitro Compound 16c: Prepared as described above from iodide **15c** (91.7 mg, 0.31 mmol). The crude product was chromatographed on silica gel; elution with pentane/ether (85:15) afforded 9.5 mg (14%) of nitrito compound, then elution with pentane/ether (60:40) afforded 42 mg (61%) of **16c**. – IR (film): $\tilde{\nu}$ = 3480 (broad, OH), 3580, 3480, 3074, 2975, 2950, 2900, 2850, 1640, 1550, 1471, 1443, 1381, 1194, 1078, 1003 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 5.93 (ddt, *J* = 17.4, 10.2, 7.5, 6.6 Hz, 1 H), 5.33 (t, *J* = 3.6 Hz, 1 H), 5.15 (d, *J* = 10.2 Hz, 1 H), 5.12 (d, *J* = 17.4 Hz, 1 H), 4.49 (t, *J* = 7.5 Hz, 2 H), 2.7 (td, *J* = 7.5, 1.5 Hz, 2 H), 2.32 (dd, *J* = 6.6, 14.1 Hz, 1 H), 2.15 (dd, *J* = 7.5, 14.1 Hz, 1 H), 2.05 (m, 2 H), 1.7 (m, 1 H), 1.6 (m, 1 H), 1.25 (broad s, 1 H, OH), 1.04 (s, 3 H), 1.11 (s, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 138, 134.7, 122, 118.5, 74.8, 74, 42.3, 38.9, 28.9, 27.7, 22.5, 21.8, 22.3. – MS (CI, NH_3); *m/z* (%): 222 (78) [M^+ – OH], 257 (100) [M^+ + NH_4]. – $C_{10}H_{16}NO_3$ [M^+ – $CH_2CH{=}CH_2$]: calcd. 198.1130; found 198.1143 (HRMS).

Nitrito Compound. – ^{1}H NMR ($CDCl_3$): δ = 5.96 (dddd, *J* = 16.8, 10.2, 7.8, 6.9 Hz, 1 H), 5.4 (t, *J* = 3.6 Hz, 1 H), 5.15 (d, *J* = 10.2 Hz, 1 H), 5.12 (d, *J* = 16.8 Hz, 1 H), 4.8 (t, *J* = 7.2 Hz, 2 H), 2.39 (t, *J* = 7.2 Hz, 2 H), 2.3 (dd, *J* = 6.9, 13.8 Hz, 1 H), 2.2 (dd, *J* = 7.8, 13.8 Hz, 1 H), 2.05 (m, 2 H), 1.7 (m, 1 H), 1.6 (m, 1 H), 1.02 and 1.10 (2s, 6 H). – ^{13}C NMR ($CDCl_3$): δ = 134.5, 122.0, 118.5, 75.0, 68.0, 42.0, 39.0, 27.8, 25.0, 22.5, 22.2, 22.0.

Isoxazoline 19: A solution of oxime **14b** (22.3 mg, 0.094 mmol) was added in 1 h (with a syringe pump) to a vigorously stirred mixture of dichloromethane (50 mL), sodium hypochlorite (0.75 mL, 1.88 mmol, 2.5 M in water) and 40% aqueous tetrabutylammonium hydroxide solution (1 drop). After stirring for 30 min at room temperature, the organic phase was washed with water (2 × 15 mL)

and brine (15 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, the residue was chromatographed on silica gel (pentane containing increasing amounts of AcOEt, from 0% to 100%, then methanol) to give a solid (18 mg) which was found to contain isoxazoline **19** as the major product, as judged by the following analyses, and some oligomeric impurities. − IR (film): $\tilde{\nu}$ = 3436 (broad, OH), 2953, 1622, 1471, 1196 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.01 (s, 3 H), 1.08 (s, 3 H), 1.42−2.07 (m, 9 H), 2.55 (m, 1 H), 2.96 (m, 1 H), 3.01 (s, 2 H), 4.46−4.64 (m, 1 H), 5.38 (s, 1 H). − MS (CI, NH_3); *m/z* (%): 235 (67) [M^+], 253 (100) [$M^+ + NH_4$]. − $C_{14}H_{21}NO_2$: calcd. 235.1572; found 235.1572 (HRMS).

Bis(isoxazoline) 21: To a solution of *p*-chlorophenylisocyanate (276 mg, 1.8 mmol) and triethylamine (248 μL, 1.8 mmol) in toluene (10 mL) heated to 80°C was added, with a syringe pump over a period of 18 h, a solution of **16c** (43 mg, 0.18 mmol) in toluene (45 mL). After cooling to room temperature, methanol (5 mL) was added. The reaction mixture was then concentrated in vacuo. The residue was chromatographed on silica gel (hexane, then hexane containing increasing amounts of acetone). The fraction eluted with hexane/acetone (80:20) was again chromatographed on silica gel (hexane/AcOEt, 1:1) to afford 4.3 mg (10%) of bis(isoxazoline) **21**. − IR (film): $\tilde{\nu}$ = 3500 (broad, OH), 3000, 2975, 2920, 2850, 1465, 1030 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 5.32 (t, *J* = 3 Hz, 2 H), 4.90 (t, *J* = 9 Hz, 2 H), 3.50 (d, *J* = 13.8 Hz, 2 H), 3.05 (dd, *J* = 15.9, 9 Hz, 2 H), 2.65 (d, *J* = 13.8 Hz, 2 H), 2.50 (d, *J* = 15.9 Hz, 2 H), 2.30−1.70 (m, 12 H), 1.55 (broad s, 1 H, OH), 1.12 (s, 3 H), 1.05 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 159.9, 139.9, 128.0, 76.9, 73.5, 43.7, 42.9, 38.1, 32.3, 31.7, 27.0, 26.2, 23.7, 22.4. − MS (CI, NH_3); *m/z* (%): 407 (15) [M^+ − 2 OH], 425 (90) [M^+ − OH], 443 (100) [M^+ + H], 460 (19) [$M^+ + NH_4$].

Bromide 22: To a solution of alcohol **4** (360 mg, 1.7 mmol) cooled to 0°C were successively added tetrabromomethane (1.25 equiv.) and triphenylphosphane (1.5 equiv.). After stirring for 1 h at 0°C, ether (20 mL) was added. The suspension was filtered and the filtrate was concentrated in vacuo. Chromatography on silica gel (hexane/AcOEt, 95:5), afforded 470 mg (100%) of bromide **22**. − ^1H NMR ($CDCl_3$): δ = 1.07 (s, 6 H), 1.74 (t, *J* = 6.6 Hz, 2 H), 2.10−2.20 (m, 2 H), 2.54 (broad t, *J* = 7.7 Hz, 2 H), 3.45 (t, *J* = Hz, 2 H), 3.90−4.00 (m, 4 H), 5.36 (broad t, *J* = 3.6 Hz, 1 H).

Diene 23: To a solution of bromide **22** (687 mg, 2.5 mmol) in THF (25 mL) cooled to 0°C were successively added copper(I) iodide (25 mg, 0.0125 mmol) and vinylmagnesium bromide (3.6 mL of a 1 M solution in THF). The reaction mixture was allowed to warm to room temperature. After stirring for 1 h, saturated aqueous ammonium chloride (15 mL) was added. The aqueous phase was extracted with ether (50 mL) and the combined organic phases were dried over magnesium sulfate. After filtration and concentration in vacuo, 525 mg (95%) of diene **23** were obtained as an oil which was used in the next step without further purification. − ^1H NMR ($CDCl_3$): δ = 1.07 (s, 6 H), 1.74 (t, *J* = 6.6 Hz, 2 H), 2.01−2.07 (m, 2 H), 2.14−2.20 (m, 4 H), 3.96 (m, 4 H), 4.91−5.04 (m, 2 H), 5.31 (m, 1 H), 5.83 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 22.2, 23.6, 26.1, 30.1, 32.5, 64.8, 112.1, 114.0, 118.4, 139.7.

Ketone 24: A solution of ketal **23** (500 mg, 2.25 mmol) and *p*-toluenesulfonic acid (20 mg, 0.112 mmol) in acetone/water (2:1, 5 mL) was refluxed for 5 h. The reaction mixture was concentrated in vacuo to eliminate acetone. The aqueous phase was extracted with ether (2 × 20 mL). The combined organic phases were successively washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and then dried over magnesium sulfate. After filtration and concentration in vacuo, 400 mg (100%) of ketone **24** were obtained as an oil which was used in the next step without further purification − ^1H NMR ($CDCl_3$): δ = 1.18 (s, 6 H), 1.74 (t, *J* = 6.7 Hz, 2 H), 1.95−2.10 (m, 2 H), 2.10−2.25 (m, 4 H), 3.97 (broad s, 4 H), 4.93 (dd, *J* = 10.7 Hz, 1.4 Hz, 1 H), 5.01 (dd, *J* = 17.4 Hz, 1.7 Hz, 1 H), 5.31 (m, 1 H), 5.75−5.95 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 215.3, 143.6, 138.4, 120.1, 114.7, 48.1, 35.8, 33.1, 29.9, 24.9, 24.1. − MS (CI, NH_3); *m/z* (%): 196 (100) [$M^+ + NH_4$].

Silylated Cyanohydrin 25: To a solution of ketone **24** (240 mg, 1.35 mmol) and trimethylsilyl chloride (1.5 equiv.) in dichloromethane (5 mL) cooled to 0°C was added zinc diiodide (2 mg.). The reaction mixture was allowed to warm to room temperature. After stirring for 1 h, the suspension was filtered and the filtrate was concentrated in vacuo. Chromatography on silica gel (pentane) afforded 315 mg (85%) of silylated cyanohydrin **25**. − ^1H NMR ($CDCl_3$): δ = 0.24 (s, 9 H), 1.04 (s, 3 H), 1.24 (s, 3 H), 2.0−2.15 (m, 2 H), 2.15−2.30 (m, 2 H), 2.35−2.45 (m, 2 H), 2.53 (t, *J* = 6.5 Hz, 2 H), 4.98 (dd, *J* = 10.5 Hz, 1.5 Hz, 1 H), 5.04 (broad d, *J* = 17.3 Hz, 1 H), 5.55 (m, 1 H), 5.75−5.95 (m, 1 H). − $C_{16}H_{27}NOSi$ [M^+]: calcd. 277.1862; found 277.1877 (HRMS).

Aldehyde 26: A solution of diisobutylaluminium hydride (4.38 mL, 1 M in toluene) was added dropwise to a solution of nitrile **25** (300 mg, 1.08 mmol) in ether (10 mL) cooled to 0°C. After stirring for 2 h at this temperature, methanol (1 mL) and a 0.7 M aqueous solution of potassium sodium tartrate (10 mL) were successively added. After stirring vigorously for 4 h the mixture was decanted, the organic layer separated, the aqueous phase extracted with ether (2 × 10 mL) and the combined organic phases washed with brine (10 mL) and then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/ether, 9:1) afforded 210 mg (70%) of aldehyde **26**. − ^1H NMR ($CDCl_3$): δ = 9.76 (s, 1 H), 5.75−5.90 (m, 1 H), 5.34 (m, 1 H), 5.04 (broad d, *J* = 17.1 Hz, 1 H), 4.96 (d, *J* = 10.3 Hz, 1 H), 2.00−2.25 (m, 6 H), 1.80−1.90 (m, 2 H), 1.16 (s, 3 H), 0.97 (s, 3 H), 0.11 (s, 9 H). − ^{13}C NMR ($CDCl_3$): δ = 204.8, 142.2, 138.4, 119.1, 114.4, 83.3, 41.2, 32.8, 30.4, 27.7, 23.9, 23.0, 21.0, 2.3.

Oxime 27: Pyridine (0.035 mL) was added to a suspension of aldehyde **26** (400 mg, 1.43 mmol) and hydroxylamine hydrochloride (150 mg, 2.14 mmol) in ethanol (0.8 mL). The reaction mixture was heated for 5 min at 50°C and then allowed to cool to room temperature. After 15 min, the reaction mixture was concentrated in vacuo. The residue was dissolved in dichloromethane and the solution was washed with water (5 mL), then dried over magnesium sulfate. Filtration and concentration in vacuo afforded 400 mg (95%) of oxime **27**, which was used in the next step without further purification. − ^1H NMR ($CDCl_3$): δ = 7.57 (s, 1 H), 5.75−5.90 (m, 1 H), 5.26 (m, 1 H), 5.04 (broad d, *J* = 17.2 Hz, 1 H), 4.96 (dd, *J* = 10.3 Hz, 1.7 Hz, 1 H), 1.90−2.20 (m, 8 H), 1.16 (s, 3 H), 0.97 (s, 3 H), 0.10 (s, 9 H). − ^{13}C NMR ($CDCl_3$): δ = 154.1, 141.9, 138.8, 116.9, 114.3, 77.7, 42.6, 32.9, 30.6, 27.9, 23.0, 22.9, 22.4, 2.1.

Nitrile Oxide 28: To a solution of oxime **27** (440 mg, 0.15 mmol) in dichloromethane (5 mL) were added a 40% solution of aqueous tetrabutylammonium hydroxide (0.01 mL) and a 7% solution of aqueous sodium hypochlorite (5 mL). After stirring for 24 h at room temperature, the two phases were separated. The organic phase was concentrated in vacuo. Chromatography of the residue on silica gel (pentane/ether, 97:3) afforded 417 mg (95%) of nitrile oxide **28**. − ^1H NMR ($CDCl_3$): δ = 5.75−5.90 (m, 1 H), 5.28 (m, 1 H), 5.04 (broad d, *J* = 17.1 Hz, 1 H), 4.96 (d, *J* = 10.3 Hz, 1 H), 1.90−2.30−2.25 (m, 8 H), 1.16 (s, 3 H), 1.03 (s, 3 H), 0.21 (s, 9 H).

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