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New entry to the synthesis of clerodane diterpenes. The first enantioselective syntheses of 7-oxo-kolavenic acid and methyl solidagonate

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Abstract—Using (1*S*,5*S*)-(−)-verbenone (**8b**), readily obtainable from (+)-nopinone (**3**), as the chiral source, we have established the general method for preparation of three kinds of key intermediates, conjugate enones **9** and **10** for the syntheses of *neo-trans*-clerodanes and **11** for those of *neo-cis*-clerodanes. Starting with the compound **10**, the first enantioselective syntheses of (−)-(5*R*,8*S*,9*S*,10*R*)-7-oxo-cleroda-3,13*E*-dien-15-oic acid (7-oxo-kolavenic acid) (**1**) and solidagonic acid (**2**) as its methyl ester (**48**) were achieved.

1. Background

Clerodanes constitute a large class of diterpenoid.[1] The numbers of isolations and structural elucidation of clerodane diterpenes reportedly amount to more than eight hundred. Most of clerodanes display unique biological activities in which the insect antifeedant and antitumour activities shown by clerodin[2] and terpentecin,[3] respectively, are well-known. Since the substituent of the C(4) position of major clerodanes presents as an olefin-methyl or *exo*-methylene group from the biosynthetic reasons,[1,4] the most important characteristic in stereochemistry of clerodanes is the contiguously arranged four chiral centers; C(5)–C(10)–C(9)–C(8) [for example, see 7-oxo-kolavenic acid (**1**) as a representative of *neo-trans*-clerodanes], so that synthetic efforts have been practically focused on realization of this unique carbon–carbon arrangement in a stereocontrolled fashion.[1b]

We have been studying the utility of (+)-nopinone (**3**), readily obtainable in large quantities by ozonolysis of (−)-β-pinene, as the chiral source in enantioselective synthesis of natural products. Since we found that cyclobutane-ring opening of **3** and alkyl substituted nopinones **4** with the combined reagent, $BF_3{\cdot}OEt_2/Zn(OAc)_2/Ac_2O$,[5] proceeded with little loss of optical integrity to give in good to high yields of enol acetates **5** and **6**, respectively, enantioselective syntheses starting with these enol acetates as the chiral building block have been carried out in some natural products, i.e. cryptone and *p*-menthan-type sesquiterpenes from **5**,[6] and elemane[7] and nardosinane sesquiterpenes[8] from **6**. In preparation of the above substituted nopinones, stereoselective conjugate additions of (+)-apoverbenone (**7**) and (+)-verbenone (**8a**), both readily available from **3**,[9] with alkyl nucleophiles were used as the key reaction. Furthermore, we have established a convenient conversion of **7** into (−)-verbenone (**8b**),[10] indicating that (+)-nopinone (**3**), consequently its precursor (−)-β-pinene as well, serves as the common chiral source for the asymmetric synthesis in terms of absolute configuration of the target natural products. In fact, starting with **8b**, enantioselective syntheses of lobane diterpenes have been accomplished.[11] As part of our natural product synthesis by use of **8b** as the chiral template, we now chose clerodane diterpenoids as the target natural product. We wish to report preparation of general key intermediates **9** and **10** for the synthesis of *neo-trans* clerodanes as well as the first enantioselective syntheses of (−)-(5*R*,8*S*,9*S*,10*R*)-7-oxo-cleroda-3,13*E*-dien-15-oic acid (7-oxo-kolavenic acid) (**1**)[12,13] and solidagonic acid (**2**)[13,14] as the application. In addition, preparation of the promising synthetic intermediate **11** necessary for the syntheses of *ent-neo-cis*-clerodanes will be discussed.

Keywords: natural products; asymmetric synthesis; cleavage reactions; ene reactions.
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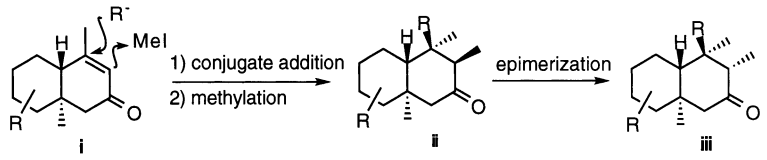
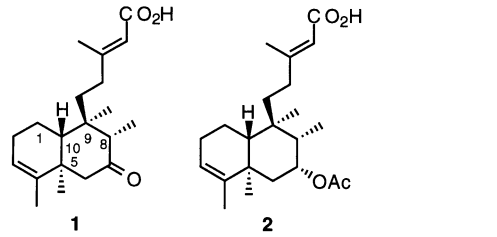
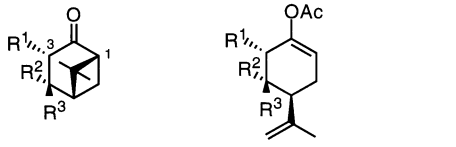
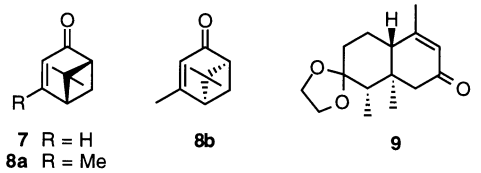
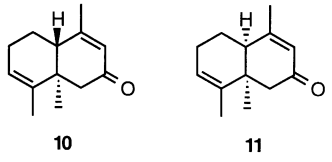


Scheme 1.







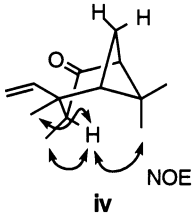


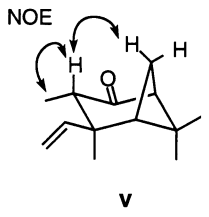
2. Results and discussion

Most of clerodanes could be regarded as 4,5,8,9-tetramethyldecalins or octalins possessing a functionalized six-carbon substituent at the C(9) position.[15] Upon installation of the substituent at this position, reductive alkylation of $\Delta^{9,10}$-8-octalones (usually, substrates derived from the Wieland–Miescher ketone and its analogue) with Li in liquid NH_3 followed by addition of some carbon electrophiles has so far been employed as the general synthetic methodology.[1b] In the present synthesis, we designed one-step stereo- and regioselective installation of not only the C(9)-alkyl group, but also the C(8)-methyl one by use of stereocontrolled conjugate addition of carbon nucleophiles (R^-) to *trans*-octalone **i** followed by trapping of the resulting enolate anion with MeI in a kinetically controlled fashion to give **ii** (Scheme 1). Subsequent epimerization of the newly introduced methyl group in **ii** with a base may lead to the thermodynamically stable isomer **iii** which possesses all alkyl substituents with the same stereochemistry as those of *neo-trans*-clerodanes. In practice, while conjugate enones **9** and **10** are employed as the *trans*-octalone **i**, the carbon nucleophile synthetically equivalent to the C(9)-substituent in the target clerodane may be chosen as the nucleophile (R^-) in the conjugate addition reaction. First, to make sure that our methodology is consistent with clerodane synthesis, conjugate addition of a vinyl group to **9** followed by methylation and epimerization was studied.

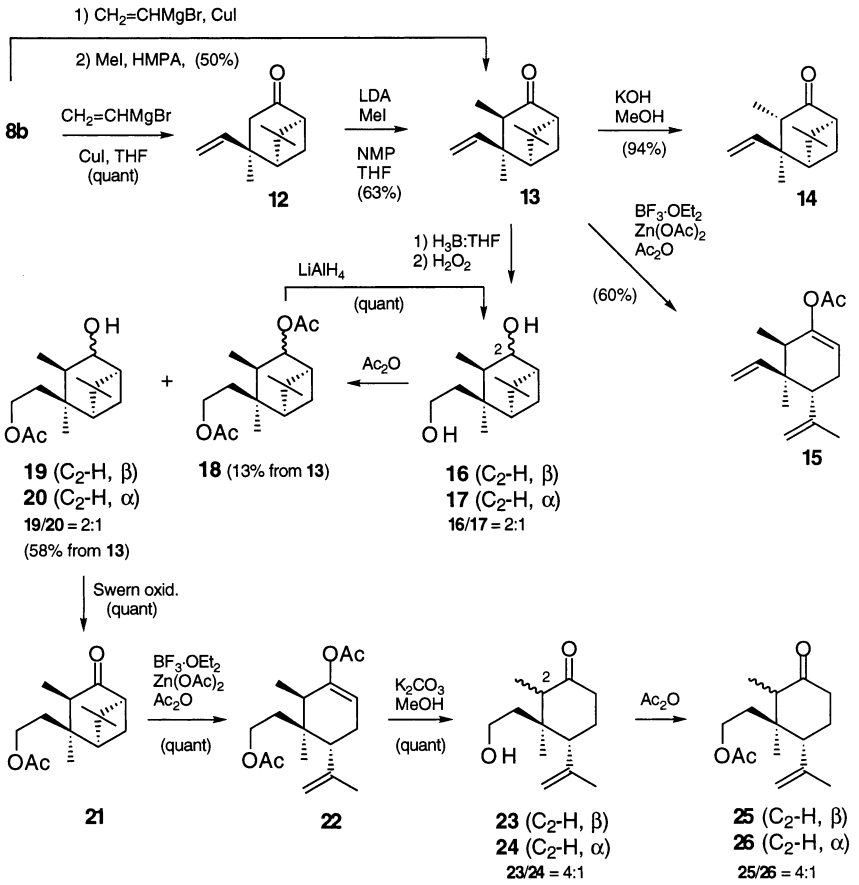
2.1. Preparation of *trans*-octalone 9 and a model study directed toward *neo-trans*-clerodane synthesis

(−)-Verbenone (**8b**) was prepared from (+)-nopinone (**3**) via **7** according to our synthetic method established earlier.[10] Conjugate addition reaction of **8b** with the vinyl Grignard reagent in the presence of copper(I) iodide in THF proceeded smoothly in a stereoselective fashion to give **12** in a quantitative yield (Scheme 2).[7a] Stereochemistry of the vinyl group was assigned as shown by the well-known reactivity characteristic of pinane-type compounds, that is, the nucleophile approaches from the less hindered side away from the *gem*-dimethyl bridge.[7a] In the above conjugate addition reaction, trapping the resulting enolate with MeI provided 50% yield of *trans*-3-methylnopinone **13**[16] along with unreacted **12** (23%). Methylation of **12** was examined next. After a few experimentation, treatment of the lithium salt of **12** with MeI in the presence of 10 equiv. of 1-methyl-2-pyrrolidinone (NMP)[17] at room temperature was employed as optimum, thus giving **13** in 63% yield (74% yield from the consumed **12**) along with unreacted **12** (15%). Epimerization of **13** with 5% KOH in methanol gave thermodymamically stable *cis*-3-methylnopinone **14**[16] in high yield. NOE correlations of **13** and **14** supported their stereostructures as shown in **iv** and **v**, respectively.[18] Cyclobutane opening of **13** with our combined reagent, $BF_3{\cdot}OEt_2/Zn(OAc)_2/Ac_2O$,[5] proceeded in a regioselective fashion to give enol acetate **15** in 60% yield as the sole product. However, attempted ring opening of **14** with the above combined reagent proved to be fruitless, mostly recovering unreacted **14** even on heating at 60°C.[19]





Our synthesis was then followed, prior to the cyclobutane opening, by chemical transformation of the vinyl group in **13**.[20] Hydroboration of **13** with H_3B/THF followed by oxidation with H_2O_2 under the alkaline conditions gave a mixture of diastereomeric diols, **16** and **17**, in ca 2:1 ratio. Configuration of the *sec*-hydroxy groups was tentatively

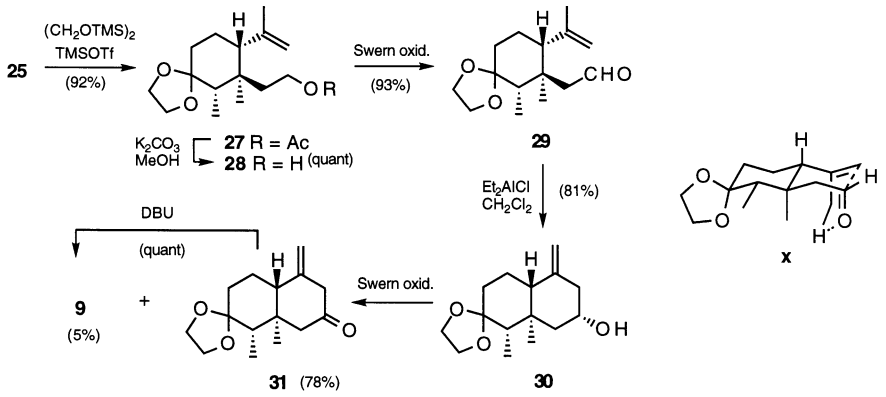


Scheme 2.

assigned as *S* for the major and *R* for the minor on the basis of characteristic reactivity of pinanes.[7a] Regioselective acetylation of the mixture of diols, **16** and **17**, provided a mixture of diacetates **18** and hydroxy acetates, **19** and **20**, in 23 and 58% overall yield from **13**, respectively. Lithium aluminum hydride reduction of **18** made possible clean reconversion to the starting diols, **16** and **17**. Swern oxidation of the mixture of hydroxy acetates, **19** and **20**, gave *trans*-3-methyl nopinone **21** in nearly quantitative yield. Although BF_3-promoted cyclobutane opening of **21** was sluggish at room temperature, this reaction underwent essentially to completion, after stirring for two days, to produce enol acetate **22**.[21] Hydrolysis of **22** with K_2CO_3 in methanol gave a mixture (a 1:4 ratio) of ketone **24** and thermodynamically stable ketone **23** which was produced by concomitant epimerization of the initial product **24**. Treatment of **24** with KOH in methanol provided an equilibrium mixture of **23** and **24** in a ratio of 4:1 (from ^{1}H NMR), indicating that the *sec*-methyl group in **23** possesses thermodynamically stable equatorial configuration.[22] Acetylation of the mixture, **23** and **24**, gave a separable mixture (a 4:1 ratio) of acetates, **25** and **26**. The former **25** was submitted to a further series of reactions.

Construction of *trans*-octalone skeleton by the intramolecular ene-reaction was performed next. Acetalization of **25** was successfully carried out upon treating with 2,2′-(ethylenedioxy)bis(trimethylsilane) in the presence of TMSOTf[23] to give acetal **27** in high yield[24] (Scheme 3). Hydrolysis followed by Swern oxidation of the resulting alcohol **28** provided, in 93% overall yield from **25**, aldehyde **29**, the precursor directed toward *trans*-decalin synthesis. Exposure of **29** upon Et_2AlCl in CH_2Cl_2 at 0°C underwent the ene reaction smoothly to give bicyclic alcohol **30** as the sole product. It can be assumed that this ene reaction proceeds predominantly via six-membered transition state **x** with chair conformation to give the *trans*-decalin with an axial hydroxyl group.[25] The ^{1}H NMR spectrum of **30** shows absorption due to the proton on the carbon bearing the newly formed hydroxy group at δ 4.17 as a broad singlet with the half band width (12 Hz), indicating the hydrogen atom to be equatorial. Swern oxidation of **30** led to deconjugate enone **31** and conjugate enone **9** in **78** and 5% yields, respectively.[26] Upon treatment with DBU, the former **31** readily isomerized to the latter **9**. After all, the requisite *trans*-conjugate enone **9** was obtainable in 13 steps and ca 21% overall yield from (−)-verbenone **8b**.

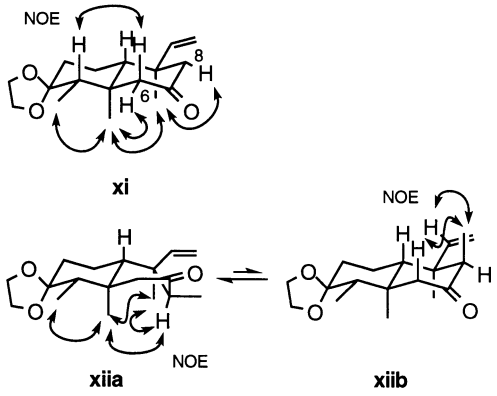
With the *trans*-enones **9** available, attention was focused on stereoselective installation of two alkyl substituents at the C(8) and (9) positions by use of the conjugate addition reaction with a carbon nucleophile followed by methylation. First, we examined stereoselectivity in the conjugate addition of **9** with the vinyl Grignard reagent. Drieding model experiments indicate that the nucleophile may approach **9** from less hindered face away from the angular methyl group. This conjugate addition reaction was performed in the presence of CuI in THF to give the adduct



Scheme 3.

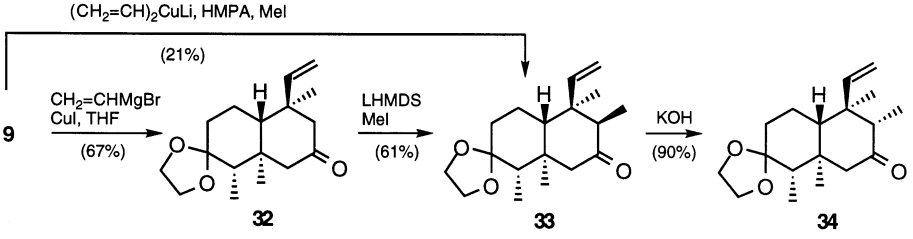
32 in a stereoselective fashion (Scheme 4). Stereostructure of **32** was assigned on the basis of detailed NMR analyses in which not only does NOE correlations **xi** indicate that configuration of the vinyl and methyl functions at the C(9) position are equatorial and axial, respectively, but also the W-letter long range coupling (2.0 Hz) between the C(6)–H (equatorial) and C(8)–H (equatorial) suggests conformation of the B ring to be a chair form. Then, methylation of the enolate anion generated in the above conjugate addition reaction with MeI was examined in the presence or absence of HMPA. However, no methylated compound was obtained except procurement of the initial adduct **32** (40~50%). No effect was observed in addition of $BF_3{\cdot}OEt_2$[27] in these reactions. One step installation of two alkyl substituents was effected by treating **9** with lithium divinyl cuprate in the presence of HMPA followed by trapping of the resulting enolate anion with excess MeI, thus giving **33** in a stereocontrolled fashion along with **32** (30%). However, the isolated yield of **33** was disappointingly low (21%). Little effect was exerted by the addition of $BF_3{\cdot}OEt_2$ in the above reaction.[27] Fortunately, methylation of the lithium salt of the adduct **32**, prepared with $(TMS)_2NLi$ in THF, resulted in formation of **33** in a regio- and stereoselective fashion in 61% isolated yield along with unreacted **32** (13%).

Stereostructure of **33** was determined by the ^1H NMR analysis, especially by NOE correlations. It is worth mentioning that the compound **33** is in equilibrium between the conformer **xiia** possessing a boat form in the B ring and the conformer **xiib** possessing a chair form. The molecular mechanics calculation (CAChe system/MM2 force field) of **33** gave the information that **xiia** is more stable by 0.56 kcal mol^{-1} than **xiib**. Finally, epimerization of **33** with 5% KOH in methanol provided in high yield the thermodynamically stable compound **34** which possesses the same four contiguously arranged asymmetric centers with those of natural *neo-trans*-clerodanes.

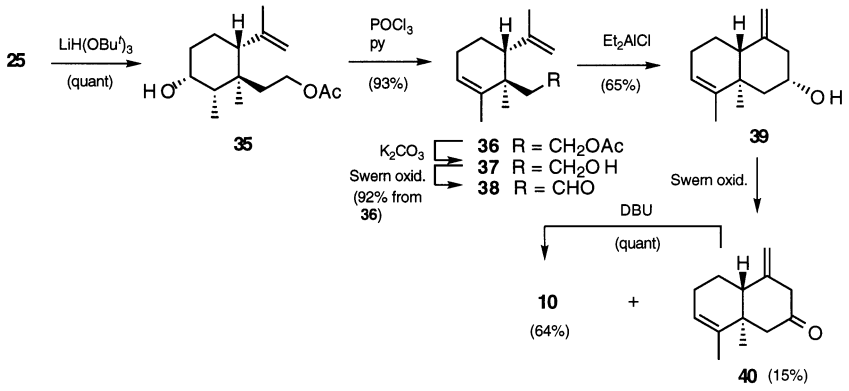


2.2. Preparation of the synthetic intermediate 10 and syntheses of some *neo-trans*-clerodanes

In view of the fact that most clerodanes possess an olefin methyl group at the C(4) position, preparation of the second key intermediate, *trans*-enone **10**, was examined next. In Scheme 5 is shown the regio- and stereoselective reduction of the ketone **25** with lithium tri-*tert*-butoxyaluminum hydride in which the hydride may approach exclusively from less hindered β face of the molecule **25** to give alcohol **35**. Stereochemistry of the hydroxy group in **35** was assigned to be axial from the ^1H NMR study in which a broad siglet (δ 3.84) due to the proton on the carbon flanking the hydroxy group shows the small half band width (12 Hz), indicating the hydrogen atom to be equatorial. Treatment of **35** with phosphorus oxychloride in



Scheme 4.

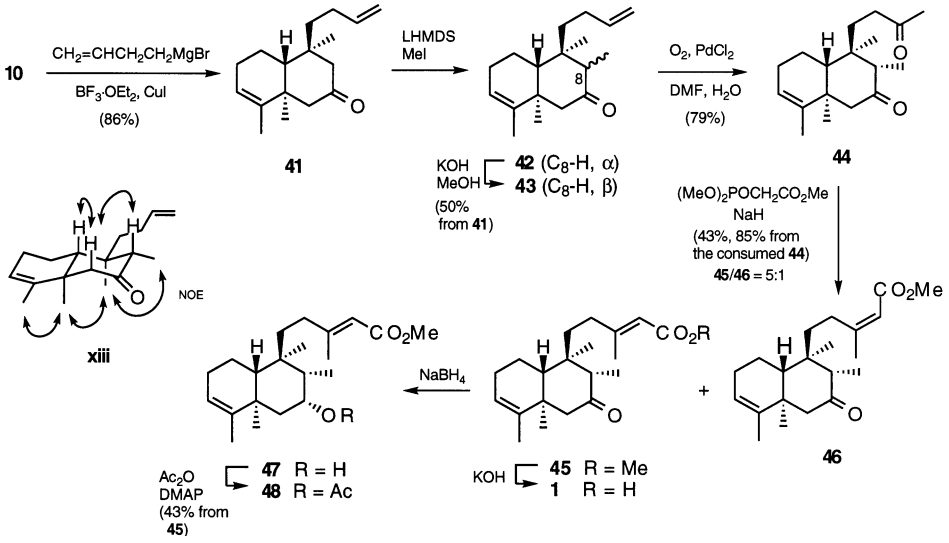


Scheme 5.

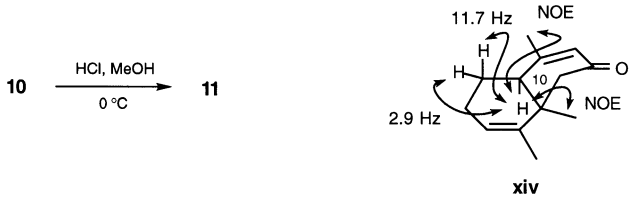
pyridine followed by deprotection of the resulting diene **36** provided alcohol **37** in a high overall yield. Chemical transformation of **37** into the target **10** was carried out straightforwardly according to the method described for preparation of **9** from **28**; Et_2AlCl-induced ene reaction of aldehyde **38**, prepared from **37** by Swern oxidation, proceeded smoothly to give bicyclic alcohol **39** possessing the axially oriented hydroxy group. Swern oxidation of **39** gave deconjugate enone **40** and conjugate enone **10** in **15** and 64% yields, respectively. The former **40** was readily converted into the latter **10** by treatment with DBU. After all, the key intermediate **10** was procured from **25** in **7** steps and more than 50% overall yield.

The key intermediate **10** may be advantageous to the synthesis of oxygenated *neo-trans*-clerodanes, especially those possessing a ketone function at the C(7) position. Then, we first envisioned the enantioselective synthesis of (5*R*,8*S*, 9*S*,10*R*)-7-oxo-clerodan-3,13*E*-dien-15-oic acid (7-oxo-kolavenic acid) (**1**), isolated as a minor component from an extract of the aerial part of *Platychaete aucheri* by Zdero et al.[12] Our synthesis began with installation of a homoallyl group at the C(9) position of **10** (Scheme 6). Attempted conjugate addition of **10** with the homoallyl Grignard reagent in the presence of CuI in THF resulted in formation of the adduct **41** in a disappointing low yield (8%) along with unreacted **10** (63%). After a few experimentation, $CH_2{=}CHCH_2CH_2Cu{\cdot}BF_3$, generated from this Grignard reagent, CuI and $BF_3{\cdot}OEt_2$ in THF, underwent smoothly the conjugate addition reaction to lead to **41** in 86% yield. Stereostructure of **41** was characterized by the ^1H NMR analysis, especially by the NOE correlations. Methylation of **41** with MeI under the kinetically controlled conditions using LHMDS gave **42**[28] which was then epimerized by 5% KOH in methanol to the thermodynamically stable octalone **43** in ca 50% overall yield from **41**. NOE correlations of **43** supported its stereostructure as shown in **xiii**.

Palladium-catalyzed oxidation of the terminal olefin in **43** provided diketone **44** in 79% yield. Construction of the 3-methyl-2-pentenoate side chain was accomplished by treating **44** with the sodium salt of trimethyl phosphonoacetate in THF to give a mixture (a 5:1 ratio) of the (*E*)-unsaturated ester **45** and the (*Z*)-isomer **46**. Since the ring carbonyl group in **44** is sterically highly hindered, as can be presumed from the Dreiding models, the above Horner–Wadsworth–Emmons condensation reaction occurred regioselectively at the ketone in the side chain to produce both **45** and **46**, not only in a large excess of the phosphonate reagent, but also on heating at 60°C. Stereochemical assignment of the esters was easily performed by



Scheme 6.



xiv

Scheme 7.

comparison of their ^{1}H NMR spectra; the chemical shift [δ 2.29 (s, 3H)] of the olefin methyl in the side chain in **45** shows deshielding (0.39 ppm) by the proximate ester group, compared with that [δ 1.90 (s, 3H)] of **46**. Finally, alkaline hydrolysis of **45** provided the target natural product **1** as an oil, $[\alpha]_D^{19}=-95.2$ ($CHCl_3$). The ^{1}H NMR (400 MHz) spectral data of our synthetic **1** and **45** were identical with those of natural **1** and its methyl ester,[12] respectively. As there are no records with respect to the specific rotation of the natural **1** and its methyl ester in the literature,[12] we could present here the synthesis of (−)-(5*R*,8*S*,9*S*,10*R*)-7-oxo-clerodan-3,13*E*-dien-15-oic acid as the natural product **1**.

Solidagonic acid (**2**) was isolated as a bitter principle from the root of *Solidago altissima* by Kotake et al.[14] We accomplished the synthesis of **2** as its methyl ester **48**. Reduction of **45** with $NaBH_4$ proceeded in a stereoselective fashion, as anticipated from the Dreiding models, to give alcohol **47** as the sole product. Configuration of the hydroxy group was assigned to be axial from the ^{1}H NMR study in which a broad siglet [δ 4.04, C(7)–H] possesses the half band width (9.0 Hz). The hydroxy group in **47** considerably resisted acetylation, probably because of steric hindrance. After all, the requisite methyl solidagonate **48**, $[\alpha]_D=-83.4$ (EtOH); lit., $[\alpha]_D=-98.8$ (EtOH),[14] was obtained in 54% yield (82% yield from the consumed **47**) upon treatment with Ac_2O in the presence of 4-dimethylaminopyridine. The ^{1}H NMR (400 MHz) spectral data of our synthetic **48** were identical with those of the methyl ester of natural **2**.

2.3. Preparation of *cis*-enone 11 as the key intermediate for the synthesis of *neo-cis*-clerodanes

We have detected that *trans*-enone **10** is thermodynamically unstable, and isomerized to the stable *cis*-enone **11**. In practice, **10** was mostly recovered unchanged on treatment with bases (DBU in toluene, heating; KOBu^t in THF, rt). However, isomerization occurred easily and quantitatively upon treatment with HCl in methanol at 0°C to give *cis*-enone **11** (Scheme 7).

The molecular mechanics calculations (CAChe system/MM2 force field) indicated the *cis*-enone **11** is more stable by 2.21 kcal mol^{-1} than the *trans*-enone **10**. In the figure **xiv** are shown the principal NOE correlations in which the presence of *cis*-fused ring system is revealed. In addition, on the basis of a doublet of doublets (δ 1.62, $J_{a,a}=11.7$ and $J_{a,e}=2.9$ Hz) due to the proton at the C(10) position in the ^{1}H NMR (C_6D_6), conformation of **11** was assigned as **xiv** in which the orientation of the C(10)-hydrogen atom in the A ring is axial. As one-fourths in number of clerodanes isolated so far are known as *cis* congener regarding the decalin-ring junction,[1a] the compound **11** could serve as the key intermediate for the synthesis of *cis*-clerodanes by use of our conjugate addition of a carbon nucleophile–methylation sequence.

3. Conclusion

Synthetic study of clerodane diterpenoids in optically active forms is of recent origin. Accordingly, asymmetric total syntheses have been small in number. In the present study, we prepared versatile bicyclic conjugate enones **9** and **10**, starting with (+)-nopinone (**3**) as the chiral source. By use of stereocontrolled conjugate addition reactions of the vinyl and homoallyl Grignard reagents to **9** and **10**, respectively, followed by methylation and epimerization, two kinds of intermediates **34** and **43**, both utilizable for the synthesis of *neo-trans*-clerodanes, were prepared. While the acetal function at the C(3) position of **34** could serve as a clue for construction of oxygenated A ring, the octalone **43** could act as the promising intermediate for the synthesis of clerodanes possessing an olefin methyl group at the C(4)-position. In common with both intermediates, **34** and **43**, the ketone function in the B-ring could be utilizable for the construction of highly oxygenated B ring. Clerodanes are generally regarded as variations of the six-carbon side chain at the C(9) position, so that a variety of carbon nucleophiles synthetically equivalent to the side chain could be employed in the conjugate addition reactions using **9** and **10**. In the present study, the synthesis of (−)-(5*R*,8*S*,9*S*,10*R*)-7-oxo-clerodan-3,13*E*-dien-15-oic acid (7-oxo-kolavenic acid) (**1**) was accomplished via **43** in **24** steps and ca 7% overall yield from (−)-verbenone (**8b**). In addition, solidagonic acid (**2**) was obtained as its methyl ester **48** from methy 7-oxo-kolavenate (**45**). Finally, we found that the *trans*-enone **10** is thermodynamically unstable, being easily convertible upon exposure to acids into the stable *cis*-enone **11**, which could be served as the promising key intermediate for the synthesis of *neo-cis*-clerodanes.

As we have established chemical transformation of (+)-nopinone (**3**) into (+)-verbenone (**8a**),[9] the present syntheses of (−)-**1** and (−)-**48** are formal syntheses of their enantiomers, (+)-**1** and (+)-**48**.

4. Experimental

4.1. General

In this study, (+)-nopinone (**3**), 98% ee, was used as the starting material. (−)-Verbenone (**8b**) was prepared according to our synthetic procedure reported earlier.[10] Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz. [α] Values are given in units of 10^{-1} deg cm^2 g^{-1}. All reactions were carried out under dry N_2 or Ar atmosphere with use of standard procedures for the exclusion of moisture. Extracts obtained on aqueous workup of the reaction mixtures were washed successively with water and brine, and dried over Na_2SO_4, unless otherwise stated. Medium-pressure chromatography (MPLC) utilized a 22∅×300 mm silica gel (10 μm) column. Column and

flash column chromatography were performed on 70–230 and 230–400 mesh silica gel (Merck), respectively. Solvents for elution are shown in parentheses. Ether refers to diethyl ether.

4.1.1. (1*S*,4*R*,5*R*)-4,6,6-Trimethyl-4-vinylbicyclo[3.1.1]-heptan-2-one (12). To a stirred mixture of copper(I) iodide (950 mg, 5.0 mmol) in THF (15 ml) was added at −78°C a solution of 1.01 M vinylmagnesium bromide in THF (24 ml, 24 mmol), followed by a solution of **8b** (1.50 g, 10 mmol) in THF (10 ml). After being stirred for 3 h, the reaction mixture was quenched with aqueous NH_4Cl, and extracted with ether. Concentration of the extract followed by purification of the oily residue by chromatography on silica gel (hexane–AcOEt, 7:1) gave **12** (1.78 g, quant) whose IR and ^1H NMR spectra were identical of those of an authentic sample.[7a]

4.1.2. (1*S*,3*R*,4*R*,5*S*)-3,4,6,6-Tetramethyl-4-vinylbicyclo-[3.1.1]heptan-2-one (13). (1) To a stirred solution of diisopropylamine (0.32 ml, 2.4 mmol) in THF (2.0 ml) was added dropwise at 0°C a solution of 1.66 M BuLi in hexane (1.4 ml, 2.2 mmol). After being stirred for 20 min, a solution of **12** (178 mg, 1.0 mmol) in THF (2.0 ml) was added dropwise, and stirring was continued for an additional 1 h. A solution of 1-methyl-2-pyrrolidinone (0.96 ml, 10 mmol) was added to the reaction mixture, and after being stirred for 10 min, MeI (0.62 ml, 10 mmol) was added. Stirring was continued for 40 min at 0°C, and then at rt for an additional 40 min. The reaction mixture was quenched with aqueous NH_4Cl, and extracted with ether. Concentration of the extract followed by purification of the residue by chromatography on silica gel (hexane–AcOEt, 6:1) gave unreacted **12** (27 mg, 15%) and **13** (121 mg, 63%; 74% based on consumed **12**) as an oil: $[\alpha]_D^{17}=-13.2$ (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3060, 1710, 1636, 911 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.18 (d, *J*=7.6 Hz, 3H), 1.28 (s, 3H), 1.38 (s, 3H), 1.60 (d with fine splittings, *J*=8.4 Hz, 1H), 2.07 (t, *J*=5.7 Hz, 1H), 2.44 (q, *J*=7.6 Hz, 1H), 2.55–2.61 (m, 2H), 4.92 (dd, *J*=17.5, 1.2 Hz, 1H), 5.04 (dd, *J*=11.2, 1.2 Hz, 1H), 5.99 (dd, *J*=17.5, 11.2 Hz, 1H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.17; H, 10.22. Found: C, 81.20; H, 10.48.

(2) To a stirred mixture of copper(I) iodide (95 mg, 0.5 mmol) in THF (3 ml) was added at −78°C a solution of 1.01 M vinylmagnesium bromide in THF (2.4 ml, 2.4 mmol). After being stirred briefly, a solution of **8b** (150 mg, 1.0 mmol) in THF (2 ml) was added. Stirring was continued for an additional 2 h, after which the reaction mixture was treated with a solution of MeI (623 μl, 10.0 mmol) and HMPA (696 μl, 4.0 mmol) in THF (1 ml). The reaction mixture was allowed to stir for 10 h, during which the reaction temperature rose slowly to rt, quenched with aqueous NH_4Cl, and extracted with ether. Concentration of the extract followed by chromatography of the residue on silica gel (hexane–AcOEt, 6:1) gave unreacted **8b** (42 mg, 23%) and **13** (96 mg, 50%).

4.1.3. (1*S*,3*S*,4*R*,5*S*)-3,4,6,6-Tetramethyl-4-vinylbicyclo-[3.1.1]heptan-2-one (14). The compound **13** (46 mg, 0.24 mmol) was dissolved in a solution of 5% aqueous KOH (1.0 ml) and methanol (1.0 ml). The reaction mixture was stirred at rt for 5 h, quenched with aqueous NH_4Cl and extracted with ether. Concentration of the extract left an oil which was chromatographed on silica gel (hexane–AcOEt, 6:1) to give **14** (40 mg, 94%) as an oil; IR ($CHCl_3$) 3060, 1708, 1635, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 3H), 1.10 (s, 3H), 1.18 (d, *J*=6.8 Hz, 3H), 1.37 (s, 3H), 1.72 (d, *J*=10.8 Hz, 1H), 2.10 (dd, *J*=5.7, 5.5 Hz, 1H), 2.40 (ddd, *J*=10.8, 5.7, 5.5 Hz, 1H), 2.57 (t, *J*=5.5 Hz, 1H), 2.62 (q, *J*=7.2 Hz, 1H), 4.94 (d, *J*=17.4 Hz, 1H), 4.98 (d, *J*=11.2 Hz, 1H), 5.87 (dd, *J*=17.4, 11.2 Hz, 1H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.17; H, 10.22. Found: C, 81.40; H, 10.01.

4.1.4. (4*R*,5*R*,6*R*)-5,6-Dimethyl-4-(1-methylvinyl)-5-vinylcyclohex-1-enyl acetate (15). To a stirred mixture of **13** (95 mg, 0.5 mmol) and zinc acetate (93 mg, 0.5 mmol) in acetic anhydride (1 ml) was added boron trifuluoride diethyl etherate (61 μl, 0.5 mmol). After being stirred for 15 h at 60°C, the reaction mixture was cooled to rt, and water was added, followed by aqueous $NaHCO_3$. After being stirred briefly, the product was extracted with ether. Concentration of the extract left an oil which was chromatographed on silica gel (hexane–AcOEt, 12:1) to give **15** (70 mg, 60%) along with unreacted **13** (5 mg, 5%). **15**: an oil; IR ($CHCl_3$) 3070, 1751, 1636, 1114, 918, 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, *J*=7.0 Hz, 3H), 1.16 (s, 3H), 1.74 (s, 3H), 2.12 (s, 3H), 2.08∼2.15 (m, 1H), 2.21 (m, 2H), 2.33 (br t, *J*=7.1 Hz, 1H), 4.82 (br s, 1H), 4.83 (d, *J*=10.8 Hz, 1H), 5.02 (d, *J*=17.8 Hz, 1H), 5.03 (br s, 1H), 5.34 (br t, *J*=3.9 Hz, 1H), 5.95 (dd, *J*=17.8, 10.8 Hz, 1H). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.52; H, 9.47.

4.1.5. 2-[(1*S*,2*R*,3*R*,4*R*,5*S*)-4-Hydroxy-2,3,6,6-tetramethylbicyclo[3.1.1]hept-2-yl]ethyl acetate (19) and 2-[(1*S*,2*R*,3*R*,4*S*,5*S*)-4-hydroxy-2,3,6,6-tetramethylbicyclo[3.1.1]-hept-2-yl]ethyl acetate (20). To a stirred solution of **13** (15.54 g, 80.9 mmol) in THF (80 ml) was added dropwise at 0°C a 1.0 M solution of BH_3·THF in THF (162 ml, 162 mmol). The reaction mixture was stirred for 1 h and allowed to warm to rt over 10 h, and then quenched by addition of 25% aqueous THF (10 ml). To the reaction mixture, 3 M aqueous NaOH (20 ml) followed by 30% aqueous H_2O_2 (20 ml) was added slowly, and stirring was continued for an additional 12 h. Extraction with $CHCl_3$ followed by concentration of the extract left a crystalline mixture of **16** and **17** [ca 17.1 g, 16/17=ca 2:1 from the ^1H NMR analysis]. Pure **16** and **17** were obtained by chromatography on silica gel (hexane–AcOEt, 2:5).

4.1.6. (1*S*,2*R*,3*R*,4*R*,5*S*)-4-(2-Hydroxyethyl)-3,4,6,6-tetramethylbicyclo[3.1.1]heptan-2-ol (16). Crystals; mp 159–160°C; IR (KBr) 3247 (br), 3227 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, *J*=10.6 Hz, 1H), 1.07 (d, *J*=7.2 Hz, 3H), 1.08 (s, 3H), 1.23 (s, 3H), 1.28 (s, 3H), 1.3–1.39 (m, 1H), 1.5 (s, 2H, OH×2), 1.70 (t, *J*=5.5 Hz, 1H), 1.84 (m, 1H), 1.98–2.07 (m, 3H), 3.45 (m, 1H), 3.52–3.65 (m, 2H). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.39; H, 11.68. Found: C, 73.54; H, 11.39.

4.1.7. (1*S*,2*S*,3*R*,4*R*,5*S*)-4-(2-Hydroxyethyl)-3,4,6,6-tetramethylbicyclo[3.1.1]heptan-2-ol (17). Semi-solid; IR (KBr) 3300 (br), 3250 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, *J*=7.5 Hz, 3H), 1.31 (s, 3H), 1.13 (s, 3H), 1.31 (s, 3H), 1.35 (m, 2H), 1.59 (d, *J*=10.2 Hz, 1H), 1.70 (t, *J*=

5.9 Hz, 1H), 1.95–2.05 (m, 3H), 2.16 (q, *J*=5.3 Hz, 1H), 2.26 (qd, *J*=7.5, 5.8 Hz, 1H), 3.45–3.56 (m, 1H), 3.67 (m, 1H), 4.14 (dd, *J*=5.9, 5.5 Hz, 1H).

The mixture, **16** and **17**, obtained above was dissolved in pyridine (50 ml) and acetic anhydride (13 ml) at 0°C. The reaction mixture was stirred for 1.5 h, and quenched by addition of methanol (13 ml). After being stirred briefly, aqueous $NaHCO_3$ was added and the product was extracted with ether. The combined extracts were washed successively with water, aqueous $CuSO_4$, water and brine, and dried. Concentration left an oil which was chromatographed on silica gel (hexane–AcOEt, 3:1) to give a mixture (11.96 g, 58%) of **19** and **20** in a 2:1 ratio, and **18** (3.23 g, 13%). Pure **19** and **20** were obtained by MPLC (hexane–AcOEt, 3:1).

Compound **19**: oil; $[\alpha]_D^{17}=-16.7$(*c* 0.67, $CHCl_3$); IR (film) 3613, 3480, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, *J*=10.4 Hz, 1H), 1.02 (d, *J*=7.2 Hz, 3H), 1.09 (s, 3H), 1.24 (s, 3H), 1.29 (s, 3H), 1.39 (m, 1H), 1.71 (s, 1H, OH), 1.75 (t, *J*=5.7 Hz, 1H), 1.87 (m, 1H), 2.03 (s, 3H), 2.04 (m, 2H), 2.22 (dt, *J*=10.4, 6.2 Hz, 1H), 3.63 (d, *J*=6.4 Hz, 1H), 3.92 and 4.01 (m, 1H each). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.78; H, 10.17. Found: C, 70.83; H, 10.30.

Compound **20**: oil; IR (film) 3620, 3471 (br), 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, *J*=7.5 Hz, 3H), 1.01 (s, 3H), 1.13 (s, 3H), 1.31 (s, 3H), 1.35 (m, 1H), 1.59 (d, *J*=10.2 Hz, 1H), 1.70 (t, *J*=5.9 Hz, 1H), 2.01 (s, 3H), 1.95–2.05 (m, 3H), 2.16 (q, *J*=5.3 Hz, 1H), 2.26 (qd, *J*=7.5, 5.8 Hz, 1H), 3.45–3.56 (m, 1H), 3.67 (m, 1H), 4.14 (dd, *J*=5.9, 5.5 Hz, 1H). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.78; H, 10.17. Found: C, 70.91; H, 10.45.

4.1.8. 2-[(1*S*,2*R*,3*R*,5*S*)-4-Acetyloxy-2,3,6,6-tetramethylbicyclo[3.1.1]hept-2-yl]ethyl acetate (18). Oil; IR (film) 1740, 1243, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, *J*=7.1 Hz, 3H), 1.06 (d, *J*=10.7 Hz, 1H), 1.11 (s, 3H), 1.20 (s, 3H), 1.26 (s, 3H), 1.40 (ddd, *J*=13.4, 10.7, 5.1 Hz, 1H), 1.77 (t, *J*=5.6 Hz, 1H), 1.89 (m, 1H), 2.07 (s, 6H), 2.09 (m, 1H), 2.21~2.28 (m, 2H), 3.90 (td, *J*=10.7, 6.1 Hz, 1H), 4.02 (td, *J*=10.7 Hz, 5.1, 1H), 4.80 (dd, *J*=7.8, 2.0 Hz, 1H). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.72; H, 9.49.

4.1.9. 2-[(1*S*,2*R*,3*R*,5*S*)-2,3,6,6-Tetramethyl-4-oxobicyclo-[3.1.1]hept-2-yl]ethyl acetate (21). To a stirred solution of oxalyl chloride (4.68 ml, 53.7 mmol) in CH_2Cl_2 (30 ml) was added a solution of DMSO (7.62 ml, 107.3 mmol) in CH_2Cl_2 (30 ml) at −78°C. After being stirred for 10 min, a solution of a mixture, **19** and **20**, (6.83 g, 26.85 mmol) in CH_2Cl_2 (60 ml) was added dropwise. Stirring was continued for an additional 45 min, after which triethylamine (18.7 ml, 134.0 mmol) was added. The reaction mixture was stirred for an additional 2 h at −78°C, and then for 2 h at 0°C, and quenched by addition of aqueous NH_4Cl. Extraction with ether followed by concentration of the combined extracts left an oil which was chromatographed on silica gel (hexane–AcOEt, 4:1) to give **21** (6.52 g, 96%) as crystals: mp 73–74°C; $[\alpha]_D^{17}=-3.7$ (*c* 1.63, $CHCl_3$); IR (film) 1733, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.19 (d, *J*=7.3 Hz, 3H), 1.24 (s, 3H), 1.38 (s, 3H), 1.46 (d, *J*=10.7 Hz, 1H), 1.54 (m, 1H), 1.89 (m, 1H), 2.04 (s, 3H), 2.05 (m, 1H), 2.52 (q, *J*=7.3 Hz, 1H), 2.53–2.62 (m, 2H), 3.97–4.10 (m, 2H). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.32; H, 9.47. Found: C, 71.39; H, 9.59.

4.1.10. 2-[(1*R*,2*R*,6*R*)-3-Acetyloxy-1,2-dimethyl-6-(1-methylvinyl)cyclohex-3-enyl]ethyl acetate (22). To a stirred mixture of **21** (1.38 g, 5.48 mmol) and zinc acetate (1.01 g, 5.48 mmol) in acetic anhydride (15 ml) was added at 0°C a solution of boron trifluoride diethyl etherate (0.33 ml, 2.74 mmol). The reaction mixture was stirred at rt for 2 d, and quenched by addition of water. After being stirred for 2 h, the aqueous mixture was extracted with ether. The combined extracts were washed successively with aqueous $NaHCO_3$, water and brine, and dried. Evaporation of the solvent left an oil which was chromatographed on silica gel (hexane–AcOEt, 5:1) to give **22** (1.61 g, quant) as an oil: $[\alpha]_D^{17}=+61.1$ (*c* 2.77, $CHCl_3$); IR (film) 3074, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, *J*=7.0 Hz, 3H), 1.07 (s, 3H), 1.59 (m, 2H), 1.72 (s, 3H), 2.04 (s, 3H), 2.12 (s, 3H), 2.0–2.19 (m, 2 H), 2.2–2.30 (m, 2H), 4.07–4.15 (m, 2H), 4.82 and 4.91 (s, 1H each), 5.29 (dd, *J*=4.6, 1.8 Hz, 1H). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.20; H, 9.21. Found: C, 69.36; H, 8.90.

4.1.11. 2-[(1*R*,2*S*,6*R*)-1,2-Dimethyl-6-(1-methylvinyl)-3-oxocyclohexyl]ethyl acetate (25) and 2-[(1*R*,2*R*,6*R*)-1,2-dimethyl-6-(1-methylvinyl)-3-oxocyclohexyl]ethyl acetate (26). A mixture of **22** (1.22 g, 4.14 mmol) and K_2CO_3 (970 mg, 7.03 mmol) in methanol (20 ml) was stirred at rt for 1 h, and quenched by addition of aqueous NH_4Cl. Extraction with ether followed by concentration of the extract left the residue, which was filtered through a short silica gel column (ether) to give a mixture of **23** and **24** in a 4:1 ratio (from ^1H NMR). Pure samples were obtained by purification with MPLC (hexane–AcOEt, 1:1).

4.1.12. (2*S*,3*R*,4*R*)-3-(2-Hydroxyethyl)-2,3-dimethyl-4-(1-methylvinyl)cyclohexan-1-one (23). Oil; $[\alpha]_D^{17}=+2.0$ (*c* 0.82, $CHCl_3$); IR (film) 3620, 3491(br), 3075, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3H), 0.99 (d, *J*=6.8 Hz, 3H), 1.19 (br s, 1H, OH), 1.5–1.71 (m, 2H), 1.79 (s, 3H), 1.71–1.85 (m, 1 H), 2.0 (m, 1H), 2.33–2.45 (m, 3H), 2.66 (dd, *J*=12.8, 3.8 Hz, 1H), 3.74 and 3.89 (m, 1H each), 4.82 and 4.95 (s, 1H each). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.86; H, 10.82.

4.1.13. (2*R*,3*R*,4*R*)-3-(2-Hydroxyethyl)-2,3-dimethyl-4-(1-methylvinyl)cyclohexan-1-one (24). Oil; IR (film) 3620, 3465(br), 3074, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3H) 1.18 (d, *J*=7.3 Hz, 3H), 1.24 (br s, 1H, OH), 1.55–1.62 (m, 1H), 1.68–1.75 (m, 1H), 1.80 (s, 3H), 1.80–1.85 (m, 1 H), 1.99 (m, 1H), 2.21–2.29 (m, 2H), 2.51–2.61 (m, 2H), 3.65 (m, 2H), 4.78 and 4.96 (s, 1H each).

A mixture of keto-alcohols, **23** and **24**, (878 mg, 4.17 mmol), acetic anhydride (5 ml) and pyridine (5 ml) was stirred at 0°C for 1.5 h. The reaction mixture was quenched by addition of methanol (5 ml), and stirring was continued for an additional 1 h. Water was added and the product was extracted with ether. The combined extracts were washed successively with water, aqueous $CuSO_4$, water and brine, and dried. Removal of the solvent followed

by chromatography of the residue with MPLC (hexane–AcOEt, 3:1) gave **25** (723 mg, 69%) and **26** (187 mg, 18%).

Compound **25**: oil; $[\alpha]_D^{17}=+4.39$ (*c* 7.13, $CHCl_3$); IR (film) 3076, 1732, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3H), 0.99 (d, *J*=6.8 Hz, 3H), 1.65–1.72 (m, 2H), 1.80 (s, 3H), 1.89 (m, 1H), 2.0 (m, 1H), 2.05 (s, 3H), 2.32–2.48 (m, 3 H), 2.65 (dd, *J*=12.6, 3.8 Hz, 1H), 4.11–4.29 (m, 2H), 4.82 and 4.97 (s, 1H each). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.29; H, 9.80.

Compound **26**: oil; IR (film) 3077, 1732, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.19 (d, *J*=6.8 Hz, 3H), 1.60 (m, 1H), 1.71–1.86 (m, 2H), 1.79 (s, 3H), 1.94–2.04 (m, 1H), 2.04 (s, 3H), 2.24–2.30 (m, 2 H), 2.52–2.62 (m, 2H), 4.00–4.12 (m, 2H), 4.78 and 4. 96 (s, 1H each). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.52; H, 9.50.

4.1.14. 2-[(6*S*,7*R*,8*R*)-6,7-Dimethyl-8-(1-methylvinyl)-1,4-dioxaspiro[4.5]dec-7-yl]ethyl acetate (27). To a stirred mixture of **25** (255 mg, 1.01 mmol) and 2,2′-(ethylenedioxy)-bis(trimethylsilane) (825 μl, 4.0 mmol) in CH_2Cl_2 (5 ml) was added at −30°C a solution of trimethylsilyl triflate (97 μl, 0.5 mmol). The reaction mixture was stirred for 2 h, quenched by addition of aqueous $NaHCO_3$, and extracted with ether. The combined extracts were washed successively with aqueous $NaHCO_3$, water, and brine, and dried. Concentration followed by purification of the residue with MPLC (hexane–AcOEt, 3:1) gave **27** (272 mg, 92%) as an oil: $[\alpha]_D^{17}=+3.20$ (*c* 1.63, $CHCl_3$); IR (film) 3074, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, *J*=6.5 Hz, 3H), 0.89 (s, 3H), 1.36–1.48 (m, 2H), 1.59–1.66 (m, 3H), 1.75 (s, 3H), 1.7–1.75 (m, 1H), 1.79–1.86 (m, 1H), 2.00 (s, 3H), 2.15 (dd, *J*=11.9, 2.2 Hz, 1H), 3.77–4.16 (m, 6H), 4.71 and 4.91 (s, 1H each). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.72; H, 9.75.

4.1.15. 2-[(6*S*,7*R*,8*R*)-6,7-Dimethyl-8-(1-methylvinyl)-1,4-dioxaspiro[4.5]dec-7-yl]ethan-1-ol (28). A mixture of **27** (1.49 g, 5.02 mmol) and K_2CO_3 (1.39 g, 10.04 mmol) in methanol (30 ml) was stirred at 0°C for 2 h and warmed at rt briefly. Filtration followed by concentration of the filtrate left an oily residue which was dissolved in ether. The ether solution was washed successively with water and brine, and dried. Concentration left an oil which was chromatographed on silica gel (hexane–AcOEt, 3:2) to give **28** (1.29 g, quant) as an oil: $[\alpha]_D^{17}=-2.90$ (*c* 1.49, $CHCl_3$); IR (film) 3619, 3463 (br), 3074, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, *J*=6.5 Hz, 3H), 0.89 (s, 3H), 1.15 (br s, 1H, OH), 1.34–1.45 (m, 2H), 1.75 (s, 3H), 1.6–1.88 (m, 4H), 1.79–1.86 (m, 1H), 2.13 (dd, *J*=11.9, 2.2 Hz, 1H), 3.59–4.02 (m, 6H), 4.72 and 4.91 (s, 1H each). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.62; H, 10.25.

4.1.16. 2-[(6*S*,7*R*,8*R*)-6,7-Dimethyl-8-(1-methylvinyl)-1,4-dioxaspiro[4.5]dec-7-yl]ethanal (29). To a stirred solution of oxalyl chloride (0.72 ml, 8.26 mmol) in CH_2Cl_2 (5 ml) was added a solution of DMSO (1.17 ml, 16.52 mmol) in CH_2Cl_2 (5 ml) at −78°C. After being stirred for 10 min, a solution of **28** (1.05 g, 4.13 mmol) in CH_2Cl_2 (10 ml) was added dropwise, and stirring was continued for additional 45 min. To the reaction mixture, triethylamine (2.88 ml, 20.65 mmol) was added, and the reaction mixture was stirred for additional 1 h, quenched by addition of aqueous NH_4Cl, and extracted with ether. Removal of the solvent left an oily residue whose purification with chromatography on silica gel (hexane–AcOEt, 3:1) gave **29** (963 mg, 93%) as an oil: $[\alpha]_D^{17}=-1.8$ (*c* 1.31, $CHCl_3$); IR (film) 3076, 1731, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, *J*=7.1 Hz, 3H), 1.36 (s, 3H), 1.48–1.63 (m, 2H), 1.73 (s, 3H), 1.69–1.75 (m, 1H), 1.76–1.93 (m, 2H), 2.19 (dd, *J*=12.1, 3.4 Hz, 1H), 2.33–2.43 (m, 2H), 3.84–3.97 (m, 4H), 4.71 and 4.91 (s, 1H each), 9.85 (dd, *J*=3.3, 2.4 Hz, 1H). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.03 H, 9.33.

4.1.17. (1*R*,3*S*,6*R*,10*S*)-1,10-Dimethyl-5-methylenespiro-[1′,3′-dioxolane-2′,9-bicyclo[4.4.0]decan]-3-ol (30). To a stirred solution of **29** (1.17 g, 4.64 mmol) in CH_2Cl_2 (50 ml) was added dropwise at 0°C a solution of 0.95 M diethylaluminum chloride in hexane (4.90 ml, 4.64 mmol). The reaction mixture was stirred for 40 min, quenched by addition of aqueous NH_4Cl, and extracted with ether–CH_2Cl_2 (1:1). The combined extracts were washed successively with aqueous $NaHCO_3$, water and brine, and dried. Removal of the solvent left an oily residue which was chromatographed on silica gel (hexane–AcOEt, 3:1) to give **30** (950 mg, 81%) as an oil: $[\alpha]_D^{17}=-26.8$ (*c* 1.70, $CHCl_3$); IR (film) 3610, 3461 (br), 3084, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, *J*=7.0 Hz, 3H), 1.01 (s, 3H), 1.34 (dd, *J*=14.2, 3.7 Hz, 1H), 1.40–1.48 (m, 2H), 1.56–1.68 (m, 3H), 1.86 (d, *J*=11.0 Hz, 1H), 1.92 (dt, *J*=13.2, 3.0 Hz, 1H), 2.04 (d, *J*=14.0 Hz, 1H), 2.39 (s, 2H), 3.77–4.03 (m, 4H), 4.17 (s with fine splittings, 1/2H=12 Hz, 1H),[29] 4.71 and 4.92 (s, 1H each). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.27; H, 9.82.

4.1.18. (1*R*,6*R*,10*S*)-1,10-Dimethyl-5-methylenespiro-[1′,3′-dioxolane-2′,9-bicyclo[4.4.0]decan]-3-one (31) and (4a*R*,8*S*,8a*R*)-4,8,8a-trimethylspiro[1′,3′-dioxolane-2′,7-1,4a,5,6,7,8,8a-heptahydronaphthalen]-2-one (9). To a stirred solution of oxalyl chloride (0.51 ml, 5.86 mmol) in CH_2Cl_2 (12 ml) was added at −78°C a solution of DMSO (0.83 ml, 11.72 mmol) in CH_2Cl_2 (15 ml). After being stirred for 10 min, a solution of **27** (740 mg, 2.93 mmol) in CH_2Cl_2 (10 ml) was added dropwise, and stirring was continued for additional 45 min, after which triethylamine (2.0 ml, 14.65 mmol) was added. The reaction mixture was stirred for additional 10 min at −78°C, and for 5 min at rt, quenched by addition of aqueous NH_4Cl, and extracted with ether. Removal of the solvent left an oily residue which was purified by MPLC (hexane–AcOEt, 1:1) to give **31** (574 mg, 78%) and **9** (36 mg, 5%).

Compound **31**: oil; $[\alpha]_D^{17}=-47.5$ (*c* 1.69, $CHCl_3$); IR (film) 3092, 1713, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (s, 3H), 0.87 (d, *J*=7.0 Hz, 3H), 1.53 (td, *J*=13.3, 4.2 Hz, 1H), 1.64 (td, *J*=12.8, 2.7 Hz, 1H), 1.73–1.83 (m, 1H), 1.80 (q, *J*=7.0 Hz, 1H), 1.95 (dt, *J*=12.5, 2.9 Hz, 1H), 2.15 (d, *J*=13.9 Hz, 1H), 2.25 (d, *J*=12.8 Hz, 1H), 2.52 (dd, *J*=13.9, 2.0 Hz, 1H), 3.08 (dd, *J*=15.1, 2.0 Hz, 1H), 3.14 (d, *J*=15.1 Hz, 1H), 3.79–4.03 (m, 4H), 4.71 and 4.85 (s, 1H each). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.71; H, 8.71.

Compound **9**: crystals; mp 88–89°C; $[\alpha]_D^{17}=-82.4$ (*c* 1.19,

$CHCl_3$); IR (film) 3016, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J=7.0 Hz, 3H), 0.92 (s, 3H), 1.48–1.61 (m, 2H), 1.79 (q, J=7.0 Hz, 1H), 1.92 (s, 3H), 1.9–2.05 (m, 2H), 2.09 (d, J=16.1 Hz, 1H), 2.39 (d, J=10.9 Hz, 1H), 2.45 (d, J=16.1 Hz, 1H), 3.81–4.04 (m, 4H), 5.87 (s, 1H). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.70; H, 8.70.

*Isomerization of **31** to **9***. A mixture of **31** (399 mg, 1.60 mmol) and DBU (0.36 ml, 2.40 mmol) in CH_2Cl_2 (20 ml) was stirred for 1 h, quenched with aqueous NH_4Cl, and extracted with ether. Concentration of the combined extracts followed by purification of the residue by chromatography on silica gel (hexane–AcOEt, 1:1) gave **9** (399 mg, quant).

4.1.19. (1*R*,5*R*,6*R*,10*S*)-1,5,10-Trimethyl-5-vinylspiro-[1′,3′-dioxolane-2′,9-bicyclo[4.4.0]decan]-3-one (32). To a stirred mixture of copper(I) iodide (230 mg, 1.14 mmol) in THF (5 ml) was added at −78°C a solution of 0.97 M vinylmagnesium bromide in THF (3.5 ml, 3.41 mmol), and stirring was continued for 30 min. To the reaction mixture, a solution of **9** (568 mg, 2.27 mmol) in THF (5 ml) was added dropwise. The reaction mixture was stirred for an additional 1.5 h, quenched by addition of aqueous NH_4Cl, and extracted with ether. Concentration of the extract followed by purification of the residue with MPLC (hexane–AcOEt, 4:1) gave **32** (422 mg, 67%) as crystals: mp 84–85°C; $[\alpha]_D^{17}$=−4.6 (c 1.36, $CHCl_3$); IR (film) 3088, 1706, 1637 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.81 (d, J=7.0 Hz, 3H), 0.94 (s, 3H), 1.04 (s, 3H), 1.42 (td, J=13.5, 4.0 Hz, 1H), 1.47 (td, J=13.7, 3.3 Hz, 1H), 1.59–1.62 (m, 2H), 1.77 (q, J=7.0 Hz, 1H), 1.88 (dt, J=12.5, 2.7 Hz, 1H), 2.09 (dd, J=13.5, 2.5 Hz, 1H), 2.13 (d, J=13.5 Hz, 1H), 2.39 (dd, J=13.1, 2.5 Hz, 1H), 2.42 (d, J=13.1 Hz, 1H), 3.74–3.81 (m, 1H, OC*H*HCH$_2$O), 3.89–3.94 (m, 2H, OCH*HC*H*H*O), 3.97–4.01 (m, 1H, OCHHCH*H*O), 4.97 (d, J=17.4 Hz, 1H), 5.03 (d, J=10.7 Hz, 1H), 5.76 (dd, J=17.4, 10.7 Hz, 1H). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.44; H, 9.34.

4.1.20. (1*R*,4*R*,5*R*,6*R*,10*S*)-1,4,5,10-Tetramethyl-5-vinylspiro[1′,3′-dioxolane-2′,9-bicyclo[4.4.0]decan]-3-one (33). (1) From **32**. To a stirred solution of 1.66 M BuLi in hexane (2.41 ml, 4.0 mmol) was added dropwise at 0°C a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.84 ml, 4.0 mmol), and stirring was continued for 30 min. The solvent was removed off under reduced pressure, and crystals thereby formed were dissolved in THF (8 ml). To a stirred solution of **32** (306 mg, 1.1 mmol) in THF (8 ml) was added at 0°C the solution of LHMDS in THF prepared above. After being stirred for 1 h at rt, methyl iodide (0.68 ml, 11.0 mmol) was added. The reaction mixture was stirred for an additional 2 h, quenched by addition of aqueous NH_4Cl, and extracted with AcOEt. Removal of the solvent left an oily residue which was purified by MPLC (hexane–AcOEt, 3:1) to give **33** (196 mg, 61%) as crystals: mp 67–69°C; $[\alpha]_D^{17}$=−47.5 (c 2.15, $CHCl_3$); IR (film) 3087, 1701, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, J=6.8 Hz, 3H), 1.02 (d, J=7.0 Hz, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.37–1.41 (m, 1H), 1.46–1.51 (m, 2H), 1.61 (m, 1H), 1.69 (q, J=6.8 Hz, 1H), 1.86 (dd, J=10.1, 1.6 Hz, 1H), 2.24 and 2.32 (d, J=15.0 Hz, 1H each), 2.42 (q, J=7.0 Hz, 1H), 3.77–4.02 (m, 4H), 4.93 (d, J=17.4 Hz, 1H), 5.06 (d, J=10.9 Hz, 1H), 5.58 (dd, J=17.4, 10.9 Hz, 1H). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.70; H, 9.54.

(2) From **9**. To a stirred mixture of copper(I) iodide (85 mg, 0.45 mmol) and isopropenyl sulfide (0.19 ml, 1.35 mmol) in THF (3 ml) was added a 1.0 M solution of vinyllithium in THF (0.74 ml, 0.87 mmol) dropwise at −78°C, and the reaction mixture was allowed to warm to −40°C over 2 h, then cooled to −78°C. To the reaction mixture was added a solution of **9** (75 mg, 0.30 mmol) in THF (1 ml). After being stirred at −78°C for 10 min, the reaction was allowed to warm to −40°C, and a solution of methyl iodide (255 mg, 1.80 mmol) in HMPA (0.3 ml) and THF (1 ml) was added. The reaction mixture was allowed to stir for 7 h, during which the reaction temperature rose to rt. Extractive workup followed by purification of the residue by MPLC (hexane–AcOEt, 3:1) gave **33** (18 mg, 21%).

4.1.21. (1*R*,4*S*,5*R*,6*R*,10*S*)-1,4,5,10-Tetramethyl-5-vinylspiro[1′,3′-dioxolane-2′,9-bicyclo[4.4.0]decane]-3-one (34). The compound **33** (132 mg, 0.45 mmol) was dissolved in 5% KOH–methanol solution (15 ml), and the reaction mixture was stirred for 12 h at rt. The solvent was mostly removed under reduced pressure, and water was added to the oily residue. Extraction with AcOEt followed by concentration of the extract left an oil which was purified by MPLC (hexane–AcOEt, 4:1) to give **34** (119 mg, 90%) as crystals: mp 104–105°C; $[\alpha]_D^{17}$=+7.8 (c 1.48, $CHCl_3$); IR (film) 3087, 1705, 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.80 (d, J=6.8 Hz, 3H), 0.85 (d, J=6.8 Hz, 3H), 0.90 (s, 3H), 1.41–1.52 (m, 2H), 1.57–1.65 (m, 2H), 1.79 (q, J=6.8 Hz, 1H), 1.87 (dd, J=10.0, 2.4 Hz, 1H), 2.18 and 2.42 (d, J=11.7 Hz, 1H each), 2.41 (q, J=6.8 Hz, 1H), 3.78–4.00 (m, 4H), 4.94 (d, J=17.3 Hz, 1H), 5.14 (d, J=10.8 Hz, 1H), 5.62 (dd, J=17.3, 10.8 Hz, 1H). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.83; H, 9.82.

4.1.22. 2-[(1*R*,2*S*,3*R*,6*R*)-3-Hydroxy-1,2-dimethyl-6-(1-methylvinyl)cyclohexyl]ethyl acetate (35). To a stirred solution of **25** (54 mg, 0.22 mmol) in THF (1.5 ml) was added dropwise at 0°C a 0.4 M solution of lithium tri-*tert*-butoxyaluminum hydride in THF (0.91 ml, 0.32 mmol). The reaction mixture was stirred for 20 min, quenched by addition of aqueous NH_4Cl, and extracted with ether. Removal of the solvent left an oil which was purified by MPLC (hexane–AcOEt, 2:1) to give **35** (58 mg, quant) as crystals: mp 38–40°C, $[\alpha]_D^{17}$=−11.1 (c 2.77, $CHCl_3$); IR (film) 3520, 3027, 1728, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H) (d, J=7.1 Hz, 3H), 1.31–1.36 (m, 1H), 1.41–1.57 (m, 3H), 1.61 (t, J=7.5 Hz, 2H), 1.77 (s, 3H), 1.86 (dq, J=13.9, 2.3 Hz, 1H), 1.97–2.06 (m, 1H), 2.04 (s, 3H), 2.13 (dd, J=12.7, 2.5 Hz, 1H), 3.84 (br s, 1H), 4.12 (m, 2H), 4.72 and 4.90 (s, 1H each). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.66; H, 10.22. Found: C, 70.83; H, 10.30.

4.1.23. 2-[(1*R*,6*R*)-1,2-Dimethyl-6-(1-methylvinyl)cyclohex-2-enyl]ethyl acetate (36). To a stirred solution of **35** (838 mg, 3.29 mmol) in pyridine (10 ml) was added dropwise at rt a solution of phosphorus oxychloride (1.54 ml, 16.5 mmol), and stirring was continued for 2 h. The reaction mixture was poured into ice water, and the product was extracted with ether. The combined extracts were washed successively with 1 M HCl solution, water, aqueous

$NaHCO_3$, water and brine, and dried. Concentration of the extract followed by chromatography of the residue on silica gel (hexane–AcOEt, 10:1) gave **36** (723 mg, 93%) as an oil: $[\alpha]_D^{17}=-78.5$ (*c* 2.47, $CHCl_3$); IR (film) 3074, 1732, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3H), 1.50–1.56 (m, 1H), 1.63–1.72 (m, 2H), 1.66 (s, 3H), 1.80 (s, 3H), 1.87–1.93 (m, 1H), 1.95–2.01 (m, 2H), 2.04 (s, 3H), 2.28 (dd, *J*=12.2, 2.7 Hz, 1H), 3.89 (dt, *J*=10.8, 4.9 Hz, 1H), 4.17 (dt, *J*=10.8, 5.9 Hz, 1H), 4.76 and 4.90 (s, 1H each), 5.46 (s, 1H). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.22. Found: C, 76.23; H, 10.23.

4.1.24. 2-[(1*R*,6*R*)-1,2-Dimethyl-6-(1-methylvinyl)cyclohex-2-enyl]ethan-1-ol (37). A mixture of **36** (29 mg, 0.12 mmol) and K_2CO_3 (34 mg, 0.25 mmol) in methanol (2 ml) was stirred at rt for 3 h, and diluted with water. Extraction with ether followed by concentration of the extract left an oily residue which was purified by MPLC (hexane–AcOEt, 2:1) to give **37** (24 mg, 99%) as crystals: mp 39–40°C, $[\alpha]_D^{17}=-127.4$ (*c* 1.84, $CHCl_3$); IR (film) 3621, 3451 (br), 3074, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3H), 1.50–1.55 (m, 2H), 1.63–1.74 (m, 2H), 1.68 (s, 3H), 1.78 (s, 3H), 1.81–1.90 (m, 1H), 1.95–2.00 (m, 2H), 2.27 (dd, *J*=12.4, 2.7 Hz, 1H), 3.50 (dt, *J*=10.3, 5.1 Hz, 1H), 3.77 (dt, *J*=10.3, 5.9 Hz, 1H), 4.73 and 4.93 (s, 1H each), 5.44 (s, 1H). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.51; H, 11.03.

4.1.25. 2-[(1*R*,6*R*)-1,2-Dimethyl-6-(1-methylvimyl)cyclohex-2-enyl]ethanal (38). According to the procedure described for the preparation of **29** from **28**, oxalyl chloride (0.15 ml, 1,72 mmol) was treated with DMSO (0.24 ml, 3.43 mmol) in CH_2Cl_2 (7 ml) at −78°C. After being stirred for 10 min, a solution of **37** (167 mg, 0.86 mmol) in CH_2Cl_2 (4 ml) was added, followed by triethylamine (0.60 ml, 4.29 mmol), and the reaction mixture was stirred for additional 1 h. Aqueous workup followed by purification of the residue by chromatography on silica gel (pentane–ether, 29:1) gave **38** (153 mg, 93%) as an oil; IR (film) 3076, 1716, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 3H), 1.61 (m, 1H), 1.72 (s, 3H), 1.76 (s, 3H), 1.72–1.80 (m, 1H), 2.04–2.09 (m, 2H), 2.38 (dd, *J*=12.2, 2.7 Hz, 1H), 2.42 (dd, *J*=16.3, 1.7 Hz, 1H), 2.58 (dd, *J*=16.3, 2.7 Hz, 1H), 4.71 and 4.96 (s, 1H each), 5.54 (s, 1H), 9.67 (dd, *J*=2.7, 1.7 Hz, 1H). The compound **38** was unstable, and used for the next reaction without further purification.

4.1.26. (2*S*,4a*R*,8a*R*)-8,8a-Dimethyl-4-methylene-1,2,3,4a,5,6,8a-heptahydronaphthalen-2-ol (39). According to the procedure described for the preparation of **30** from **29**, a solution of **38** (153 mg, 0.80 mmol) in CH_2Cl_2 (8 ml) was treated with a solution of 0.97 M diethylaluminum chloride in hexane (0.82 ml, 0.80 mmol). Aqueous workup followed by purification with MPLC (hexane–AcOEt, 2:1) gave **39** (100 mg, 65%) as crystals: mp 57–58°C, $[\alpha]_D^{17}=-233.9$ (*c* 1.29, $CHCl_3$); IR (film) 3611, 3454 (br), 3082, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.40 (m, 1H), 1.53 (dd, *J*=14.4, 3.7 Hz, 1H), 1.62–1.68 (m, 2H), 1.66 (s, 3H), 2.03–2.11 (m, 4H), 2.41 (m, 2H), 4.23 (s, 1/2H=10.9 Hz, 1H),[29] 4.72 and 4.95 (s, 1H each), 5.20 (s, 1H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.50; H, 10.75.

4.1.27. (4a*R*,8a*R*)-8,8a-Dimethyl-4-methylene-1,3,4a,5,6,8a-hexahydronaphthalen-2-one (40) and (4a*R*,8a*R*)-4,8,8a-trimethyl-1,4a,5,6,8a-pentahydronaphthalen-2-one (10). According to the procedure described for the preparation of the mixture of **9** and **31** from **30**, a solution of oxalyl chloride (0.11 ml, 1.22 mmol) and DMSO (0.17 ml, 2.43 mmol) in CH_2Cl_2 (5 ml) was stirred at −78°C for 10 min. To the reaction mixture was added a solution of **39** (117 mg, 0.61 mmol) in CH_2Cl_2 (3 ml), followed by triethylamine (0.60 ml, 4.29 mmol), and stirring was continued for an additional 2 h. Aqueous workup followed by purification of the residue by MPLC (hexane–AcOEt, 3:1) gave **40** (18 mg, 15%) and **10** (74 mg, 64%).

Compound **40**: oil; $[\alpha]_D^{17}=-250.1$ (*c* 0.77, $CHCl_3$); IR (film) 3080, 1712, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (s, 3H), 1.57–1.67 (m, 1H), 1.64 (s, 3H), 1.82 (m, 1H), 2.12–2.18 (m, 2H), 2.29 (d, *J*=14.0 Hz, 1H), 2.47 (d, *J*=12.0 Hz, 1H), 2.59 (dd, *J*=14.0, 1.2 Hz, 1H), 3.14 (br s, 2H), 4.57 and 4.88 (s, 1H each), 5.38 (br s, 1H). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.00; H, 9.52.

Compound **10**: crystals; mp 41–42°C; $[\alpha]_D^{17}=-214.2$ (*c* 0.64, $CHCl_3$); IR (film) 3033, 1655, 1619 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 3H), 1.48–1.62 (m, 1H) 1.64 (s, 3H), 1.97 (s, 3H), 2.02–2.06 (m, 1H), 2.13–2.22 (m, 3H), 2.60 (d, *J*=16.0 Hz, 2H), 5.32 (s, 1H), 5.94 (s, 1H). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.95; H, 9.50.

According to the procedure described for the preparation of **9** from **31**, treatment of **40** with DBU provided **10** quantitatively.

4.1.28. (4*S*,4a*R*,8a*R*)-4-(But-3-enyl)-4,8,8a-trimethyl-1,3,4,4a,5,6,8a-heptahydronaphthalen-2-one (41). To a stirred mixture of copper(I) iodide (931 mg, 4.60 mmol) in THF (5 ml) was added dropwise at −20°C a solution of 1.02 M homoallylmagmesium bromide in THF (5.0 ml, 5.10 mmol). After being stirred briefly, the reaction mixture was cooled at −78°C, and boron trifluoride diethyl etherate (0.57 ml, 4.6 mmol) was added. After being stirred for 30 min, a solution of 10 (442 mg, 2.30 mmol) in THF (5 ml) was added dropwise, and stirring was continued for 6 h, during which the reaction temperature rose slowly to −20°C. The reaction mixture was quenched by addition of aqueous NH_4Cl, and extracted with ether. Concentration of the extract followed by chromatography of the residue on silica gel (hexane–AcOEt, 3:1) gave **41** (491 mg, 86%) as an oil: $[\alpha]_D^{17}=-130.1$ (*c* 0.94, $CHCl_3$); IR (film) 3075, 1714, 1641, 990, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 3H), 1.06 (s, 3H), 1.37 (m, 1H), 1.46–1.57 (m, 2H), 1.58 (s, 3H), 1.72 (dd, *J*=13.4, 6.4 Hz, 1H), 1.82 (dd, *J*=12.5, 2.0 Hz, 1H), 2.03 (m, 2H), 2.07–2.12 (m, 2H), 2.12 (dd, *J*=13.4, 1.9 Hz, 1H), 2.25 (d, *J*=12.7 Hz, 1H), 2.41 (d, *J*=13.4 Hz, 1H), 2.44 (dd, *J*=12.7, 1.9 Hz, 1H), 4.95 (d, *J*=11.9 Hz, 1H), 5.03 (d, *J*=17.0 Hz, 1H), 5.28 (s, 1H), 5.80 (ddt, *J*=17.0, 11.9, 6.4 Hz, 1H). Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.60 H, 10.61.

4.1.29. (3*R*,4*R*,4a*R*,8a*R*)-4-(But-3-enyl)-3,4,8,8a-tetramethyl-1,3,4,4a,5,6,8a-heptahydronaphthalen-2-one (42). To a stirred solution of **41** (141 mg, 0.57 mmol) in THF (4 ml) was added dropwise at 0°C a 0.5 M solution of

LHMDS in THF (1.75 ml, 0.88 mmol), and stirring was continued at rt for an additional 1 h. After cooling at −20°C, methyl iodide (0.36 ml, 5.7 mmol) was added. The reaction mixture was stirred overnight, quenched by addition of aqueous NH_4Cl, and extracted with ether. Concentration of the extract followed by purification of the residue with MPLC (hexane–AcOEt, 9:1) gave **42** (44 mg, 30%; 50% from the consumed **41**) and unreacted **41** (63 mg). **42**: oil; $[\alpha]_D^{17}=-144.1$ (*c* 0.38, $CHCl_3$); IR (film) 3080, 1709, 1641, 995, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.10 (d, *J*=6.8 Hz, 3H), 1.18 (s, 3H), 1.31–1.59 (m, 3H), 1.60 (s, 3H), 1.71 (dd, *J*=13.2, 6.6 Hz, 1H), 1.78 (dd, *J*=12.8, 2.0 Hz, 1H), 1.90 (m, 2H), 2.02–2.16 (m, 2H), 2.32 (d, *J*=15.4 Hz, 1H), 2.39 (d, *J*=15.4 Hz, 1H), 2.46 (d, *J*=6.8 Hz, 1H), 4.93 (d, *J*=10.3 Hz, 1H), 5.00 (d, *J*=17.1 Hz, 1H), 5.26 (s, 1H), 5.75 (ddt, *J*=17.1, 10.3, 6.6 Hz, 1H). Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.58 H, 10.99.

4.1.30. (3*S*,4*R*,4a*R*,8a*R*)-4-(But-3-enyl)-3,4,8,8a-tetramethyl-1,3,4,4a,5,6,8a-heptahydronaphthalen-2-one (43). According to the procedure described for the preparation of **34** from **33**, a solution of **42** (29 mg, 0.11 mmol) in 5% KOH–methanol (2 ml) was stirred at rt for 1 d. Workup followed by purification with MPLC (hexane–AcOEt, 9:1) gave **43** (29 mg, quant) as an oil: $[\alpha]_D^{17}=-99.9$ (*c* 0.93, $CHCl_3$); IR (film) 3075, 1713, 1641, 996, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (s, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 0.98 (s, 3H), 1.35 (m, 1H), 1.51–1.68 (m, 4H), 1.57 (s, 3H), 2.00 (dd, *J*=10.5, 1.9 Hz, 1H), 2.02 (m, 1H), 2.12 (m, 2H), 2.29 (d, *J*=11.7 Hz, 1H), 2.46 (d, *J*=11.7 Hz, 1H), 2.59 (q, *J*=6.6 Hz, 1H), 4.98 (d, *J*=11.0 Hz, 1H), 5.03 (d, *J*=17.0 Hz, 1H), 5.27 (s, 1H), 5.81 (ddt, *J*=17.0, 11.0, 6.4 Hz, 1H). Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.70; H, 10.51.

4.1.31. (3*S*,4*R*,4a*R*,8a*R*)-3,4,8,8a-Tetramethyl-4-(3-oxobutyl)-1,3,4,4a,5,6,8a-heptahydronaphthalen-2-one (44). A mixture of palladium chloride (3 mg, 0.02 mmol) and copper(I) chloride (8.8 mg, 0.08 mmol) in 10% aqueous DMF (2.2 ml) was stirred for 30 min in a stream of oxygen, after which a solution of **43** (22 mg, 0.09 mmol) in 10% aqueous DMF (1.1 ml) was added. The reaction mixture was stirred for an additional 3 h, and filtered through a short silica gel column (ether). The filtrate was washed with water and brine, and dried. Concentration followed by chromatography of the residue on silica gel (hexane–AcOEt, 4:1) gave **44** (19 mg, 79%) as crystals: mp 87–88°C, $[\alpha]_D^{17}=-83.3$ (*c* 0.39, $CHCl_3$); IR (film) 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 0.98 (s, 3H), 1.50–1.68 (m, 4H), 1.58 (s, 3H), 1.80–1.89 (m, 1H), 1.87 (dd, *J*=12.2, 1.7 Hz, 1H), 2.01–2.09 (m, 1H), 2.18 (s, 3H), 2.29 (d, *J*=11.7 Hz, 1H), 2.37–2.47 (m, 3H), 2.47 (d, *J*=11.7 Hz, 1H), 5.28 (s, 1H). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.26; H, 10.12.

4.1.32. Methyl (2*E*)-5-[(1*R*,2*S*,4a*R*,8a*R*)-1,2,4a,5-tetramethyl-3-oxo-1,2,4,4a,7,8,8a-heptahydronaphthyl]-3-methylpent-2-enoate (45) and methyl (2*Z*)-5-[(1*R*,2*S*,4a*R*,8a*R*)-1,2,4a,5-tetramethyl-3-oxo-1,2,4,4a,7,8,8a-heptahydronaphthyl]-3-methylpent-2-enoate (46). To a stirred mixture of NaH (13.2 mg, 0.33 mmol) in THF (2.5 ml) was added at 0°C a solution of trimethyl phosphonoacetate (60.7 mg, 0.33 mmol) in THF (0.5 ml). The reaction mixture was stirred for 1 h, after which a solution of **44** (18 mg, 0.065 mmol) in THF (1 ml) was added. The resulting mixture was heated at 60°C with stirring for 12 h, after cooling to rt, quenched with aqueous NH_4Cl, and extracted with ether. Removal of the solvent followed by purification of the residue with MPLC (hexane–AcOEt, 4:1) gave **45** (15 mg, 69%) and **46** (3.5 mg, 16%) along with unreacted **44** (2 mg, 11%).

Compound **45**: crystals; mp 65–65.5°C; $[\alpha]_D^{24}=-94.2$ (*c* 0.47, $CHCl_3$); IR (film) 1721, 1715, 1646, 1228, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (s, 3H), 0.94 (d, *J*=6.8 Hz, 3H), 0.97 (s, 3H), 1.41 (m, 1H), 1.57 (s, 3H), 1.65–1.73 (m, 3H), 1.98 (dd, *J*=12.2, 1.7 Hz, 1H), 2.00–2.17 (m, 4H), 2.29 (d, *J*=1.2 Hz, 3H), 2.30 (d, *J*=11.7 Hz, 1H), 2.46 (d, *J*=11.7 Hz, 1H), 2.55 (q, *J*=6.8 Hz, 1H), 3.69 (s, 3H), 5.29 (s, 1H), 5.69 (s, 1H). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.53; H, 9.60.

Compound **46**: oil; $[\alpha]_D^{24}=-104.4$ (*c* 0.39, $CHCl_3$); IR (film) 1718, 1652, 1210, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.37(s, 3H), 0.98 (s, 3H), 0.99 (d, *J*=6.8 Hz, 3H), 1.36 (m, 1H), 1.55–1.58 (m, 1H), 1.58 (s, 3H), 1.71 (m, 1H), 1.83 (dd, *J*=13.1, 6.1 Hz, 1H), 1.90 (s, 3H), 2.04 (dd, *J*=12.2, 1.5 Hz, 1H), 2.17–2.21 (m, 2H), 2.33 (d, *J*=11.7 Hz, 1H), 2.46 (d, *J*=11.7 Hz, 1H), 2.60 (m, 2H), 2.69 (q, *J*=6.8 Hz, 1H), 3.67 (s, 3H), 5.29 (s, 1H), 5.67 (s, 1H).

4.1.33. (2*E*)-5-[(1*R*,2*S*,4a*R*,8a*R*)-1,2,4a,5-Tetramethyl-3-oxo-1,2,4,4a,7,8,8a-heptahydronaphthyl]-3-methylpent-2-enoic acid (7-oxo-kolavenic acid) (1). To a stirred solution of **45** (25 mg, 0.08 mmol) in methanol (1.5 ml) was added a 0.5 M KOH aqueous solution (1.5 ml, 0.75 mmol). The reaction mixture was heated at 40°C for 6 h, cooled to rt, made acidic with 0.5 M HCl solution, and extracted with ether. Concentration followed by purification of the residue with HPLC (hexane–AcOEt, 4:1) gave **1** (17 mg, 69%) as an oil: $[\alpha]_D^{19}=-95.2$ (*c* 0.82, $CHCl_3$) whose spectral data (IR and ^1H NMR) were identical with those of natural **1**.[12]

4.2. Methyl solidagonate (48)

To a stirred solution of **45** (14 mg, 0.04 mmol) in methanol (1.5 ml) was added at −50°C sodium borohydride (1.5 mg, 0.04 mmol), and stirring was continued for 3.5 h. The solvent was mostly removed off under reduced pressure, and the oily residue was filtered through a short silica gel column (ether). Concentration of the filtrate followed by purification of the residue with MPLC (hexane–AcOEt, 4:1) gave **47** (14 mg, 99%).

4.2.1. Methyl (2*E*)-5-[(1*R*,2*R*,3*S*,4*R*,6*R*)-4-hydroxy-2,3,6,7-tetramethylbicyclo[4.4.0]dec-7-en-2-yl]-3-methylpent-2-enoate (47). Oil; $[\alpha]_D^{13}=-76.8$ (*c* 0.73, $CHCl_3$); IR (film) 3536, 1717, 1645, 1210, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (s, 3H), 1.03 (d, *J*=7.0 Hz, 3H), 1.29 (s, 3H), 1.35–1.43 (m, 3H), 1.46–1.62 (m, 5H), 1.63 (s, 3H), 1.88–2.12 (m, 4H), 2.11 (dd, *J*=14.3, 2.8 Hz, 1H), 2.17 (d, *J*=1.2 Hz, 3H), 3.69 (s, 3H), 4.04 (s, 1/2H=9.0 Hz, 1H),[29] 5.16 (s, 1H), 5.66 (s, 1H).

A mixture of **47** (11.4 mg, 0.034 mmol), 4-dimethylaminopyridine (a catalytic amount), acetic anhydride (0.01 ml, 0.11 mmol), and pyridine (0.5 ml) was stirred for 1 h, quenched with methanol (0.01 ml) followed by aqueous NH_4Cl, and extracted with ether. Concentration of the extract left an oily residue, which was filtered through a short silica gel column (ether). Removal of the solvent followed by purification of the residue with MPLC (hexane–AcOEt, 6:1) gave unreacted **47** (2 mg, 18%) and **48** (6 mg, 44%): crystals; 104–105°C; $[\alpha]_D^{13}=-83.4$ (*c* 0.24, EtOH), $[\alpha]_D^{13}=-75.9$ (*c* 0.29, $CHCl_3$); lit.[14] $[\alpha]_D^{12}=-98.8$ (*c* 1.80, EtOH); IR (KBr) 1732, 1720, 1645, 1252, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, *J*=7.0 Hz, 3H), 0.99 (s, 3H), 1.18 (s, 3H), 1.45 (m, 3H), 1.49–1.70 (m, 4H), 1.59 (s, 3H), 1.88–2.14 (m, 4H), 2.06 (s, 3H), 2.13 (dd, *J*=14.8, 2.8 Hz, 1H), 2.15 (d, *J*=1.2 Hz, 3H), 3.63 (s, 3H), 5.12 (m, 1H), 5.16 (s, 1H), 5.66 (s, 1H). Spectral data (IR and ^1H NMR) of synthetic **48** were identical with those of methyl ester of natural **2**.[14]

4.2.2. (4a*S*,8a*R*)-4,8,8a-Trimethyl-1,4a,5,6,8a-pentahydronaphthalen-2-one (11). A solution of **10** (52 mg, 0.27 mmol) and acetyl chloride (0.04 ml, 0.54 mmol) in methanol (1 ml) was stirred at 0°C for 1 h, and filtered through a short silica gel column (ether). Evaporation of the solvent followed by purification of the oily residue by MPLC (hexane–AcOEt, 4:1) gave **11** (48 mg, 92%): oil; $[\alpha]_D^{26}=-125.3$ (*c* 0.27, $CHCl_3$); IR (film) 3026, 1668, 1619, 882, 836, 803 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.53–1.61 (m, 1H), 1.65 (s with fine splittings, 3H), 1.87–1.93 (m, 1H), 2.01 (d, *J*=1.2 Hz, 3H), 2.04–2.13 (m, 2H), 2.40 (m, 3H), 5.42 (d, *J*=1.2 Hz, 1H), 5.86 (s, 1H); ^1H NMR (C_6D_6) δ 0.91 (s, 3H), 1.16–1.26 (m, 1H), 1.39–1.42 (m 1H), 1.42 (d, *J*=1.2 Hz, 3H), 1.44 (s with fine splittings, 3H), 1.62 (dd, *J*=11.7, 2.9 Hz, 1H), 1.70–1.79 (m, 2H), 2.27 (d, *J*=16.4 Hz, 1H), 2.39 (d, *J*=16.4 Hz, 1H), 5.19 (s with fine splittings, 1H), 5.87 (d, *J*=1.2 Hz, 1H); HRMS *m/z* calcd for $C_{13}H_{18}O$ $[M]^+$: 190.1358; found 190.1350. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.10; H, 9.60.

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15. The numbering system used here except that in Section 4 follows the natural product numbering for clerodanes.
16. The term *trans* and *cis* refer to whether the C(3)-methyl group points away from (*trans*) or toward (*cis*) the *gem*-dimethyl bridge.
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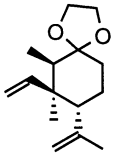
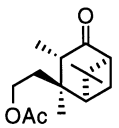
18. For discussion on isomerization of a substituent at the C(3) position, see Ref. 9.
19. Such a trend was observed in cyclobutane-ring opening of 3,4,4-trisubstituted nopinones possessing the C(3)-alkyl group with *cis* configuration toward the *gem*-dimethyl bridge. This may be caused by competing facile enolization of the ketone function in these nopinones. Details will be reported elsewhere together with results on other related substrates.
20. This is because there is no regioselectivity in the hydroboration reaction using 9-BBN between the two double bonds of the diene **vi** which was prepared from **15** with hydrolysis followed by acetallization.

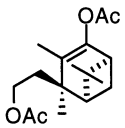


vi

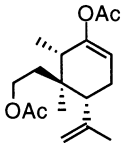
21. In analogy with **14**, cyclobutane opening of *cis*-3-methyl nopinone **vii**, prepared from **14** according to the method described for preparation of *21* from *13*, was unsuccessful at room temperature. On heating at 60°C, the reaction provided enol acetate **viii** (44%) and ring-opened enol acetate **ix** (11%) along with unreacted **vii** (30%). See Ref. 19.



vii



viii



ix

22. Stereochemistry of the C(3) chiral center in this compound was evidenced by the NOE correlations of **32** (vide infra).
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28. NOE correlations indicated that the compound **42** is in equilibrium between the boat and chair conformation with regard to the B-ring, in analogy with **33** mentioned above.
29. The term 1/2H refers to the half band width.