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TETRAHEDRON

Synthesis of A-Ring Fragments of 1α,25-Dihydroxyvitamin D$_3$ and Taxane Diterpenoids: Effective Construction of Conjugated Formylcyclohexene Frameworks from Isoxazolines

Teruhiko Ishikawa,* Shushiro Ikeda, Masataka Ibe, and Seiki Saito

Department of Bioscience and Biotechnology, Faculty of Engineering
Okayama University, Tsushima, Okayama, Japan 700-0082

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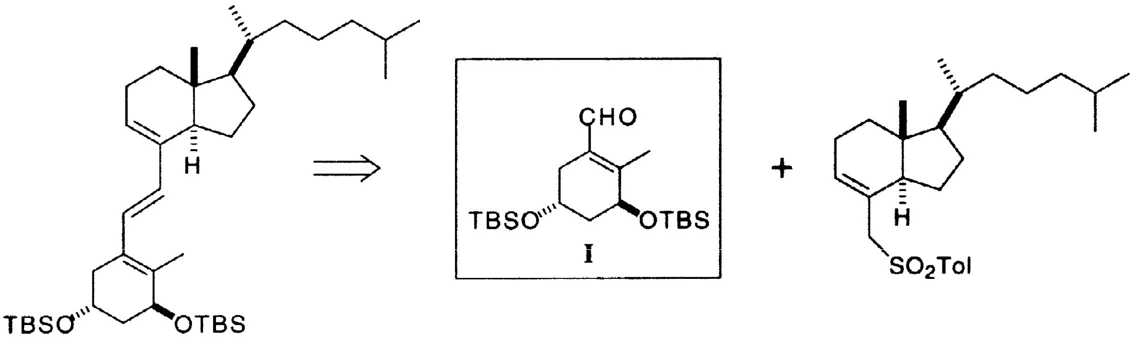
Abstract: This paper have delineated the effectiveness of [3+2] cycloaddition process in the synthesis of multifunctional 6-membered rings. The novel synthesis of chiral A-ring fragment of 1α,25-dihydroxyvitamin D$_3$ and also a novel route to A-ring fragment of taxane diterpenoids have been established.

INTRODUCTION

Synthesis of 1α,25-dihydroxyvitamin D$_3$ (1α,25-D$_3$) and its analogues is still under active field in organic synthesis[1] because they exhibit potent physiological properties such as regulation of cell differentiation and proliferation, bone mobilization and formation, and calcium absorption. Horner-Wittig olefination between A- and CD-ring moieties including simultaneous triene formation is one of the most prevailing ways in such a synthesis, which was pioneered by Lythgoe,[2] because it is a highly convergent and versatile method for producing analogues directed to the examination of structure-activity relationship of vitamin D$_3$ drugs. Lythgoe has also developed the convergent Julia olefination approach to 1α,25-D$_3$ and representative one is outlined in Scheme 1.[3] In this method, a proper conjugate triene system was constructed not directly but by isomerization after the Julia coupling between CD ring moiety and **I**.

Scheme 1



Chemistry of taxane diterpenoids is also one of the current topics in organic synthesis.[4] The total synthesis of taxol has been accomplished so far by five groups (Holton,[5] Nicolaou,[6] Danishefsky,[7] Wender[8] and Mukaiyama[9]), which is the recent scientific landmark. The total synthesis of taxusin has also been done by

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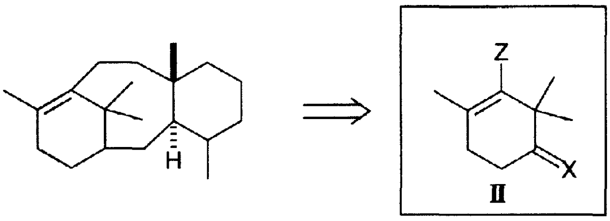
two groups (Holton[10] and Kuwajima[11]). Since the synthesis of the A-ring unit of taxoids constitutes an important part in their convergent approaches, a number of strategies for the synthesis of related intermediate **II** (Scheme 2) have been reported.[12]

Scheme 2

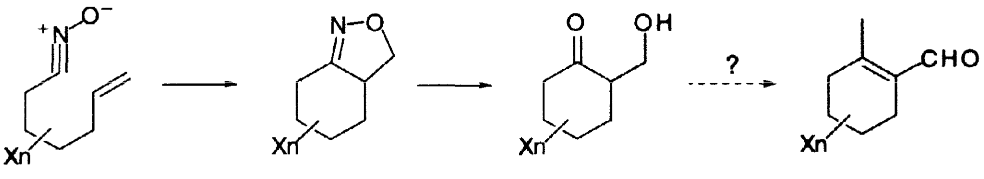


II

X = O, $-OCH_2CH_2O-$, etc.
Z = CH_2OH, CHO, Vinyl, etc.

A structural characteristic recognized commonly in these two important intermediates **I** and **II** is a tetrasubstituted cyclohexene backbone bearing additional functionalizable substituents on it. Hence we were intrigued with the common strategy leading to these intermediates which features the intramolecular nitrile oxide-olefin [3+2] cycloaddition reaction (Scheme 3).[13] Thus, a synthetic route leading to **I** or **II** relaying on such well-known reaction should involve not only the inevitable intermediate **V**, which would be available from cycloadduct **IV** by reductive hydrolysis as reported by Curran[14] and Kozikowski,[15] but also a reasonable answer to the question how to convert **V** into **I** and/or **II**. In this paper we will exemplify the novel and concise approaches to functionalized formylcyclohexene derivatives by the successful synthesis of **I** and **II**.

Scheme 3



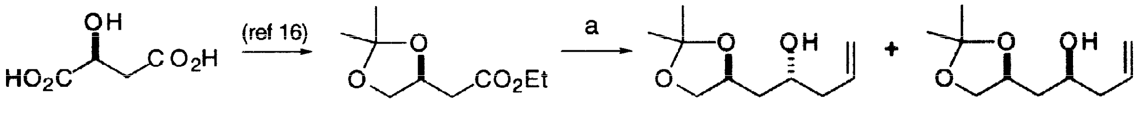
III **IV** **V** **I** or **II**

RESULTS AND DISCUSSION

Synthesis of A-ring moiety of 1α,25-D₃.

We chose natural (*S*)-malic acid as a starting chiral template to adopt its stereogenic center to that of **I** bearing an α-oriented hydroxyl group. Chemoselective reduction of diethyl (*S*)-malate after our procedure[16] gave the diol, which was protected as the acetonide **1**. Reduction of ester **1** with DIBAL-H followed by the addition of allylmagnesium bromide in one pot afforded a homoallylic alcohol (**2a** and **2b**) as a mixture of separable diastereomers (1:1). Although asymmetric allylation leading to anti-1,3-diol (92% de) from (*S*)-3,4-*O*-(1-ethyl)propylidene-3,4-dihydroxybutanal using Brown's allyl(diiso-pinocamphenyl)borane has been reported by Smith,[17] we employed the conventional way because it turned out that these diastereomers are able to be easily separated by simple silica gel column chromatography. The both isomers, after isolation, were subjected to the synthetic route: the anti one **2a** has the desired stereochemistry for **I** and **2b** was led to the diastereomer of **I**.

Scheme 4

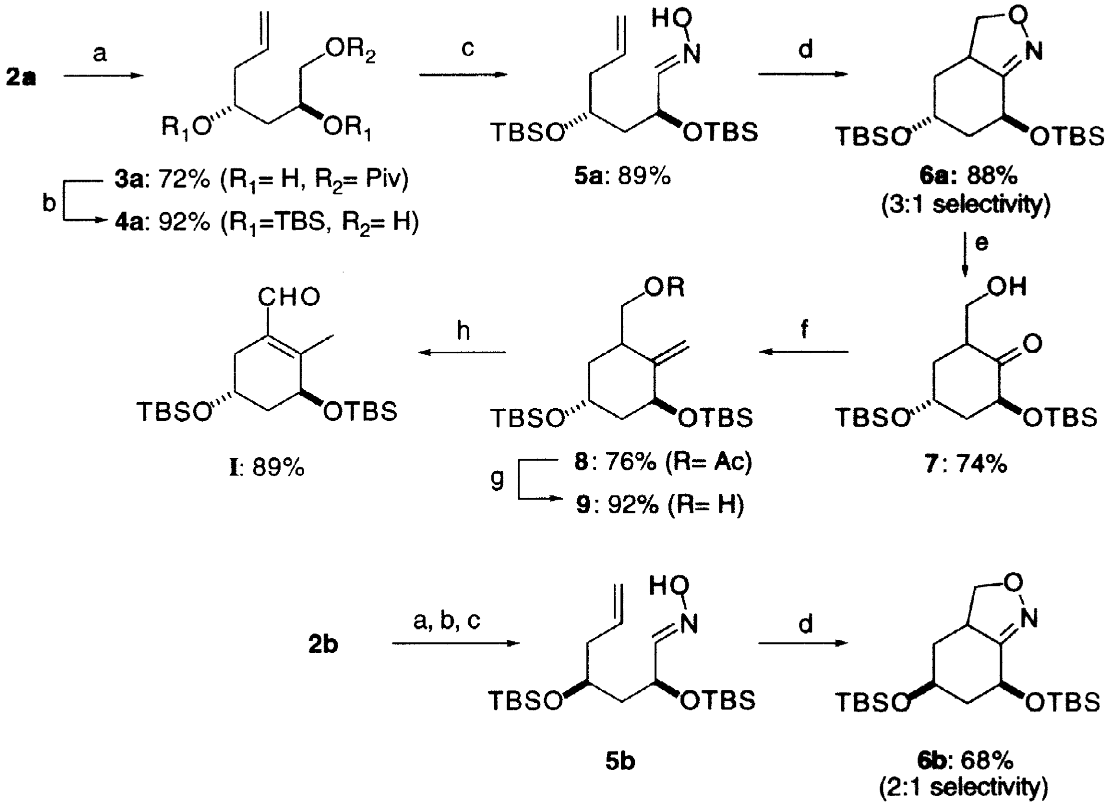


(*S*)-Malic acid **1** **2a** 78% (1 : 1) **2b**

a) DIBAL-H (1 eq.) / toluene, –78 °C then allylmagnesium bromide

The conversion of **2** to the key intermediate **I** was outlined in Scheme 5. Deprotection of acetonide of **2a** under acidic conditions followed by the selective protection of thus-generated primary hydroxyl group using pivaloyl chloride with pyridine in dichloromethane gave the diol **3a** in 74% yield. Silylation (TBSOTf, triethylamine) of 2,4-dihydroxyl group of **3a** and removal of the pivaloyl group by DIBAL-H reduction afforded **4a** in high yield. The oxime **5a**, which was the precursor of nitrile oxide for intramolecular cycloaddition reaction, was prepared by Swern oxidation of **4a** followed by the condensation with hydroxylamine. The syn isomer **2b** was also transformed to the oxime **5b** likewise.

Scheme 5



(a) (1) 2N-HCl / EtOH, (2) pivaloyl chloride, pyridine / CH_2Cl_2; (b) (1) TBSOTf / Et_3N / THF, (2) DIBAL-H / toluene; (c) Swern oxidation, then NH_2OH-HCl / Et_3N; (d) NaOCl / CH_2Cl_2-H_2O; (e) H_2 / Pd-C / $B(OH)_3$ / MeOH-H_2O; (f) (1) Ac_2O / Et_3N, (2) Ph_3P=CH_2 / THF; (g) DIBAL-H / toluene; (h) (1) PCC / CH_2Cl_2, (2) DBU / THF.

Oxidation of the oxime **5a** to nitrile oxide with aqueous NaOCl[18] in dichloromethane was followed by spontaneous intramolecular cycloaddition reaction to give the isoxazoline **6a** in 88% yield as a mixture of two diastereomers (3:1). Although no stereochemical consequence of this process is trouble to the synthesis of **I**, the stereochemistry of major diastereomer was determined by NOESY experiment and the observed NOEs were shown in Fig. 1. The isoxazoline **6b** was obtained likewise from **5b**. In this case diastereomeric mixture (2:1) was also obtained and the stereochemistry of major diastereomer was determined by NOESY measurement, which is shown also in Fig. 1.[19]

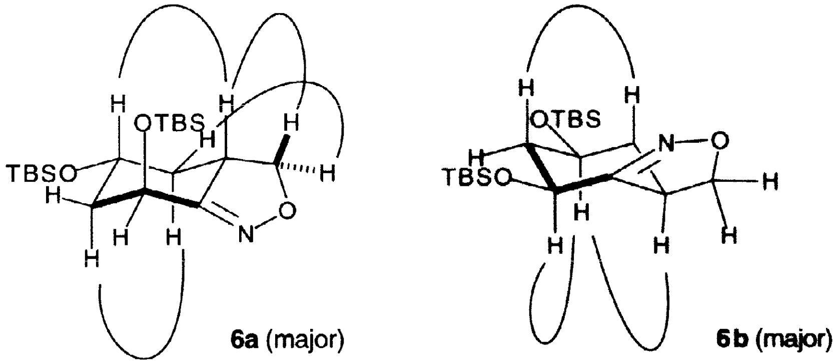


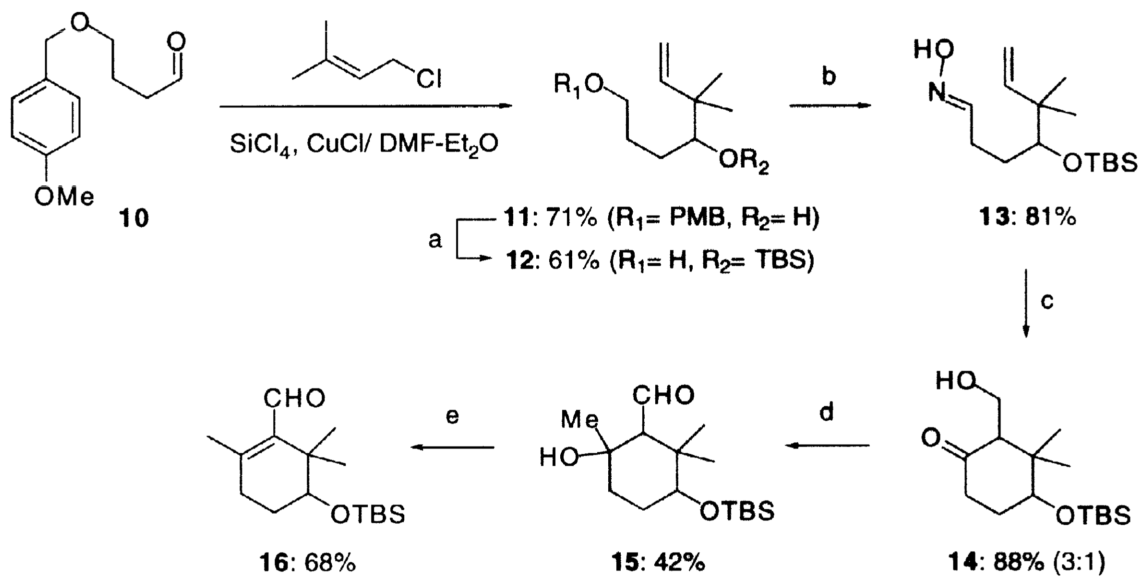
Fig. 1. The typical NOEs observed in NOESY experiments of the major stereoisomers of **6a** and **6b**.

Conversion of the isoxazoline **6a** to **I** was carried out as follows. Reductive hydrolysis[14] of the isoxazoline part of **6a** with Pd-charcoal in the presence of boric acid under a hydrogen atmosphere in aqueous MeOH afforded the 2-hydroxymethylcyclohexanone **7** in 74% yield. Acetylation of **7** followed by Wittig olefination gave **8** in 76% yield. At this stage the partial epimerization on the carbon bearing acetoxymethyl group was observed, whereas the stereochemistry of carbon bearing siloxy group neighboring to the carbonyl group was kept intact. Reduction (DIBAL-H) of **8** gave the homoallylic alcohol **9** in 92% yield, which was subjected to PCC oxidation followed by isomerization to α,β-unsaturated aldehyde in the presence of DBU to afford **I** in 89% yield from **9**. Spectroscopic properties (^{1}H-NMR, ^{13}C-NMR, IR) and optical rotation of **I** were completely identical with those reported.[20] The overall yield from **2a** available from natural (*S*)-malic acid in multi-gram quantities is 22% in 13 steps.

Synthesis of A-ring moiety of taxoids .

Application of above strategy to the synthesis of **II** necessarily requires the oxime **13** as a key intermediate. The way to **13** is simple and straightforward. Thus, the aldehyde **10** was readily prepared from 1,4-butanediol (monoprotection with *p*-methoxybenzyl group and Swern oxidation). Allylation of **10** was carried out after Kobayashi's method[21] to afford the homoallylic alcohol **11** in 71% yield. The regiochemistry of this prenylation was perfectly controlled. Silylation (TBSOTf, triethylamine) of **11** followed by deprotection of the *p*-methoxybenzyl group using DDQ in a binary mixture of water and dichloromethane gave the alcohol **12** in 61% yield, from which the alkenyloxime **13** was prepared by Swern oxidation followed by condensation with hydroxylamine. Intramolecular [3+2] cycloaddition reaction of **13** and reductive hydrolysis of the resulting isoxazoline smoothly proceeded to afford the 2-hydroxylmethylcyclohexanone **14**. However, on the contrary to the case of **7**, attempted Wittig olefination of the acetylated **14** was not effected. Hence we turned our attention to an alternative route to the backbone of **II** from **14** which involves the addition of organometallic reagents to the carbonyl group, oxidation of the primary hydroxyl group to aldehyde, and mesylation of the tertiary hydroxyl group to trigger spontaneous elimination. Indeed, a series of these routine reactions took place to give the A-ring framework of taxoids **16**.

Scheme 6



(a) (1) TBSOTf / Et_3N, (2) DDQ / CH_2Cl_2-H_2O; (b) Swern oxidation, then NH_2OH-HCl / Et_3N; (c) (1) NaOCl / CH_2Cl_2-H_2O, (2) H_2, Pd-C / $B(OH)_3$ / MeOH-H_2O; (d) (1) MeMgBr, (2) Swern oxidation; (e) MsCl / Et_3N.

CONCLUSION

We have established the novel synthesis of chiral A-ring fragment of 1α,25-dihydroxyvitamin D_3 and also a novel route to A-ring fragment of taxane diterpenoids. In these syntheses acyclic precursors were transformed into 6-hepten-1-al frameworks, which were condensed with hydroxylamine to the corresponding oxime derivatives that were the immediate precursors for the nitrile oxide bearing a terminal carbon-carbon double bond. We believe that we have delineated the effectiveness of the [3+2] cycloaddition process in the synthesis of multifunctional 6-membered rings. In addition, it should be noted that while the previous methods for the synthesis of **I** utilized chiral cyclic starting materials, we have made it from acyclic one.[22] This might make easier access to A-ring analogues of vitamin D drugs possible, which would serve for the study on structure-activity relationship.

EXPERIMENTAL SECTION

Instrumentation. IR spectra ware recorded on a Horiba fourier transform infrared spectrophotometer Model FT-210 instrument. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian VXR-200 (200 MHz for proton and 50 MHz for carbon-13), Varian Mercury-300 (300 MHz for proton and 75 MHz for carbon-13) or Varian VXR-500 (500 MHz for proton and 126 MHz for carbon-13) instrument. The chemical shifts are given in δ unit relative to internal $CHCl_3$ (7.26 ppm for ^{1}H) or $CDCl_3$ (77 ppm for ^{13}C). All NMR experiments were performed using deuteriochloroform as a solvent unless otherwise indicated. Optical rotations were measured on a digital polarimeter (Horiba SEPA-300) using a 3.5 mm × 0.5 dm pyrex cell. Mass spectra were obtained on a JEOL JMS-DX303 instrument relying on a JMA-DA5000 mass data system. Elemental analyses were made with a Perkin-Elmer 2400 CHN Elemental Analyzer.

Analytical Procedure and Data Presentation. Analytical thin layer chromatography was performed on Merck pre-coated silica gel 60 F-254 (0.25 mm thickness). ^{1}H-NMR spectral data were indicated in the form: δ-value of signal (peak multiplicity, integrated number of protons, and coupling constant, if any). Splitting patterns are abbreviated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. When 3- or 4-spin system in which spin-spin coupling constants are quite similar values to result in not "dd" but apparent "t" or not "ddd" but apparent "q", they are expressed as 3-line dd (m, n Hz) or 4-line ddd (x, y, z Hz) with regard to the peak multiplicity: alphabetical letters in parenthesis are numerical values of gaps between the neighboring lines in Hz as indicated.

General Reaction Procedure. All reactions, unless otherwise noted, were conducted under a nitrogen or an argon atmosphere. Liquid reagents were transferred via a dry hypodermic syringe from sure seal bottles to a reaction flask through a rubber septa wired on to the reaction flask. The septa can also serve to permit evacuation to eliminate air and introduce the inert gas by means of a steady stream of inert gas flowing system. Organic extracts were concentrated by evaporation with a rotary evaporator evacuated at around 60 mmHg. Column chromatography, unless otherwise specified, was performed on a Merck silica gel 60 7734 using an appropriate ratio of ethyl acetate-hexane mixed solvent and abbreviated as CC.

Materials. Unless otherwise noted, materials were obtained from commercial suppliers and reagent grade materials were used without further purification. Pyridine, toluene, dimethylsulfoxide (DMSO), triethylamine (Et_3N), dichloromethane (CH_2Cl_2), and benzene were freshly distilled from CaH_2 prior to use. Methanol and Ethanol were distilled from the corresponding magnesium alkoxides under argon. Tetrahydrofuran and diethyl ether were distilled from benzophenone/ketyl prior to use.

(2*S*,4*R*)-1,2-*O*-(Isopropylidene)hept-6-ene-1,2,4-triol (**2a**) and **(2*S*,4*S*)-1,2-*O*-(Isopropylidene)hept-6-ene-1,2,4-triol** (**2b**). To a solution of **1** (5.00 g, 0.0265 mol) in toluene (100 ml) precooled at –78 °C was added dropwise DIBAL-H (1.02 M in toluene, 1.02 eq) over 30 min and the mixture was stirred at –78 °C for 30 min. To the mixture was added allylmagnesium bromide (1.0 M, 2.0 eq) at –78 °C. The mixture was stirred at –78 °C to 0 °C for 1 h. The reaction was quenched by the addition of water and filtered through a celite pad, the filter cake being thoroughly rinsed with AcOEt. The combined organic solutions were dried with Na_2SO_4 and concentrated to give an oil, which, on careful CC, gave pure **2a** (1.92 g, 39%) together with its diastereomer **2b** (1.91 g, 39%). **2a**: $[\alpha]^{19}_D$ –8.87 (c 3.46, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 1.35 (s, 3H), 1.42 (s, 3H), 1.60—1.80 (m, 2H), 2.1—2.37 (m, 3H), 3.55 (dd, 1H, *J* = 6.0, 8.0 Hz), 3.78—3.95 (m, 1H), 4.08 (dd, 1H, *J* = 6.0, 8.1 Hz), 4.25—4.40 (m. 1H), 5.05—5.20 (m, 2H), 5.71—5.92 (m, 1H); ^{13}C-NMR (50 MHz) δ 25.3, 26.5, 39.6, 42.1, 67.4, 69.2, 73.2, 108.2, 117.3, 134.2; IR (film) 3450 cm^{-1}. **2b**: $[\alpha]^{18}_D$ +14.6 (c 3.33, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 1.34 (s, 3H), 1.40 (s, 3H), 1.55—1.80 (m, 2H), 2.15—2.35 (m, 2H), 3.09 (m, 1H), 3.55 (dd, 1H, *J* = 8.0 Hz), 3.79—3.92 (m, 1H), 4.08 (dd, 1H, *J* = 8.0 Hz), 4.19—4.32 (m, 1H), 5.04—5.16 (m, 2H), 5.70—5.92 (m, 1H); ^{13}C-NMR (50 MHz) δ 25.6, 26.7, 39.5, 41.7, 69.5, 69.8, 75.3, 109.1, 117.5, 134.4 ; IR (film) 3500 cm^{-1}.

(2*S*,4*R*)-1-*O*-(Pivaloyl)hept-6-ene-1,2,4-triol (3a). To a solution of **2a** (1.70 g, 9.0 mmol) in EtOH (20 ml) was added 2N-HCl (5.4 ml, 1.2 eq) at 0 °C. The mixture was stirred at rt for 4 h, concentrated by a rotary evaporator to eliminate HCl and dried under high vacuum for overnight to give a purple oil (1,2,4-triol). To a stirred solution of the 1,2,4-triol in CH_2Cl_2 (20 ml) were added pyridine (0.73 ml, 1.2 eq) and pivaloyl chloride (1.1 ml, 1.1 eq) at –40 °C. The mixture was stirred at –40 °C to rt for 20 h, quenched by the addition of water, and extracted with CH_2Cl_2 (3 times). The combined extracts were dried with Na_2SO_4 and concentrated by a rotary evaporator to give an oil, which, on CC, gave **3a** (1.50 g, 72%): $[\alpha]^{22}_D$ –7.80 (c 2.50, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 1.18 (s, 9H), 1.51—1.71 (m, 2H), 2.18—2.42 (m, 4H), 3.93—4.24 (m, 4H), 5.08—5.22 (m, 2H), 5.70—5.92 (m, 1H); ^{13}C-NMR (50 MHz) δ 26.8, 38.5 , 38.7, 41.8, 66.5, 67.2, 67.9, 117.5, 134.2, 178.5; IR (film) 3400, 1740 cm^{-1}; exact mass, m/z 230.15181 (calcd for $C_{12}H_{22}O_4$ m/z 230.15179). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.57; H, 9.63. Found: C, 62.32; H, 9.84.

(2*S*,4*R*)-2,4-Di-(*O*-*tert*-butyldimethylsilyl)hept-6-ene-1,2,4-triol (4a). To a solution of **3a** (440 mg, 1.91 mmol) in CH_2Cl_2 (4 ml) was added TBSOTf (0.96 ml, 2.2 eq) followed by the addition of Et_3N (0.58 ml, 2.2 eq) at 0 °C. The reaction was continued at 0 °C for 30 min, quenched by the addition of water, and extracted with AcOEt. The combined extracts were dried with Na_2SO_4 and concentrated to give a clear colorless oil, which, on CC, gave (2*S*,4*R*)-1-*O*-pivaloyl-2,4-di-*O*-(*tert*-butyldimethylsilyl)hept-6-ene-1,2,4-triol (861 mg, 98%): $[\alpha]^{24}_D$ –20.0 (c 1.03, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 0.05 (s, 6H), 0.08 (s, 6H), 0.87 (s, 18H), 1.19 (s, 9H), 1.55—1.65 (m, 2H), 2.19—2.30 (m, 2H), 3.79—4.02 (m, 4H), 4.95—5.12 (m, 2H), 5.68—5.90 (m, 1H); ^{13}C-NMR (50 MHz) δ –4.47, –4.39, –4.16, –3.94, 17.95, 18.0, 25.7, 25.8, 27.2, 38.6, 42.4, 42.6, 68.1, 68.4, 69.2, 117.1, 134.4, 178.1; IR (film) 1733 cm^{-1}.

To a solution of (2*S*,4*R*)-1-*O*-pivaloyl-2,4-di-*O*-(*tert*-butyldimethylsilyl)hept-6-ene-1,2,4-triol (1.3 g, 2.83 mmol) in THF (15 ml) was added dropwise DIBAL-H (0.95 M in toluene, 2.0 eq) at –78 °C. The mixture was stirred at –78 °C for 1.5 h and quenched by the addition of an EtOH–water mixture. Thus-produced precipitates were removed by filtration through a celite pad, which was rinsed with several portions of ethyl acetate. The combined organic solutions were dried with Na_2SO_4 and concentrated to give an oil, which, on CC, afforded **4a** (996 mg, 94%): $[\alpha]^{20}_D$ –7.7 (c 1.66, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 0.06 (s, 6H), 0.08 (s, 6H), 0.89 (s, 18H), 1.60—1.71 (m, 2H), 2.18—2.29 (m, 2H), 3.39—3.65 (m, 2H), 3.75—3.87 (m, 2H), 4.98—5.12 (m, 2H), 5.69—5.91 (m, 1H); ^{13}C-NMR (50 MHz) δ –4.3, –4.1, 17.9, 25.8, 41.6, 42.3, 66.8, 69.6, 70.9, 117.1, 134.5; IR (film) 3400 cm^{-1}.

(2*S*,4*R*)-2,4-Di-(*O*-*tert*-butyldimethylsilyl)-2,4-dihydroxy-6-heptenecarbaldehyde oxime (5a). A solution of **4a** (270 mg, 0.720 mmol) in CH_2Cl_2 (3 ml) was mixed with Swern reagent prepared from $(COCl)_2$ (0.157 ml, 1.80 mmol) and DMSO (0.255 ml, 3.6 mmol) in CH_2Cl_2 (2 ml) at –78 °C. After 15 min stirring, Et_3N (1.0 ml) was added to the mixture at –78 °C and stirring was continued for additional 30 min at 0 °C. The reaction was quenched by the addition of water and extracted with AcOEt-hexane (1:1) mixed solvent. The combined organic solutions were dried with Na_2SO_4 and concentrated to give the corresponding aldehyde. To a solution of the crude aldehyde in EtOH (5 ml) were added NH_2OH-HCl (500 mg, 7.2 mmol) and Et_3N (1.0 ml, 7.2 mmol) at 0 °C and the mixture was stirred at rt for 11 h. The reaction was diluted with water and extracted with AcOEt. The combined extracts were dried with Na_2SO_4 and concentrated to afford an oil, which, on CC, gave **5a** (251 mg, 89%): $[\alpha]^{20}_{D}$ +3.11 (c 1.06, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 0.03 (s, 6H), 0.05 (s, 6H), 0.87 (s, 9H), 0.88 (s, 9H), 1.55—1.86 (m, 3H), 2.20—2.35 (m, 2H), 3.79—3.92 (m, 1H), 4.29—4.42 (m, 1H), 4.95—5.13 (m, 2H), 5.70—5.92 (m, 1H), 7.21—7.30 (m, 1H); ^{13}C-NMR (75 MHz) δ –4.6, –4.4, –4.0, –3.8, 18.0, 25.8, 25.9, 42.1, 43.5, 67.7, 68.3, 117.1, 134.5, 153.7; IR (film) 3400 cm^{-1}.

(2*S*,4*S*)-2,4-Di-(*O*-*tert*-butyldimethylsilyl)-2,4-dihydroxy-6-heptenecarbaldehyde oxime (5b). This compound was prepared from **2b** through a series of reactions done for **2a**: $[\alpha]^{22}_{D}$ –2.4 (c 1.0, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 0.03 (s, 6H), 0.04 (s, 6H), 0.88 (s, 9H), 0.89 (s, 9H), 1.70—1.82 (m, 2H), 2.15—2.32 (m, 2H), 3.78—3.88 (m, 1H), 4.32—4.41 (m, 1H), 5.00—5.12 (m, 2H), 5.74—5.86 (m, 1H), 7.26 (d, 1H, *J* = 7.4 Hz); ^{13}C-NMR (75MHz) δ –4.9, –4.5, –4.3, 18.02, 18.07, 25.78, 25.88, 41.7, 43.2, 67.7, 68.2, 117.2, 134.6, 153.3; IR (film) 3338 cm^{-1}.

(5*S*,7*S*,9*R*)-7,9-Bis(*tert*-butyldimethylsilyloxy)-2-aza-3-oxabicyclo[4.3.0]non-1-ene (6a). To a stirred solution of **5a** (201 mg, 0.518 mmol) in CH_2Cl_2 (5 ml) was added an aqueous NaOCl solution (1.5 ml) and the mixture was stirred at rt for 2.5 h. The reaction was diluted with water and extracted with AcOEt. The combined extracts were dried with Na_2SO_4 and concentrated to give an oil which, on CC, gave **6a** (177 mg, 88%) as an epimeric mixture at C(5). The corresponding diastereomers were separated by CC. Data for major isomer (5*S*,7*S*,9*R*)-7,9-bis(*tert*-butyldimethylsilyloxy)-2-aza-3-oxabicyclo[4.3.0]non-1-ene: $[\alpha]^{20}_{D}$ +108 (c 0.099, $CHCl_3$); ^{1}H-NMR (500 MHz) δ 0.03 (s, 3H, $SiCH_3$), 0.055 (s, 3H, $SiCH_3$), 0.057 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.87 (s, 18H, $SiC(CH_3)_3$), 1.41 {4-line ddd (11.6, 11.9, 11.9 Hz), 1H, $C(6)H_{ax}$}, 1.53—1.60 (m, 1H, $C(8)H_{ax}$), 2.13 (ddd, 1H, *J* = 2.9, 6.0, 13.4 Hz, $C(8)H_{eq}$), 2.17—2.23 (m, 1H, $C(6)H_{eq}$), 3.50—3.59 (m, 1H, C(5)H), 3.86—3.91 {3-line dd (8.2, 8.6 Hz), 1H, C(4)*H*H}, 4.19—4.27 (m, 1H, C(7)H), 4.45 (dd, 1H, *J* = 8.2, 10.1 Hz, C(4)H*H*), 4.75 (t, 1H, *J* = 2.9 Hz, C(9)H); ^{13}C-NMR (50 MHz) δ –4.8, –5.3, 17.8, 18.1, 25.5, 25.7, 41.1, 43.9, 44.3, 63.6, 65.1, 73.8, 159.5; IR (film) 2952, 1463 cm^{-1}; exact mass, m/z 385.24679 (calcd for $C_{19}H_{39}O_3NSi_2$ m/z 385.24683). Anal. Calcd for $C_{19}H_{39}O_3NSi_2$: C, 59.18; H, 10.20. Found: C, 59.01; H, 10.44.

Data for minor isomer (5*R*,7*S*,9*R*)-7,9-bis(*tert*-butyldimethylsiloxy)-2-aza-3-oxabicyclo[4.3.0]non-1-ene: $[\alpha]^{20}_{D}$ –70.5 (c 1.38, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.12 (s, 3H), 0.87 (s, 9H), 0.90 (s, 9H), 1.38—1.75 (m, 2H), 1.98—2.22 (m, 2H), 3.51—3.71 (m, 1H), 3.82 (dd, 1H, *J* = 7.6, 10.1 Hz), 4.20—4.30 (m, 1H), 4.52 (dd, 1H, *J* = 7.6, 10.5 Hz), 4.80—4.92 (m, 1H); ^{13}C-NMR (50 MHz) δ –5.6, –5.2, –5.1, 17.6, 18.1, 25.4, 25.5, 38.6, 43.7, 44.0, 64.8, 67.5, 73.2, 161.5; IR (KBr) 2952, 1471 cm^{-1}.

(5*S*,7*S*,9*S*)-7,9-Bis(*tert*-butyldimethylsilyloxy)-2-aza-3-oxabicyclo[4.3.0]non-1-ene (6b). The oxime **5b** was led to this isoxazoline by the similar procedure as that for the preparation of **6a** from **5a**. Data for major isomer (5*S*,7*S*,9*S*)-7,9-bis(*tert*-butyldimethylsilyloxy)-2-aza-3-oxabicyclo[4.3.0]non-1-ene: $[\alpha]^{23}{}_D$ −68.2 (c 1.90, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.42 {4-line ddd (12.1, 11.3, 12.1 Hz), 1H, C(6)H_{ax}}, 1.72 {4-line ddd (11.8, 11.5, 11.8 Hz), 1H, C(8)H_{ax}}, 2.11—2.20 (m, 1H, C(6)H_{eq}), 2.20—2.29 (m, 1H, C(8)H_{eq}), 3.22 (m, 1H, C(5)H), 3.75—3.86 (m, 1H, C(7)H), 3.88 (dd, 1H, *J* = 8.0, 10.1 Hz, C(4)*H*H), 4.45 (dd, 1H, *J* = 5.7, 11.8 Hz, C(9)H), 4.52 (dd, 1H, *J* = 8.0, 10.7 Hz, C(4)H*H*); ^{13}C-NMR (75 MHz) δ −5.2, −4.8, −4.7, −4.6, 18.0, 18.4, 25.7, 40.2, 45.5, 45.6, 65.9, 67.7, 73.7, 160.8; IR (KBr) 2954, 1471 cm^{-1}; exact mass, m/z 385.24686 (calcd for $C_{19}H_{39}O_3NSi_2$ m/z 385.24683). Anal. Calcd for $C_{19}H_{39}O_3NSi_2$: C, 59.18; H, 10.20. Found: C, 59.16; H, 10.21.

Data for minor isomer (5*R*,7*S*,9*S*)-7,9-bis(*tert*-butyldimethylsiloxy)-2-aza-3-oxabicyclo[4.3.0]non-1-ene: $[\alpha]^{22}{}_D$ +13.6 (c 1.60, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 0.04 (s, 6H), 0.08 (s, 3H), 0.13 (s, 3H), 0.86 (s, 9H), 0.88 (s, 3H), 1.49—1.58 (m, 1H), 1.70—1.78 (m, 1H), 2.04—2.10 (m, 1H), 2.08—2.17 (m, 1H), 3.80—3.97 (m, 2H), 4.09—4.14 (m, 1H), 4.41 (dd, 1H, *J* = 7.2, 10.0 Hz), 4.77 (dd, 1H, *J* = 1.7, 3.9 Hz); ^{13}C-NMR (75 MHz) δ −5.0, −4.8, −4.7, −4.6, 18.1, 18.2, 25.80, 25.88, 25.9, 40.2, 40.5, 41.8, 63.3, 65.8, 73.1, 161.4; IR (film) 2929, 1471 cm^{-1}.

(2*RS*,4*S*,6*R*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)cyclohexanone (7). To a solution of the isoxazoline **6a** (166 mg, 0.430 mmol) in MeOH-water (5:1, 6 ml), placed in a hydrogenation vessel were added boric acid (66 mg, 2.5 eq) and a spatula tip of 10% Pd-C. The reaction vessel was flushed with hydrogen gas and the mixture was stirred vigorously under a positive pressure of hydrogen for 20 h. The mixture was filtered through a celite pad and the filtrate was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with several portions of CH_2Cl_2. The combined organic solutions were dried over Na_2SO_4 and concentrated to give an oil, which, on CC, gave **7** (123 mg, 74%) as a diastereomeric mixture at C(2). One of the isomers was obtained by means of CC. Data for major diastereomer (2*R*,4*R*,6*S*)-4,6-bis(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)cyclohexanone: $[\alpha]^{26}{}_D$ −38.7 (c 1.10, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.09 (s, 6H), 0.89 (s, 18H), 1.51—1.57 (m, 2H), 2.00—2.42 (m, 2H), 2.54—2.64 (m, 1H), 2.98—3.13 (m, 1H), 3.59—3.82 (m, 2H), 4.12 (dd, 1H, *J* = 3.2, 5.3 Hz), 4.37—4.52 (m, 1H); ^{13}C-NMR (50 MHz) δ −5.5, −5.1, −5.0, −4.9, 17.8, 18.2, 25.5, 25.6, 37.3, 44.6, 45.3, 61.7, 65.9, 72.7, 211.9; IR (film) 3534, 1726 cm^{-1}.

[(1*RS*,3*S*,5*R*)-2-Oxo-3,5-bis(*tert*-butyldimethylsilyloxy)cyclohexyl]methyl acetate (8). To a solution of **7** (93 mg, 0.24 mmol) in CH_2Cl_2 were added excess Et_3N, excess Ac_2O, and DMAP (cat amount) at rt and the mixture was stirred at rt for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution and extracted with several portions of AcOEt. The combined extracts were dried over Na_2SO_4 and concentrated to give an oil, which, on CC, gave (2*RS*,4*S*,6*R*)-1-acetoxymethyl-4,6-bis(*O-tert*-butyldimethylsilyloxy)cyclohexanone (102 mg, 98%).

Data for major (2*R*,4*S*,6*R*)-isomer: $[\alpha]^{22}{}_D$ +28.4 (c 1.06, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.08 (s, 6H), 0.88 (s, 9H), 0.89 (s, 9H), 1.48—1.63 (m, 1H), 1.75—1.89 (m, 1H), 2.02 (s, 3H), 2.04—

2.18 (m, 2H), 4.09 (dd, 1H, J = 5.5, 11.3 Hz), 4.16—4.22 (m, 1H), 4.36—4.48 (m, 2H); ^{13}C-NMR (50 MHz) δ –5.3, –5.0, –4.8, 18.1, 20.7, 25.5, 25.7, 38.3, 43.1, 44.3, 63.1, 65.5, 73.9, 170.7, 209.0; IR(film) 1747 cm^{-1}.

Data for minor (2*S*,4*S*,6*R*)-isomer: $[\alpha]^{22}_D$ –42.5 (c 1.30, CHCl$_3$); ^{1}H-NMR (200 MHz) δ 0.03 (s, 3H), 0.11 (s, 3H), 0.12 (s, 6H), 0.89 (s, 9H), 0.91 (s, 9H), 1.54—1.71 (m, 1H), 1.75—1.92 (m, 1H), 2.00 (s, 3H), 2.00—2.15 (m, 1H), 2.20—2.35 (m, 1H), 3.06—3.21 (m, 1H), 4.12 (dd, 1H, J = 5.9, 11.3 Hz), 4.21—4.30 (m, 1H), 4.38 (dd, 1H, J = 5.5, 11.3 Hz), 4.65 (dd, 1H, J = 6.5, 11.9 Hz); ^{13}C-NMR (50 MHz) δ –5.5, –5.1, –5.0, –4.8, 17.9, 18.3, 20.7, 25.6, 25.7, 38.0, 42.5, 44.7, 62.3, 65.8, 72.8, 170.8, 207.8; IR (film) 1747 cm^{-1}.

To a suspension of Ph_3PCH_3I (284 mg, 0.730 mmol) in THF (10 ml) was added BuLi (1.68 M in hexane, 1.10 ml, 0.65 mmol) at 0 °C in a dropwise manner. The mixture was stirred at 0 °C for 15 min. To this was introduced a solution of above acetoxymethylcyclohexanone derivative (70 mg, 0.16 mmol) in THF (5 ml) in a dropwise manner and the mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of water, filtered through a celite pad, dried over Na_2SO_4, and concentrated by a rotary evaporator to give an oil, which, on CC, gave **8** (53 mg, 76%) together with deacetylated product (**9**) (7 mg, 10%). Data for major (1*S*,3*S*,5*R*)-isomer: $[\alpha]^{22}_D$ –32 (c 0.20, CHCl$_3$); ^{1}H-NMR (200 MHz) δ 0.02 (s, 3H), 0.06 (s, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 1.18—1.41 (m, 1H), 1.55—1.68 (m, 1H), 1.80—1.97 (m, 2H), 2.04 (s, 3H), 2.71—2.85 (m, 1H), 4.05—4.42 (m, 4H), 4.69 (s, 1H), 4.93 (s, 1H); ^{13}C-NMR (50 MHz) δ –5.2, –4.8, 18.0, 20.9, 25.7, 25.8, 37.2, 38.4, 44.9, 66.1, 67.2, 71.9, 107.6, 149.5, 171.0; IR (film) 1745 cm^{-1}.

(1*RS*,3*S*,5*R*)-3,5-Di-*O*-*tert*-butyldimethylsilyl-1-hydroxymethyl-2-methylenecyclohexane-3,5-diol (9). To a solution of **8** (46 mg, 0.107 mmol) in THF (2 ml) was added DIBAL-H (1.01 M in hexane, 2.2 eq) at –78 °C. The mixture was stirred at –78 °C to –50 °C for 30 min. The reaction was quenched by the addition of water and thus-formed solid was removed by filtration through a celite pad. The combined organic solutions were dried with Na_2SO_4 and concentrated to give a colorless oil, which, on CC, afforded **9** (38 mg, 92%). Data for major isomer: ^{1}H-NMR (200 MHz) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.07 (s, 6H), 0.89 (s, 18H), 1.39—1.51 (m, 1H), 1.51—1.67 (m, 1H), 1.71—1.79 (m, 2H), 1.85—1.98 (m, 1H), 2.60—2.72 (m, 1H), 3.55—3.66 (m, 1H), 3.79—3.91 (m, 1H), 4.16—4.28 (m, 1H), 4.45—4.54 (m, 1H), 4.78 (s, 1H), 5.04 (s, 1H); ^{13}C-NMR (50 MHz) δ –5.1, –4.9, –4.8, 18.0, 18.2, 25.8, 38.0, 42.4, 44.7, 65.8, 67.7, 70.2, 107.6, 150.6; IR (film) 3419 cm^{-1}; exact mass, m/z 386.26725 (calcd for $C_{20}H_{42}O_3Si_2$ m/z 386.26723). Anal. Calcd for $C_{20}H_{42}O_3Si_2$: C, 62.13; H, 10.96. Found: C, 62.35; H, 10.71.

(4*S*,6*R*)-4,6-Bis(*O*-*tert*-butyldimethylsiloxy)-2-methyl-1-cyclohexenecarbaldehyde (A-ring Synthon **I**). To a solution of **9** (28 mg, 0.074 mmol) in CH_2Cl_2 (4 ml) was added PCC (96 mg) in one portion at 0 °C. The mixture was stirred at rt for 2.5 h. The reaction was quenched by the addition of water and extracted with AcOEt. The combined organic solution were dried over Na_2SO_4 and concentrated to give an oil, which, on CC, afforded an disiloxyaldehyde (26 mg, 91%). To a solution of the aldehyde (17 mg, 0.044 mmol) in CH_2Cl_2 (0.5 ml) was added DBU (0.91 ml, 2 eq) at 0 °C. The reaction was stirred at rt for 2 h, quenched by the addition of water and extracted with AcOEt. The combined extracts were dried over Na_2SO_4 and concentrated by a rotary evaporator to give an oil, which, on CC, gave **I** (16 mg, 94 %). $[\alpha]^{25}_D$ –85.6 (c 0.656, CHCl$_3$) [lit.[20c] $[\alpha]^{25}_D$ –91.1 (c 0.3, EtOH); lit.[20d] $[\alpha]^{29}_D$ –86.1 (c 0.32, EtOH); lit.[20d] $[\alpha]^{28}_D$ –85.6 (c 1.08, CHCl$_3$)]; ^{1}H-NMR (300 MHz) δ 0.05 (s, 3H, SiCH$_3$), 0.06 (s, 3H, SiCH$_3$), 0.13 (s, 3H, SiCH$_3$), 0.14 (s, 3H, SiCH$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.92 (s, 9H, SiC(CH$_3$)$_3$), 1.80 {3-line dd (5.2, 6.1 Hz), 2H, SiOCCH$_2$COSi}, 1.96—2.12 (bdd, 1H, J = 6.5, 17.7 Hz, =C-CHH-COSi), 2.17 (distorted s, 3H, =C-CH_3), 2.45—2.62 (bdd, 1H, J = 4.7, 17.7 Hz, =C-CHH-COSi), 4.08—4.17 (m, 1H, OHC-C-CH-OSi), 4.30—4.39 {3-line dd (4.4, 5.2 Hz), 1H, CH_3-C-CH-OSi}, 10.1 (s, 1H, CHO); ^{13}C-NMR (50 MHz) δ –4.8, –4.7, –4.2, 14.6, 17.9, 18.0, 25.7, 25.8, 32.0, 40.3, 64.2, 70.8, 131.6, 154.5, 192.0; IR (film) 1675 cm^{-1}.

4-*O*-(4-Methoxybenzyl)-4-hydroxybutanal (10). To a solution of 1,4-butanediol (7.32 ml, 1.2 eq) in DMF-THF (1:1) mixed solvent (100 ml) was added NaH (3.30 g, 1.2 eq) at 0 °C. After 20 min stirring, 4-methoxybenzyl chloride (10 ml, 68.8 mmol) was added dropwise to the solution at 0 °C. The mixture was stirred overnight at rt, quenched by the addition of water and extracted with AcOEt-hexane (1:1) mixed solvent. The combined organic solutions were dried over Na_2SO_4 and concentrated to give a colorless oil, which, on CC, afforded 1-*O*-(4-methoxybenzyl)butane-1,4-diol (13.0 g, 90 %) as a colorless oil.

A solution of 1-*O*-(4-methoxybenzyl)butane-1,4-diol (13.0 g, 61.5 mmol) in CH_2Cl_2 (50 ml) was mixed with Swern reagent prepared from $(COCl)_2$ (10.7 ml, 123 mmol) and DMSO (17.5 ml, 246 mmol) in CH_2Cl_2 (100 ml) at –78 °C. After 20 min stirring, Et_3N (51.4 ml, 369 mmol) was added to the mixture at –78 °C and stirring was continued for additional 30 min at 0 °C. The reaction was quenched by the addition of water and extracted with AcOEt-hexane (1:1) mixed solvent. The combined organic solutions were dried with Na_2SO_4 and concentrated to give a colorless oil, which, on CC, afforded **10** (11.54 g, 90%) as a colorless oil. ^{1}H-NMR (200 MHz) δ 1.52—1.72 (m, 4H), 2.45 (dt, 2H, J = 1.7, 7.2 Hz), 3.45 (t, 2H, J = 6.1 Hz), 3.80 (s, 3H), 4.42 (s, 2H), 6.88 (dt, 2H, J = 8.7 Hz for doublet), 7.25 (dt, 2H, J = 8.7 Hz for doublet), 9.75 (t, 1H, J = 1.7 Hz); ^{13}C-NMR (50 MHz) δ 22.3, 40.6, 55.3, 70.1, 72.6. 129.4, 130.4, 145.6, 160.2, 201.8; IR (film) 1710 cm^{-1}.

1-*O*-(4-Methoxybenzyl)-5,5-dimethylhept-6-ene-1,4-diol (11). To a suspension of CuCl (3 mg) in Et_2O (3 ml) were added Et_3N (0.16 ml, 1.2 mmol) and prenyl chloride (0.12 ml, 1.1 mmol) at 0 °C. To this mixture was added trichlorosilane (0.11 ml, 1.1 mmol) at 0 °C. The resulting mixture was stirred at rt for 16 h followed by the addition of DMF (1 ml). Then the mixture was cooled to 0 °C and a solution of **10** (100 mg, 0.48 mmol) in DMF (1 ml) was added to it. The mixture was stirred for further 21 h at 0 °C, quenched by the addition of water, and extracted with AcOEt-hexane (1:1) mixed solvent. The combined organic solutions were dried with Na_2SO_4 and concentrated to give a colorless oil, which, on CC, afforded **11** (95 mg, 71%) as a colorless oil. ^{1}H-NMR (200 MHz) δ 1.01 (s, 6H), 1.15—1.40 (m, 1H), 2.19 (b, 1H), 3.25 (dd, 1H, J = 1.57, 10.7 Hz), 3.40—3.52 (m, 2H), 3.80 (s, 3H), 4.45 (s, 2H), 5.02 (dd, 1H, J = 1.51, 11.0 Hz), 5.05 (dd, 1H, J = 1.15, 17.3 Hz), 5.84 (dd, 1H, J = 11.0, 17.3 Hz), 6.88 (dt, 2H, J = 8.7 Hz for doublet), 7.25 (dt, 2H, J = 8.7 Hz for doublet); ^{13}C-NMR (50 MHz) δ 22.4, 22.9, 27.2, 28.6, 41.5, 55.2, 70.0, 72.5, 78.0, 112.9, 113.7, 129.3, 130.4, 145.5, 159.1; IR (film) 3400 cm^{-1}; exact mass, m/z 278.18821 (calcd for $C_{17}H_{26}O_3$ m/z 278.18818). Anal. Calcd for $C_{11}H_{26}O_3$: C, 73.33; H, 9.42. Found: C, 73.61; H, 9.29.

4-*O*-(*tert*-Butyldimethylsilyl)-5,5-dimethylhept-6-ene-1,4-diol (12) To a solution of **11** (2.40 g, 8.62 mmol) and Et_3N (2.40 ml, 17.2 mmol) in THF (30 ml) was added TBSOTf (2.70 ml, 11.7 mmol) at 0 °C. The mixture was stirred at rt for 1 h, quenched by the addition of water, extracted with AcOEt, dried over Na_2SO_4, and concentrated to give a crude product, which, on CC, afforded the silylated **11** as a colorless oil (3.31 g, 98%). Thus protected diol (7.94 g, 20.2 mmol) was dissolved in CH_2Cl_2 (80 ml) and to this was added water (8 ml) and DDQ (6.89 g, 30.3 mmol) in one portion. The mixture was stirred at rt for 6 h, diluted with water, and extracted with AcOEt. The combined extracts were dried with Na_2SO_4 and concentrated to afford an oil, which, on CC, gave **12** (3.39 g, 63%) as a colorless oil. ^{1}H-NMR (200 MHz) δ 0.04 (s, 6H), 0.90 (s, 9H), 0.96 (s, 6H), 1.20—1.80 (m, 4H), 3.34 (dd, 1H, *J* = 3.2, 6.5 Hz), 3.52—3.62 (m, 2H), 4.95 (dd, 1H, *J* = 1.6, 10.7 Hz), 4.97 (dd, 1H, *J* = 1.6, 18.0 Hz), 5.88 (dd, 1H, *J* = 10.7, 18.0 Hz); ^{13}C-NMR (50 MHz) δ –3.9, –3.5, 18.3, 22.9, 24.6, 26.1, 29.9, 30.5, 42.4, 63.3, 79.5, 111.3, 146.2; IR (film) 3400 cm^{-1}.

4-*tert*-Butyldimethylsiloxy-5,5-dimethyl-6-heptenecarbaldehyde oxime (13). This compound was prepared by the similar procedure as that for **5a**. **13** (3.09 g) was obtained from **12** (3.66 g) in 81% yield: ^{1}H-NMR (200 MHz) δ 0.06 (s, 6H), 0.91 (s, 9H), 0.98 (s, 6H), 1.45—1.55 (m, 1H), 1.62—1.75 (m, 1H), 2.10—2.20 (m, 1H), 2.30—2.40 (m, 1H), 3.37 (dd, 1H, *J* = 3.4, 8.3 Hz), 4.95 (dd, 1H, *J* = 1.6, 10.7 Hz), 4.97 (dd, 1H, *J* = 1.6, 18.0 Hz), 5.88 (dd, 1H, *J* = 10.7, 18.0 Hz), 6.65 (bt, 1H, *J* = 4.9 Hz); ^{13}C-NMR (50 MHz) δ –3.9, –3.5, 18.3, 22.8, 24.6, 26.1, 27.1, 30.4, 42.4, 78.8, 111.7, 145.9, 152.2; IR (film) 3400 cm^{-1}.

4-*tert*-Butyldimethylsiloxy-2-(hydroxymethyl)-3,3-dimethylcyclohexan-1-one (14). To a stirred solution of **13** (3.09 g, 10.8 mmol) in CH_2Cl_2 (20 ml) was added an aqueous NaOCl solution (20 ml) and the mixture was stirred overnight at rt. The reaction was diluted with water and extracted with AcOEt. The combined extracts were dried with Na_2SO_4 and concentrated to afford a crude isoxazoline as an epimeric mixture. To a solution of the isoxazoline in MeOH-water (5:1, 30 ml), which was placed in a hydrogenation vessel, were added boric acid (1.34 g, 2 eq) and a spatula tip of 10% Pd-C. The reaction vessel was flushed with hydrogen gas and the mixture was stirred vigorously overnight under a positive pressure of hydrogen. The mixture was filtered through a celite pad and the filtrate were partitioned between water and AcOEt. The aqueous layer was extracted with several portions of AcOEt, and the combined extracts were dried over Na_2SO_4 and concentrated to give an oil, which, on CC, gave **14** (2.56 g, 88%) as a diastereomeric mixture at C(2). One of the isomers was isolated by means of CC. Data for major diastereomer: ^{1}H-NMR (200 MHz) δ 0.10 (s, 6H), 0.77 (s, 3H), 0.93 (s, 9H), 1.07 (s, 3H), 1.85—1.90 (m, 1H), 1.98—2.07 (m, 1H), 2.17—2.22 (m, 1H), 2.50 (b, 1H), 2.70 (dt, 1H, *J* = 7.3, 14.2 Hz), 2.92 (dd, 1H, *J* = 2.9, 8.8 Hz), 3.44—3.48 (m, 1H), 3.60 (dd, 1H, *J* = 2.9, 11.2 Hz), 3.95 (dd, 1H, *J* = 8.8, 11.2 Hz); ^{13}C-NMR (50 MHz) δ –4.9, –4.4, 18.1, 22.6, 25.6, 25.9, 29.6, 36.3, 43.3, 55.7, 58.6, 75.8, 215.8; IR (film) 3534, 1726 cm^{-1}; exact mass, m/z 286.19652 (calcd for $C_{15}H_{30}O_3Si$ m/z 286.19641). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.56. Found: C, 62.66, H, 10.77.

4-*tert*-Butyldimethylsiloxy-1,3,3-trimethyl-1-cyclohexene-2-carbaldehyde (16). To a solution of **14** (1.94 g, 6.79 mmol) in THF (10 ml) was introduced MeMgBr in Et_2O (3.0 M solution, 6.8 ml, 3 eq) at 0 °C. The mixture was stirred at rt for 6 h. The reaction was quenched by the addition of water and thus-produced precipitates were removed by filtration through a celite pad, which was rinsed with several portions of ethyl acetate. The combined organic solutions were dried with Na_2SO_4 and concentrated to give an oil, which, on CC, afforded a diol (1.28 g, 62%) as a colorless oil. A solution of the diol (1.28 g, 4.23 mmol) in CH_2Cl_2 (10 ml) was mixed with Swern reagent prepared from $(COCl)_2$ (0.74 ml, 8.46 mmol) and DMSO (1.20 ml, 16.9 mmol) in CH_2Cl_2 (20 ml) at –78 °C. After 15 min stirring, Et_3N (3.54 ml, 25.4 mmol) was added at –78 °C and stirring was continued for additional 20 min at 0 °C. The reaction was quenched by the addition of water and extracted with AcOEt-hexane (1:1) mixed solvent. The combined organic solutions were dried with Na_2SO_4 and concentrated to give a colorless oil, which, on CC, afforded the aldehyde (**15**: 855 mg, 67%) as a colorless oil.

To a solution of **15** (855 mg, 2.80 mmol) in CH_2Cl_2 (10 ml) were added Et_3N (0.87 ml, 2.2 eq) and MsCl (0.23 ml, 1.1 eq) at 0 °C. After 2 h stirring at rt, additional Et_3N (1.70 ml, 4.4 eq) and MsCl (0.69 ml, 3.3 eq) were introduced to the mixture and stirring was continued overnight at rt. The reaction was quenched by the addition of water and extracted with AcOEt-hexane (1:1) mixed solvent. The combined organic solutions were dried with Na_2SO_4 and concentrated to give a colorless oil, which, on CC, afforded **16** (543 mg, 68%) as a colorless oil. ^{1}H-NMR (300 MHz) δ 0.055 (s, 3H, $SiCH_3$), 0.062 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.16 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.60—1.80 (m. 2H, CH_2-COSi), 2.08 (s, 3H, =CCH_3), 2.05—2.40 (m, 2H, =C-CH_2), 3.45 (dd, 1H, J = 3.3, 8.0 Hz, SiOCH), 10.1 (s, 1H, CHO); ^{13}C-NMR (75 MHz) δ –4.9, –4.1, 18.1, 19.1, 21.7, 25.8, 25.9, 26.2, 32.6, 38.4, 76.2, 139.1, 154.5, 192.5; IR (film) 1675, 1255 cm^{-1}; exact mass, m/z 282.20152 (calcd for $C_{16}H_{30}O_2Si$ m/z 282.20149). Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.04; H, 10.71. Found: C, 68.27; H, 10.55.

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