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Synthetic study of hetisine-type aconite alkaloids. Part 1: Preparation of tetracyclic intermediate containing the C14–C20 bond

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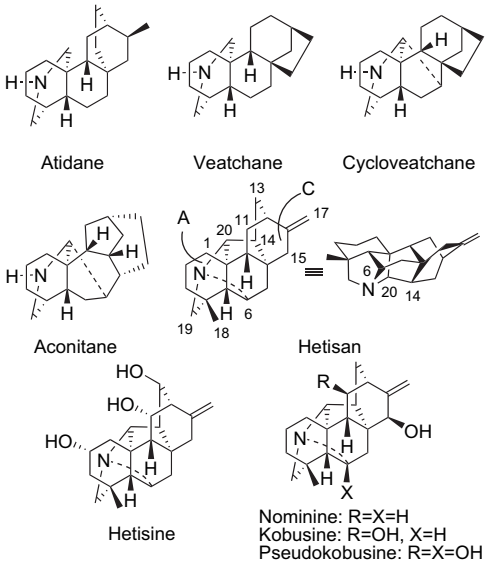
Abstract—Full details for the total synthesis of (±)-nominine, a hetisine-type aconite alkaloid, are presented in three parts. Here (part 1), we describe the preparation of the key tetracyclic intermediate **6**. Our palladium-catalyzed intramolecular α-arylation was adopted for preparation of the intermediate **4** with an angular formyl group. An acetal–ene reaction was then employed for C14–C20 bond formation to secure **6** from **5**. The reaction mechanism of the acetal–ene reaction is discussed, and a method for removal of the 2-hydroxyethyl group from **6** is developed.

1. Introduction

1.1. The aconite alkaloids

Aconitum, which has a beautiful blue-purple flower, is well-known as a poisonous herb, which occasionally results in fatalities following accidental ingestion. The aconite alkaloids, mainly contained in the tuberous root, have long been of interest to researchers, because of both their pharmacological activity and their structural complexity.[1,2] Alkaloids with similar structures have also been isolated from plants of the species *Delphinium*, *Consolida*, *Thalictrum*, and *Spiraea*, and these are included in the so-called aconite alkaloids. Over 400 aconite alkaloids have so far been isolated and structurally characterized.[1,2]

The fundamental structural frameworks of these alkaloids are generally classified into five skeletons, i.e., atidane, veatchane, cycloveatchane, aconitane, and hetisan (Scheme 1). Extensive synthetic studies of these pharmacologically important alkaloids for about 40 years have led to the total synthesis of several alkaloids belonging to the first four of the above five groups: atisine[3] (atidane), veatchine[4] (veatchane), garryine[5] (veatchane), napelline[6] (cycloveatchane), delphinine[7] (aconitane), talatisamine[8] (aconitane), and chasmanine[9] (aconitane). However, attempts to construct even a simple hetisan skeleton (the name of which is derived from hetisine), not to mention total synthesis of a hetisan alkaloid, have remained unsuccessful since the structure of hetisine was first clarified by X-ray crystal-structure analysis in 1962.[10] The heptacyclic hetisan skeleton is the most structurally complex among the above five frameworks, and incorporates two additional bonds, N–C6 and C14–C20, relative to the atidane skeleton, as exemplified by nominine, kobusine, and pseudokobusine (Scheme 1). The synthetic difficulty of the skeleton stems from the presence of these two bonds.



Scheme 1. Five representative aconite skeletons and examples of hetisine-type alkaloids.

Keywords: Aconite; Alkaloid; α-Arylation; Palladium catalyst; Acetal–ene reaction.
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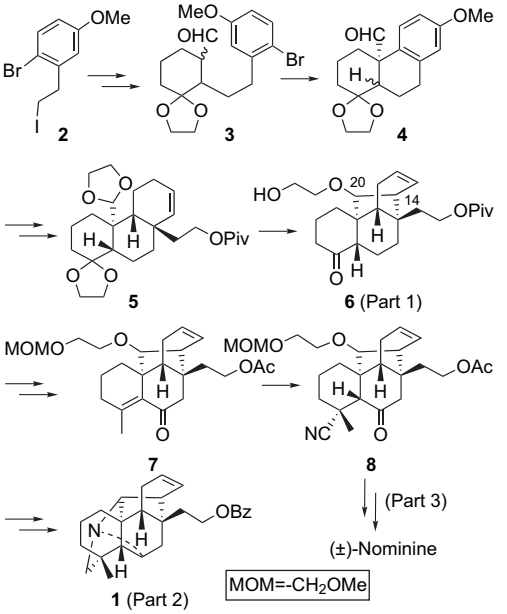
1.2. Synthetic background

Several years ago, we developed a novel palladium-catalyzed intramolecular α-arylation of aliphatic ketone, formyl, and nitro groups[11] during the course of our synthetic studies of duocarmycin SA analogs.[12] As an application of this reaction, we embarked on synthetic studies of the hetisine-type aconite alkaloids. Our fundamental synthetic strategy was to form the N–C6 and C14–C20 bonds at an early stage of the synthetic route, because it would become more difficult to connect them at a later stage, as these two bonds greatly restrict the molecular conformation. Thus, stereocontrol was expected to be easier with early introduction of these two bonds.

We first reported the preparation of the hexacyclic compound **1** lacking the C-ring of the hetisan skeleton, starting from compound **2** by way of the intermediates **3**–**8** (Scheme 2).[13] Our further synthetic efforts culminated in a total synthesis of (±)-nominine (Scheme 1), the simplest hetisine-type aconite alkaloid.[14] In this and the next papers (parts 1 and 2), we present full details for the preparation of **1**. In part 3, we describe the total synthesis of (±)-nominine, diverging from the intermediate **8**. These three papers thus describe the first synthesis of a hetisine-type aconite alkaloid. Five synthetic investigations have been reported so far, leading toward the total synthesis of this class of aconite alkaloids.[15–19]

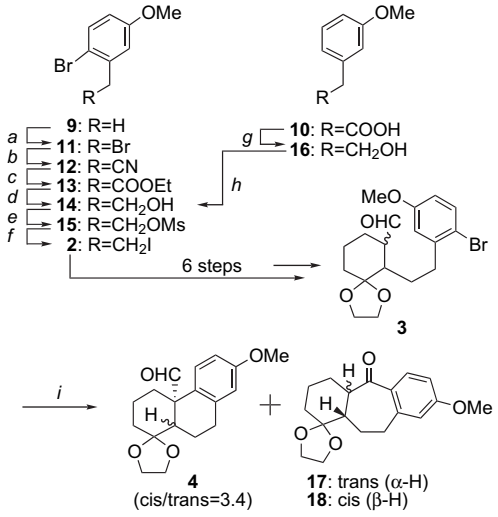


Scheme 2. Outline of the preparation of **1** from **2**.

2. Results and discussion

2.1. Preparation of tetracyclic intermediate 4

We have already reported in detail the preparation of compound **4**, starting from **2** via the precursor **3** by means of a palladium-catalyzed intramolecular cyclization reaction (Scheme 2).[11b,c] While the starting material **2** is a known compound,[21] the literature methods seemed inappropriate for large-scale preparation.[20,21] Therefore, we prepared it from 1-bromo-4-methoxy-2-methylbenzene (**9**) or 3-methoxyphenylacetic acid (**10**) by modification of the method of Ghatak[20] or Meyers[21] (Scheme 3), respectively. The cyclization step of **3** to **4** was also improved for the large-scale preparation.



Scheme 3. Large-scale preparation of **2** and **4**: (a) NBS, BPO, CCl_4, Ref. 20; (b) KCN, EtOH–H_2O, **12** 92%; (c) H_2SO_4, EtOH, **13** 90%; (d) DIBAL-H, CH_2Cl_2, **14** 96%; (e) MsCl, Et_3N, CH_2Cl_2, **15** 99%; (f) NaI, acetone, **2** 96%; (g) ClCOOMe, Et_3N, THF, then $NaBH_4$, THF–H_2O, **16** 95%; (h) Br_2, $CHCl_3$, Ref. 21; (i) $PdCl_2(Ph_3P)_2$, Cs_2CO_3, Ph_3P, THF, **4** 71%, **17** 4%, **18** 2%.

2.1.1. Preparation of 1-bromo-2-(2-iodoethyl)-4-methoxybenzene (2). 1-Bromo-2-bromomethyl-4-methoxybenzene (**11**), prepared from **9** according to the literature,[20] was treated with potassium cyanide (KCN) in ethanol–water (EtOH–H_2O) to afford **12** in 92% yield (Scheme 3). Alcoholysis of **12** with sulfuric acid (H_2SO_4) in EtOH afforded the ethyl ester **13** in 90% yield. Transformation of **13** to **2** was carried out readily by (i) reduction with diisobutylaluminum hydride (DIBAL-H), (ii) methanesulfonylation of the resulting primary alcohol to form **15**, and (iii) iodination with sodium iodide (NaI) in acetone to give **2** in yields of 96, 99, and 96%, respectively. Alternatively, compound **14** was prepared from **10** as follows: reduction of the carboxylic acid **10** to an alcohol **16** was carried out with (i) methyl chloroformate (ClCOOMe), triethylamine (Et_3N), and (ii) sodium borohydride ($NaBH_4$) in 95% yield, and subsequent bromination according to the literature[21] readily afforded the intermediate **14**.

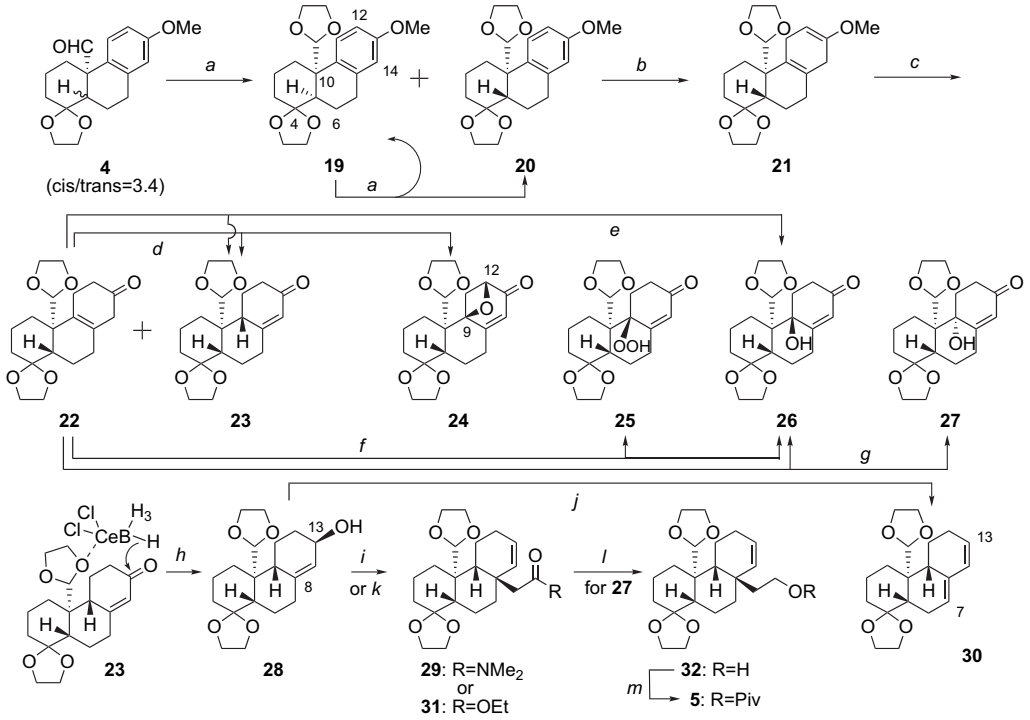
2.1.2. Palladium-catalyzed cyclization of 3. Transformation of the above-obtained **2** to the precursor **3** was executed according to the reported route in six steps.[11c] In our previous reports, **4** (cis/trans = 4.2, the structure of the major cis isomer had been established by the X-ray analysis[11c]) was obtained by the treatment of **3** with dichlorobis(triphenylphosphine)palladium(II) [$PdCl_2(Ph_3P)_2$], cesium carbonate (Cs_2CO_3) in tetrahydrofuran (THF) in 65% yield. On a larger scale, however, precipitation of black palladium metal was observed and the reaction ceased in mid-course. The reaction proceeded reproducibly to completion in the presence of triphenylphosphine [Ph_3P, 0.2 equiv, $PdCl_2(Ph_3P)_2$

(9 mol %), Cs_2CO_3 (1.6 equiv) in refluxing THF for 60 h on a 32 mmol scale], though a longer reaction time was required than in the case without the addition of Ph_3P. Under these conditions, the desired **4** (inseparable mixture of cis and trans isomers in a ratio of cis/trans = 3.4) was obtained in 71% yield, accompanied with by-products **17** (4%) and **18** (2%).

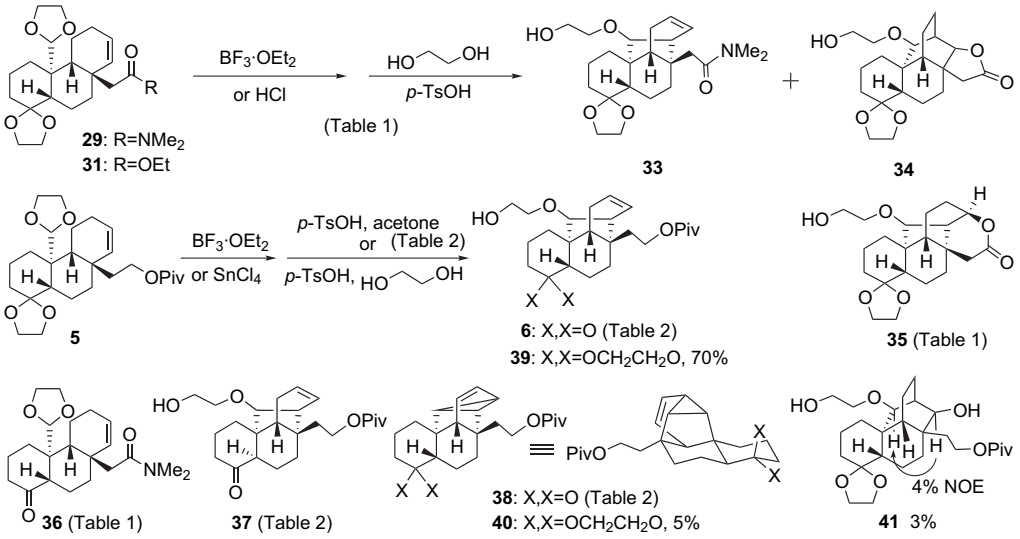
2.2. Transformation of 4 to 5

2.2.1. Transformation of 4 to the enone–diacetal 23. Acetalization of **4** (cis/trans = 3.4) with *p*-toluenesulfonic acid (*p*-TsOH) and ethylene glycol in refluxing benzene afforded readily separable *cis* (**19**) and *trans* (**20**) diacetals in 61% and 34% yields, respectively (Scheme 4). An acid-catalyzed equilibration was observed at the C5 position adjacent to the original acetal group at C4, and the ratio of the desired trans isomer **20** improved (**19**/**20**=1.8). This equilibration was conveniently leveraged for the conversion of **19** to **20** by repeated acetalization of the isolated cis isomer **19** to give recovered **19** (61%) and **20** (35%). For the elaboration of the anisole ring, the diacetal **20** was submitted to Birch reduction with lithium (Li) metal in liq. ammonia (NH_3) and THF–EtOH to give the dihydro compound **21** in 92% yield. Brief exposure of **21** to 0.5% hydrochloric acid (HCl) in THF–H_2O (4:1) afforded the β,γ-enone **22** (88%) along with the α,β-enone **23** (7%), the two acetal groups being kept intact. The former was treated with sodium methoxide (NaOMe) in methanol (MeOH) to yield **23** (55%) and an oxetane **24** (10%), accompanied with recovery of **22** (10%). It is likely that partial air oxidation took place at C9 of **23** during the alkaline treatment, and the resulting hydroperoxide **25** was attacked nucleophilically by the enolate anion at C12 (hetisan numbering) to yield **24**. This was confirmed by the fact that on further addition of dimethyl sulfide (Me_2S) to the alkaline treatment, the γ-hydroxy-α,β-enone **26** was obtained in 14% yield in place of **24**, in addition to **23** (58%) and recovered **22** (13%). Treatment of **22** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene gave **25** (18%), **26** (19%), and recovered **22** (40%).[22] To prove the structure, compound **26** was synthesized through an alterative approach, as follows. Epoxidation of **22** was carried out with *m*-chloroperbenzoic acid (*m*-CPBA) as usual, and then the resulting mixture was treated with DBU to provide **26** (61%) along with its stereoisomer **27** (34%).

2.2.2. Preparation of 5 from 23. Reduction of the above-obtained enone **23** with $NaBH_4$ in the presence of cerium chloride ($CeCl_3$) was found to afford the desired β-allyl alcohol **28** exclusively in 94% yield. The half height *J* value (19 Hz) of H13 (hetisan numbering) in the ^1H NMR spectrum of **28** implies an axial orientation, and this means that the 13-hydroxy group must take equatorial β-configuration. The reason why we need the β-allyl alcohol **28** is that the stereochemistry of C8 accurately reflects that of the angular C13 in the next two carbons (corresponding to C15 and C16 of the hetisan skeleton) elongation at C13 by Claisen rearrangement. Coordination of the oxygen atom of the 1,3-dioxolanyl group at C10 to the cerium borohydride species resulted in the desired one-sided reduction of the carbonyl group from the α side to give **28**, as depicted in Scheme 4.[23]



Scheme 4. Transformation of **4** to **5**: (a) $(CH_2OH)_2$, *p*-TsOH, benzene, **19** 61% and **20** 34% from **4**; **19** 61% and **20** 35% from **19**; (b) Li, EtOH, liq. NH_3–THF, **21** 92%; (c) 0.5% HCl, THF–H_2O (4:1), **22** 88%, **23** 7%; (d) NaOMe, MeOH, **23** 55%, **24** 10%, recovery of **22** 10%; (e) NaOMe, Me_2S, MeOH, **23** 58%, **26** 14%, recovery of **22** 13%; (f) DBU, benzene, **25** 18%, **26** 19%, recovery of **22** 40%; (g) *m*-CPBA, CH_2Cl_2, then DBU, benzene, **26** 61%, **27** 34%; (h) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, **28** 94%; (i) *N*,*N*-Dimethylacetamide dimethyl acetal, toluene, 160 °C (sealed tube), **29** 69%; (j) Ac_2O, pyridine, CH_2Cl_2, **30** 86%; (k) $MeC(OEt)_3$, *t*-BuCOOH, 160 °C (sealed tube), **31** 21%; (l) $BH_3 \cdot NH_3$, BuLi, THF, **32** 94%. (m) Piv_2O, Et_3N, 4-DMAP, CH_2Cl_2, **5** 98%.



Scheme 5. Acetal–ene reaction of **29**, **31**, and **5**.

Then **28** was exposed to *N*,*N*-dimethylacetamide dimethyl acetal in toluene at 160 °C (sealed tube) to obtain the acetamide **29** in 69% yield.[24] An inseparable mixture of dehydrated dienes was formed as by-products. Of the two dienes, the $\Delta_{7,8}$ and $\Delta_{13,14}$ isomer **30** was formed exclusively on acetylation of **28** with acetic anhydride (Ac_2O) in pyridine by spontaneous elimination of acetic acid from the intermediary allyl acetate. Usual Claisen reaction with ethyl orthoacetate and pivalic acid afforded only 21% yield of **31**. As the next acetal–ene reaction of **29** was subject to a serious side reaction due to the side chain at C8 (vide infra), the amide **29** was reduced with the reagent prepared in situ from *n*-butyllithium (*n*-BuLi) and borane–ammonia complex ($BH_3\cdot NH_3$) to provide **32** in 94% yield.[25] The alcohol **32** was protected as the pivaloate with pivalic anhydride (Piv_2O) and Et_3N in the presence of 4-dimethylaminopyridine (4-DMAP) to afford **5** in 98% yield. The bulky pivaloyl protecting group was selected to prevent the side reaction in the next acetal–ene reaction. Pivaloylation with pivaloyl chloride (PivCl) and Et_3N is much faster than that with Piv_2O, but it occasionally afforded an intractable mixture, especially on large-scale reaction, probably due to ring opening of the dioxolane ring at C4 to form (2-pivaloyloxy)ethyl enol ether.

2.3. Formation of the C14–C20 bond

2.3.1. Acetal–ene reaction of 29, 31, and 5. First, the substrate **29** was subjected to the acetal–ene reaction[26] (Scheme 5). A dichloromethane (CH_2Cl_2) solution of **29** was treated with boron trifluoride diethyl etherate ($BF_3\cdot OEt_2$) at −18 °C to provide the expected compound **33** in only 21% yield, along with the pentacyclic lactone **34** in 72% yield as a by-product after reacetalization of the partially deprotected 4-carbonyl group (Table 1, run d). Since the employment of CH_2Cl_2 as the reaction solvent resulted in the desired **33** being a minor product, we looked for other reaction solvents in order to improve the yield of **33** (Table 1). Among the solvents tested, toluene was found to be the best, giving **33** (41%) and **34** (48%) (run b). The reaction temperature also affected the yield, and reaction at −18 °C (run b) gave the best yield of **33** among runs b, f, and g. A less polar solvent, cyclohexene–$PhCH_3$ (6:1) resulted in a lower yield of **33** with a new by-product **35** in 10% yield. The acetal–ene reaction of the ester **31** under the best conditions for **29** gave no desired compound corresponding to **33**, but only **34** in 66% yield (run i). Treatment of **29** with dilute HCl also afforded the lactone **34** in 64% yield, together with a ketone **36** in 26% (run h).

Table 1. Acetal–ene reaction of **29**, **31** to form **33**, **34**, **35**, **36** (Scheme 5)

Run	Substrate	Acid	Solvent	Temp (°C)	Time (h)	Yield (%)			
						33	**34**	**35**	**36**
a	**29**	$BF_3\cdot OEt_2$		−18	2	18	63	10	—
b	**29**	$BF_3\cdot OEt_2$	$PhCH_3$	−18	2	41	48	—	—
c	**29**	$BF_3\cdot OEt_2$	$ClCH_2CH_2Cl$	−18	3	14	69	—	—
d	**29**	$BF_3\cdot OEt_2$	CH_2Cl_2	−18	2	21	72	—	—
e	**29**	$BF_3\cdot OEt_2$	CH_3NO_2	−18	2	—	77	—	—
f	**29**	$BF_3\cdot OEt_2$	$PhCH_3$	−80 to −40	4	16	62	—	—
g	**29**	$BF_3\cdot OEt_2$	PhH	19	1	28	42	—	—
h[a]	**29**	0.5% HCl	THF–H_2O (4:1)	0	1	—	64	—	26
i	**31**	$BF_3\cdot OEt_2$	$PhCH_3$	−18	2	—	66	—	—

[a] Products were separated without reacetalization with ethylene glycol and *p*-TsOH.

Judging from the above result that even an ester group cyclized to form the lactone **34**, it seemed possible that not only the alcohol **32** but also its acetate would give the corresponding cyclized products in their acetal–ene reactions. Therefore, as mentioned in Section 2.2, we selected a bulky pivaloyl group to protect the alcohol **32**, affording **5**, which was subjected to the acetal–ene reaction under a variety of reaction conditions (Table 2). The products were, this time, purified after deprotection of the C4 acetal group by treatment with *p*-TsOH in acetone. When the reaction was carried out in toluene at below −18 °C, we obtained compound **6** in a good yield of 66% (runs d, e). Careful separation of the reaction products of run d provided two more compounds, **37** (3%) and **38** (3%), as by-products. The ene reaction under the conditions of run d followed by reacetalization as above provided **39** (70%), together with **40** (5%) and **41** (3%).

Table 2. Acetal–ene reaction of **5** to form **6**

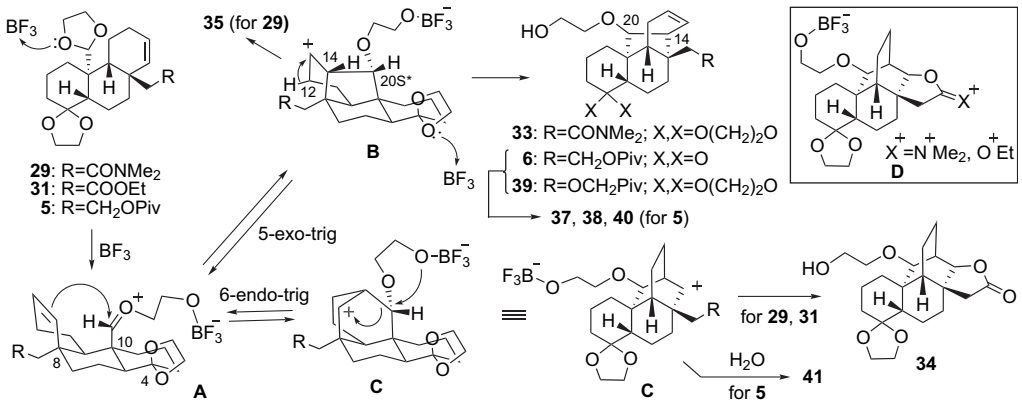
Run	Lewis acid	Solvent	Temp (°C)	Time (h)	**6** (%)
a	$BF_3\cdot OEt_2$	CH_2Cl_2	−18	2	55
b	$BF_3\cdot OEt_2$	$ClCH_2CH_2Cl$	−18	2	50
c	$BF_3\cdot OEt_2$	CS_2	−18	2	55
d	$BF_3\cdot OEt_2$	$PhCH_3$	−18	1	66[a]
e	$BF_3\cdot OEt_2$	$PhCH_3$	−70 to −50	2	66
f	$BF_3\cdot OEt_2$	$PhCH_3$	−18	0.17	59
g	$SnCl_4$	$PhCH_3$	−18	2	45

[a] By-products **37** (3%) and **38** (3%) were also isolated.

2.3.2. Reaction mechanism of the acetal–ene reaction. The reaction mechanism for the acetal–ene reaction is considered to be as follows. Coordination of the dioxolane oxygen at C10 (hetisan numbering) of **29**, **31**, and **5** to BF_3 gives rise to an intermediate **A**, in which the oxonium cation is arrayed so as to circumvent the steric congestion between the two 1,3-diaxial substituents at C4 and C8, as depicted in **A** (Scheme 6). Nucleophilic attack from the olefin to the oxonium cation takes place in two different modes, 5-*exo-trig* and 6-*endo-trig*, giving intermediates **B** and **C**, respectively. These reaction paths can explain the *S** stereochemistry of C20 in **B** and the corresponding carbon in **C**. Deprotonation from C12 of **B** affords **33** from **29** and **6** from **5**. In the case of **C**, on the other hand, there are no eliminable protons to form an olefin, because the two carbons lying adjacent to the cation are a tertiary bridgehead carbon and a quaternary carbon. Therefore, when the intermediate **C** carrying a nucleophilic C8 side chain is derived from **29** and **31**, intramolecular cyclization occurs to form the lactone **34** by way of the intermediary cation **D**. On the contrary, this cyclization is not able to occur from **C**, derived from **5**, because the bulkiness of the pivaloyl group prevents the cyclization and results in retro-ene reaction to afford **6** eventually, by way of **A** and **B**. The stereochemistry of **33** was born out by the fact that 4% NOE enhancement was observed at H20 (δ 4.44, d, J=6.5 Hz) on irradiation at H14 (δ 2.91, ddd, J=7, 6.5, 1.5 Hz) in the ^{1}H NMR spectrum. Analogously, observation of the NOE enhancement between two protons of **34** at δ 3.85 (d, J=3 Hz) and at δ 4.26 (d, J=4 Hz) supports the structure; they were assigned to the two protons on the carbons bearing the (2-hydroxyethyl)oxy group and the lactone O atom, respectively. The IR spectrum of **34** (ν_{max}=1767 cm^{-1}) is also consistent with the 5-membered lactone structure.

Partial cyclization from the intermediate **B** from **29** gives rise to the by-product **35**, whose IR spectrum (ν_{max}=1719 cm^{-1}) is consistent with the 6-membered lactone structure. Formation of the cis isomer **37** is attributable to enolization brought about by coordination of the C4 acetal or carbonyl group to BF_3. A sequence of reactions on **6**, coordination of the oxygen at C20 to BF_3 followed by cyclization from $\Delta_{12,13}$ to C20 in 3-*exo-trig* mode, and deprotonation from C11 provides an explanation for the formation of the by-products **38** and **40**. Compound **41**, obtained in a small amount, is a by-product generated by trapping of the intermediary cation of the 6-*endo-trig* route with water at quenching of the reaction. The orientation of the secondary hydroxy group of **41** was determined by the fact that there is a 4% NOE enhancement between the two protons on the carbons bearing oxygen in the bicyclo[2.2.2]octane framework, as depicted in Scheme 5.

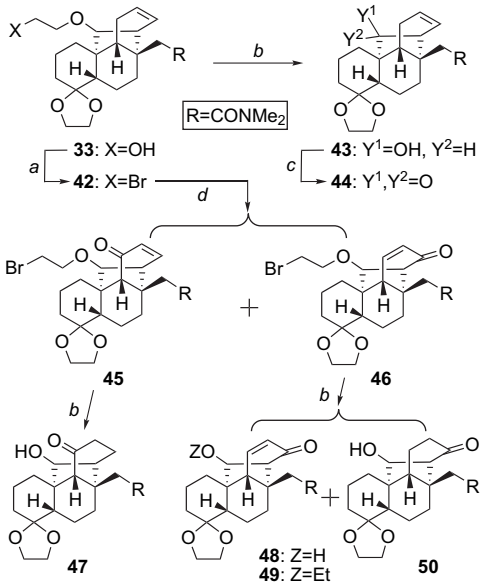
2.3.3. Suitability of 2-hydroxyethyl group to protect the C20 hydroxy group and model study for its removal. The above acetal–ene reaction furnished the desired tetracyclic products **33**, **6**, and **39** with a 2-hydroxyethyl protecting group at the C20 hydroxy group. The ene reaction proceeds, needless to say, starting from an aldehyde as well as an acetal. However, this protecting group plays a critical role in the total synthesis of (±)-nominine in the following respects. (1) The compound without a protecting group on the C20 hydroxy group is in danger of undergoing C14–C20 bond fission through the retro-ene reaction. In addition, it would



Scheme 6. Reaction mechanism of the acetal–ene reaction to form the C14–C20 bond.

be difficult to protect the hydroxy group on C20 because of steric hindrance. In the case of the compounds **33**, **6**, and **39**, the 2-hydroxyethyl group (originated from ethylene glycol) conveniently protected the hydroxy group. (2) As the 2-hydroxyethyl group is an extremely stable protecting group, provided the terminal primary hydroxy group is protected appropriately, it can readily tolerate a variety of reaction conditions encountered in the subsequent synthetic route. (3) The 2-hydroxyethyl group can be removed with ease by bromination followed by mild reduction with zinc in alcohol–H_2O.

We confirmed these features by means of the following model reactions with compound **33** (Scheme 7). Compound **33** was readily brominated with carbon tetrabromide (CBr_4) and Ph_3P to afford **42** in 87% yield. Then smooth removal of the 2-bromoethyl group was carried out by exposure of **42** to zinc (Zn) in refluxing 2-propanol–H_2O (14:1) with ammonium chloride (NH_4Cl) to afford **43** in the high yield of 94%. Taking into consideration the prospective construction of the azabicyclo ring system of the hetisan framework, we tried to protect this hydroxy group with an acyl group, such as acetyl, methanesulfonyl, or trifluoromethanesulfonyl. However, these trials resulted in a recovery of **43** due to the steric congestion around the hydroxy group. Oxidation of **43** with Dess–Martin periodinane[27] provided **44** in a good yield.



Scheme 7. Model deprotection of the 2-hydroxyethyl group and allylic oxidation of **33**: (a) Br_4C, Ph_3P, CH_2Cl_2, **42** 87%; (b) Zn, NH_4Cl, 2-PrOH-H_2O (14:1), **43** 94% from **42**; **47** 89% from **45**; **48** 49%, **49** 9%, **50** 39% from **46**; (c) Dess–Martin periodinane, CH_2Cl_2, **44** 92%; (d) CrO_3, 3,5-dimethylpyrazole, **45** 28%, **46** 28%, recovery of **42** 29%.

2.4. Further transformation from the acetal–ene reaction products

With the desired compounds **33**, **6**, and **39** in hand, we next examined further transformation toward the hetisan skeleton, including nominine. The basicity of the nitrogen on the azabicyclo ring system is so strong that it would be troublesome to carry on the synthesis employing the intermediates bearing the ring system. So we envisioned construction of the azabicyclo ring preferably at a later stage of the total synthesis. Thus, we directed our attention to functionalization of C11, C6, or the side chain at C8. Here, we describe an attempt to functionalize C11 of **33** by allylic oxidation.

A number of aconite alkaloids, such as kobusine and pseudokobusine, carry an oxygen function (carbonyl or hydroxy group) at C11 (Scheme 1). To begin with, allylic oxidation of **42** was examined (Scheme 7). Chromium trioxide (CrO_3, 12 equiv) oxidation in the presence of 3,5-dimethylpyrazole[28] gave favorable results, giving **45** and **46** in 28% yield each, along with a recovery of **42** in 29% yield. Further excess of the oxidizing reagent caused a significant drop in the yields. Although the oxidation did not afford the desired product **45** in satisfactory yield and the regioisomeric enone **46** was obtained in the same amount, some alkaloids such as hetisine and spirasine IV have an oxygen function at this position, C13.[1,2]

The above reductive deprotection of the hydroxy group at C20 was carried out for **45** and **46**. The sole product from **45** was a saturated keto–alcohol **47**: the enone group was incompatible with the reductive conditions. The enone–alcohol **48** was produced from **46**, but compound **50**, corresponding to **47** and the debrominated product **49**, were also isolated. Thus, it proved complicated to functionalize C11 of **33**. However, some clues were obtained for functionalization of C11 and for C-ring formation by the connection of C12 and the side chain at C8.

In part 2, we will describe some attempts at C-ring formation and the functionalization of C6 for the construction of the pyrrolidine ring, leading to the synthesis of a hexacyclic compound **1** lacking the C-ring of the hetisan skeleton.

3. Conclusion

In summary, we have synthesized the tetracyclic synthetic intermediates **33**, **6**, and **39** for hetisine-type aconite alkaloids, utilizing the following key reactions: (i) palladium-catalyzed intramolecular α-arylation at the formyl group (**3**→**4**), and (ii) acetal–ene reaction to form the C14–C20 bond (**29**→**33**, **5**→**6**, **5**→**39**). This was a substantial step toward the first total synthesis of hetisine-type aconite alkaloids. In the subsequent papers, we report further efforts toward this goal.

4. Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus (hot plate), and are not corrected. MS and high-resolution MS (HRMS) were recorded on a Hitachi M-80B spectrometer in a gas chromatography (GC) or direct inlet (DI) mode at an ionizing voltage of 70 eV, and figures in parentheses indicate the relative intensities. IR spectra were measured on a Hitachi 215 or Shimadzu IR-460 spectrophotometer. ^1H NMR spectra were obtained on a Varian Mercury 300 (300 MHz) in $CDCl_3$ unless otherwise specified and coupling constants (J values) are rounded to the nearest 0.5 Hz. ^{13}C NMR spectra were measured on a Varian Mercury 300 (75 MHz) in

$CDCl_3$ and ^{13}C multiplicities are shown in parentheses as CH_3 (primary), CH_2 (secondary), CH (tertiary), and C (quaternary). The NMR signals were assigned using proton decoupling techniques, as well as gCOSY, DEPT, gHSQC, gHMBC, and/or NOESY spectra. Some characteristic ^1H and ^{13}C NMR signals were selected and assigned as HX and CX, respectively, where X represents hetisan carbon numbering. Column chromatography was conducted on silica gel (SiO_2, Fuji Davison BW 200), and the weight of SiO_2 and the eluting solvent is indicated in parentheses. Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) coated with Merck Silica gel $60PF_{254}$ (0.8 mm thick) unless otherwise specified, and the developing solvent is indicated in parentheses. Usual work-up refers to washing of the organic layers with water or brine, drying over anhydrous Na_2SO_4, and evaporating off the solvents under reduced pressure. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl prior to use.

4.1. Large-scale preparation of 2 and 4 (Scheme 3)

4.1.1. (2-Bromo-5-methoxy)phenylacetonitrile (12). KCN (7.48 g, 0.115 mol) was added to a solution of **11**[21] (7.48 g, 36.7 mmol) in EtOH (30 ml) and H_2O (15 ml) and the mixture was refluxed with stirring for 5 h. After having been cooled, the mixture was extracted with EtOAc. Usual work-up followed by recrystallization provided **12** (5.58 g, 92%) as colorless prisms, mp 54–55 °C (Et_2O–hexane). Anal. Calcd for C_9H_8BrNO: C, 47.81; H, 3.57; Br, 35.35; N, 6.20. Found: C, 47.66; H, 3.56; Br, 35.34; N, 6.21. GC–HRMS Calcd for C_9H_8BrNO: 226.9770, 224.9789. Found: 226.9780, 224.9814. GC–MS *m/z*: 227, 225 (M^+, 100, 95), 212, 210 (12, 13), 184, 182 (28, 30), 146 (34), 116 (23), 103 (41), 76 (26), 63 (25). IR (KBr) cm^{-1}: 2240. ^1H NMR δ: 3.80 (2H, s), 3.82 (3H, s), 6.77 (1H, dd, *J*=9, 3 Hz), 7.07 (1H, d, *J*=3 Hz), 7.47 (1H, d, *J*=9 Hz). ^{13}C NMR δ: 24.9 (CH_2), 55.5 (CH_3), 113.5 (C, C2), 115.2 (CH, C6), 115.4 (CH, C4), 116.7 (C, CN), 130.5 (C, C1), 133.4 (CH, C3), 159.1 (C, C5).

4.1.2. Ethyl (2-bromo-5-methoxy)phenylacetate (13). A solution of **12** (13.54 g, 59.9 mmol) in EtOH (40 ml) and concd H_2SO_4 (16.0 ml, 0.300 mol) was stirred under reflux for 6 h. The mixture was cooled in an ice bath and was diluted with H_2O. Extraction with EtOAc, washing with saturated $NaHCO_3$–H_2O, usual work-up, and distillation afforded **13** (14.71 g, 90%) as a colorless oil, bp 174–176 °C/13 mmHg. GC–HRMS Calcd for $C_{11}H_{13}BrO_3$: 274.0028, 272.0048. Found: 274.0032, 272.0050. GC–MS *m/z*: 274, 272 (M^+, 13, 12), 201, 199 (46, 48), 193 (50), 165 (100), 77 (31), 51 (27). IR (neat) cm^{-1}: 1737. ^1H NMR δ: 1.26 (3H, t, *J*=7 Hz), 3.73 (2H, s), 3.77 (3H, s), 4.18 (2H, q, *J*=7 Hz), 6.70 (1H, dd, *J*=9, 3 Hz), 6.84 (1H, d, *J*=3 Hz), 7.43 (1H, d, *J*=9 Hz). ^{13}C NMR δ: 14.2 (CH_3), 41.8 (CH_2), 55.3 (CH_3), 60.9 (CH_2), 114.3 (CH), 115.2 (C), 116.9 (CH), 133.0 (CH), 134.9 (C, C1), 158.6 (C), 170.1 (C).

4.1.3. 2-(2-Bromo-5-methoxyphenyl)ethanol (14). DIBAL-H (0.94 M in hexane, 93.0 ml, 87.4 mmol) was added dropwise to a cooled (−78 °C) solution of **13** (9.50 g, 34.8 mmol) in CH_2Cl_2 (120 ml) under an Ar atmosphere, and the mixture was stirred at −78 to −8 °C for 3 h. The mixture was slowly poured into saturated NH_4Cl–H_2O containing NH_4Cl solid with efficient stirring to decompose an excess reagent. The mixture was dredged with Celite (200 g) and the whole was filtered through a Celite bed in vacuo. The filtered Celite was washed thoroughly with CH_2Cl_2. Usual work-up and separation by SiO_2 column chromatography [120 g, benzene–hexane (19:1)] gave **14** (7.74 g, 96%) as a colorless oil. GC–HRMS Calcd for $C_9H_{11}BrO_2$: 231.9923, 229.9942. Found: 231.9923, 229.9926. GC–MS *m/z*: 232, 230 (M^+, 51, 53), 201, 199 (58, 56), 150 (72), 121 (100), 91 (51), 77 (65), 51 (55), 31 (74). ^1H NMR δ: 2.95 (2H, t, *J*=6.5 Hz), 3.76 (3H, s), 3.82 (2H, t, *J*=6.5 Hz), 7.76 (1H, br s, OH), 6.64 (1H, dd, *J*=9, 3 Hz), 6.82 (1H, d, *J*=3 Hz), 7.40 (1H, d, *J*=9 Hz). ^{13}C NMR δ: 39.4 (CH_2), 55.3 (CH_3), 61.8 (CH_2), 113.5 (CH, C4), 114.8 (C, C2), 116.7 (CH, C6), 133.1 (CH, C3), 138.6 (C, C1), 158.6 (C, C5).

4.1.4. 2-Bromo-5-methoxyphenethyl methanesulfonate (15). A solution of MsCl (2.85 ml, 36.8 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a cooled (−20 °C) solution of **14** (7.74 g, 33.5 mmol) and Et_3N (6.06 ml, 43.6 mmol) in CH_2Cl_2 (45 ml) and the mixture was stirred for 1 h under an Ar atmosphere. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. The organic layer was washed with saturated $CuSO_4$–H_2O and then with saturated $NaHCO_3$–H_2O. Usual work-up and purification by SiO_2 column chromatography [100 g, hexane–EtOAc (5:2)] gave **15** (10.27 g, 99%) as a colorless syrup. DI-HRMS Calcd for $C_{10}H_{13}BrO_4S$: 309.9698, 307.9717. Found: 309.9684, 307.9692. DI-MS *m/z*: 310, 308 (M^+, 21, 23), 214, 212 (90, 100), 201, 199 (18, 19), 79 (33), 51 (22). ^1H NMR δ: 2.91 (3H, s), 3.16 (2H, t, *J*=7 Hz), 3.78 (3H, s), 4.44 (2H, t, *J*=7 Hz), 6.70 (1H, dd, *J*=9, 3 Hz), 6.84 (1H, d, *J*=3 Hz), 7.43 (1H, d, *J*=9 Hz). ^{13}C NMR δ: 36.0 (CH_2), 37.2 (CH_3), 55.4 (CH_3), 68.3 (CH_2), 114.4 (CH), 114.5 (C), 116.9 (CH), 133.3 (CH), 136.2 (C), 158.8 (C).

4.1.5. 1-Bromo-2-(2-iodoethyl)-4-methoxybenzene (2). NaI (7.48 g, 49.9 mmol) was added to a solution of **15** (10.27 g, 33.2 mmol) in acetone (120 ml) and the mixture was refluxed with stirring for 8 h. After the mixture had been cooled in an ice bath, H_2O was added and the whole was extracted with EtOAc. Usual work-up and separation by SiO_2 column chromatography [100 g, hexane–EtOAc (99.9:0.1)] yielded **2** (10.91 g, 96%) as a colorless syrup. The product **2** is a known compound.[20] GC–HRMS Calcd for $C_9H_{10}BrIO$: 341.8942, 339.8962. Found: 341.8930, 339.8954. GC–MS *m/z*: 342, 340 (M^+, 42, 44), 215, 213 (77, 79), 134 (100), 91 (42), 63 (48). ^1H NMR δ: 3.21–3.29 (2H, m), 3.31–3.39 (2H, m), 3.79 (3H, s), 6.70 (1H, dd, *J*=9, 3 Hz), 6.79 (1H, d, *J*=3 Hz), 7.42 (1H, d, *J*=9 Hz). ^{13}C NMR δ: 3.0 (CH_2, *C*H_2I), 40.7 (CH_2), 55.4 (CH_3), 114.0 (CH), 114.2 (C), 116.2 (CH), 133.3 (CH), 140.5 (C, C1), 158.7 (C).

4.1.6. 2-(3-Methoxyphenyl)ethanol (16). A solution of methyl chloroformate (24.5 ml, 0.317 mol) in THF (50 ml) was added slowly to a cooled (−20 °C) solution of 3-methoxyphenylacetic acid (50.0 g, 0.301 mol) and Et_3N (44.5 ml, 0.320 mol) in THF (400 ml) and the mixture was stirred at −20 °C for 1 h. The precipitate was filtered under reduced pressure and the filtered salt was washed with THF (50 ml). The combined THF solution was added to a slurry

of $NaBH_4$ (57.2 g, 1.51 mol) in H_2O (300 ml) and the mixture was stirred at 0–24 °C for 40 h. Another portion of $NaBH_4$ (11.5 g, 0.303 mol) was added and the resulting mixture was further stirred for 24 h. The mixture was gradually poured into saturated NH_4Cl–H_2O and the whole was extracted with CH_2Cl_2. Distillation afforded **16** (43.6 g, 96%) as a colorless oil (bp: 135–140 °C/10 mmHg). The compound **16** was prepared in the literature[20] by treatment of 3-methoxyphenylacetic acid with $NaBH_4$ and I_2 in 89% yield, and is also available from Aldrich Chemical Co. (bp: 141–143 °C/12 mmHg).

4.1.7. Improved Pd cyclization of 3 to form 4 and by-products 17, 18. A slurry of **3** (12.24 g, 32.0 mmol), $PdCl_2(Ph_3P)_2$ (2.00 g, 2.85 mmol), Cs_2CO_3 (16.70 g, 51.2 mmol), and Ph_3P (1.67 g, 6.37 mmol) in THF (200 ml) was refluxed with vigorous stirring under an Ar atmosphere for 60 h. After the mixture had been cooled, saturated NH_4Cl–H_2O was added and the mixture was extracted with EtOAc. Usual work-up followed by purification by SiO_2 column chromatography (250 g, benzene) and PTLC provided **4** (6.83 g, 71%, cis/trans = 3.4), **17** (61 mg, 4%), and **18** (29 mg, 2%) in order of increasing polarity. Spectral data of the three products and single crystal X-ray analysis data of *cis*-**4** have already been reported.[11c]

4.2. Transformation of 4 to 5 (Scheme 4)

4.2.1. Acetalization of 4 to form 19 and 20. Ethylene glycol (2.50 ml, 44.9 mmol) and *p*-TsOH·H_2O (160 mg, 0.842 mmol) were added to a solution of **4** (2.68 g, 8.87 mmol, cis/trans = 3.4) in benzene (40 ml), and the mixture was refluxed with stirring for 6 h with a Dean–Stark apparatus. After the mixture had been cooled in an ice bath, saturated $NaHCO_3$–H_2O was added and the whole was extracted with EtOAc. Usual work-up and subsequent SiO_2 column chromatography [80 g, hexane–EtOAc (14:1∼9:1)] afforded **20** (1.05 g, 34%) and **19** (1.87 g, 61%) in order of increasing polarity. **19**: Colorless prisms, mp 99–100 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.18; H, 7.53. GC–HRMS Calcd for $C_{20}H_{26}O_5$: 346.1779. Found: 346.1781. GC–MS *m*/*z*: 346 (M^+, 1), 273 (17), 99 (100), 73 (28), 55 (9), 45 (10). ^{1}H NMR δ: 1.41–1.56 (2H, m), 1.60–1.75 (2H, m), 1.77–1.94 (2H, m), 2.04–2.19 (2H, m), 2.27 (1H, dd, *J*=5.5, 5.5 Hz, H5), 2.75 (1H, ddd, *J*=17, 6.5, 6.5 Hz, H7), 2.88 (1H, ddd, *J*=17, 7.5, 7.5 Hz, H7), 3.52–3.62 (1H, m), 3.68–3.97 (7H, m), 3.76 (3H, s), 5.24 (1H, s), 6.58 (1H, d, *J*=3 Hz), 6.68 (1H, dd, *J*=9, 3 Hz), 7.41 (1H, d, *J*=9 Hz). ^{13}C NMR δ: 19.0 (CH_2, C6), 19.2 (CH_2, C3), 28.6 (CH_2, C7), 28.8 (CH_2, C1), 33.7 (CH_2, C2), 43.2 (CH, C5), 45.4 (C, C10), 54.8 (CH_3), 64.0 (CH_2), 64.5 (CH_2), 65.0 (CH_2), 65.1 (CH_2), 107.7 (CH), 111.2 (×2, CH and C, C4 and C12), 112.8 (CH, C14), 128.3 (CH, C11), 129.8 (C), 140.2 (C, C8), 157.1 (C). **20**: Colorless needles, mp 108–109 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.25; H, 7.52. GC–HRMS Calcd for $C_{20}H_{26}O_5$: 346.1779. Found: 346.1783. GC–MS *m*/*z*: 346 (M^+, 1), 273 (18), 99 (100), 73 (29), 55 (10), 45 (9). ^{1}H NMR δ: 1.31 (1H, ddd, *J*=13.5, 13.5, 4 Hz, H1), 1.42–1.55 (1H, m), 1.66–1.97 (5H, m), 2.10–2.27 (1H, m), 2.67–2.78 (1H, m, dioxolane proton, anisotropy), 2.76–2.99 (3H, m), 3.50–3.64 (3H, m), 3.77 (3H, s), 3.82–3.92 (1H, m), 3.94–4.03 (2H, m), 4.06–4.16 (1H, m), 5.80 (1H, s), 6.60 (1H, d, *J*=2.5 Hz), 6.63 (1H, dd, *J*=8.5, 2.5 Hz), 7.29 (1H, d, *J*=8.5 Hz). ^{13}C NMR δ: 16.7 (CH_2, C6), 19.7 (CH_2, C2), 29.4 (CH_2, C7), 33.9 (CH_2, C1), 35.6 (CH_2, C3), 44.8 (C, C10), 49.0 (CH, C5), 54.9 (CH_3), 64.1 (CH_2), 64.4 (CH_2), 64.9 (CH_2), 65.6 (CH_2), 105.0 (CH), 110.3 (CH, C12), 112.6 (CH), 128.1 (C), 128.3 (CH), 131.6 (C, C9), 139.4 (C, C8), 157.4 (C). Under the same conditions, **19** (920 mg, 2.66 mmol) was acetalized to give **20** (323 mg, 35%) and recovered **19** (561 mg, 61%).

4.2.2. Birch reduction of 20 to form 21. Li (7.89 g, 1.13 mol) was added in small portions during 2.5 h to a cooled (−78 °C) solution of **20** (6.50 g, 18.8 mmol) in liq. NH_3 (ca. 150 ml), THF (80 ml), and EtOH (80 ml) with efficient stirring by a mechanical stirrer. After the addition completed, stirring was continued for 3 h. Solid NH_4Cl (10.0 g) was slowly added and the cooling bath was removed. Stirring was further continued at room temperature with trapping evaporating NH_3 with concd HCl and ice. Saturated NH_4Cl–H_2O was added and the mixture was filtered through a Celite bed, and the Celite was washed with $CHCl_3$. Extraction with $CHCl_3$ followed by usual work-up afforded crystalline material, which was purified by recrystallization and SiO_2 column chromatography [hexane–EtOAc (8:1)] to yield **21** (5.99 g, 92%) as colorless prisms, mp 167–168.5 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.73; H, 8.07. GC–HRMS Calcd for $C_{20}H_{28}O_5$: 348.1935. Found: 348.1923. GC–MS *m*/*z*: 348 (M^+, 4), 275 (35), 213 (10), 99 (100), 73 (38), 55 (12), 45 (18). IR (KBr) cm^{-1}: 1697, 1663. ^{1}H NMR δ: 1.17 (1H, ddd, *J*=13, 13, 4.5 Hz, H1), 1.43 (1H, ddd, *J*=13, 13, 5 Hz, H3), 1.59–2.04 (8H, m), 2.45 (1H, dddd, *J*=13, 3, 3, 1.5 Hz, H1), 2.60 (2H, dd, *J*=7.5, 7 Hz, H14), 2.74–3.04 (2H, m, H11), 3.54 (3H, s), 3.61–4.11 (8H, m), 4.60 (1H, dd, *J*=4, 3.5 Hz, H12), 5.66 (1H, s). ^{13}C NMR δ: 16.4 (CH_2), 19.6 (CH_2), 28.0 (CH_2, C11), 30.2 (CH_2), 32.3 (CH_2), 34.3 (CH_2, C14), 35.6 (CH_2), 44.8 (C, C10), 49.5 (CH), 53.6 (CH_3), 63.6 (CH_2), 64.3 (CH_2), 65.1 (CH_2), 65.5 (CH_2), 90.9 (CH, C12), 105.5 (CH), 110.3 (C, C4), 127.4 (C, C9), 127.9 (C), 151.8 (C, C13).

4.2.3. Hydrolysis of vinyl ether 21 to form 22 and 23. HCl–H_2O (2.5%, 5.0 ml) was added to a cooled (0 °C) solution of **21** (590 mg, 1.70 mmol) in THF (20 ml) and the mixture was stirred at the temperature for 1.5 h. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and separation by SiO_2 column chromatography [25 g, hexane–EtOAc (4:1∼1:1)] afforded **22** (497 mg, 88%) and **23** (41 mg, 7%) in order of increasing polarity. **22**: Colorless prisms, mp 142–144 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.18; H, 7.82. GC–HRMS Calcd for $C_{19}H_{26}O_5$: 334.1779. Found: 334.1772. GC–MS *m*/*z*: 334 (M^+, 1), 261 (2), 199 (1), 99 (22), 73 (100), 55 (7), 45 (11). IR ($CHCl_3$) cm^{-1}: 1713. ^{1}H NMR δ: 1.15 (1H, ddd, *J*=13, 13, 4.5 Hz, H1), 1.44 (1H, ddd, *J*=13, 13, 5.5 Hz, H3), 1.60–1.80 (4H, m), 1.82–2.05 (4H, m), ca. 2.26–2.48 (3H, m), 2.50 (1H, dddd, *J*=13, 3, 3, 1 Hz, H1), 2.64–2.74 (1H, m), 2.72 (1H, d, *J*=21 Hz, H14), 2.82 (1H, d, *J*=21 Hz, H14), 3.65–4.10 (8H, m), 5.56 (1H, s). ^{13}C NMR δ: 16.4 (CH_2), 19.5 (CH_2), 26.1 (CH_2, C12), 30.5 (CH_2), 32.1 (CH_2), 35.6 (CH_2), 39.4 (CH_2), 45.0 (C), 45.1 (CH_2, C14), 49.7 (CH), 63.4 (CH_2), 64.3 (CH_2), 65.3 (CH_2), 65.5 (CH_2), 105.2 (CH), 110.0 (C),

128.9 (C), 131.7 (C), 211.9 (C). **23**: Colorless prisms, mp 172–173 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.78; H, 7.71. GC–HRMS Calcd for $C_{19}H_{26}O_5$: 334.1779. Found: 334.1782. GC–MS *m/z*: 334 (M^+, 10), 289 (4), 261 (4), 99 (21), 73 (100), 55 (8), 45 (15). IR ($CHCl_3$) cm^{-1}: 1652, 1611. ^1H NMR δ: 1.03–1.14 (1H, m), 1.40–1.52 (1H, m), 1.53–1.69 (2H, m), 1.72 (1H, dd, *J*=13, 3 Hz, H5), 1.75–1.96 (3H, m), 1.99–2.21 (4H, m), 2.29–2.47 (2H, m), 2.54 (1H, br dddd, *J*=13, 3, 3, 1.5 Hz, H1), 2.64 (1H, br ddd, *J*=17, 5, 1.5 Hz, H7), 3.66–4.05 (8H, m), 5.46 (1H, s), 5.73 (1H, br s, H14). ^{13}C NMR δ: 19.0 (CH_2), 19.6 (CH_2), 23.4 (CH_2), 34.15 (CH_2), 34.18 (CH_2), 35.6 (CH_2), 38.2 (CH_2), 44.9 (C), 49.7 (CH, C9), 51.4 (CH), 62.8 (CH_2), 64.2 (CH_2), 64.6 (CH_2), 65.5 (CH_2), 104.9 (CH), 109.6 (C), 122.5 (CH, C14), 168.1 (C, C8), 199.8 (C).

4.2.4. NaOMe treatment of 22. NaOMe (150 mg, 2.78 mmol) was added to a cooled (0 °C) slurry of **22** (305 mg, 0.913 mmol) in MeOH (15 ml) and the mixture was stirred at 0 °C for 0.5 h and at 18 °C for 16 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by PTLC [benzene–EtOAc (5:1)] gave recovered **22** (30 mg, 10%), **23** (169 mg, 55%), and an oxetane **24** (31 mg, 10%) in order of increasing polarity. **24**: Colorless glass. DI-HRMS Calcd for $C_{19}H_{24}O_6$: 348.1571. Found: 348.1557. DI-MS *m/z*: 348 (M^+, 2), 257 (5), 99 (100), 73 (75), 55 (11), 45 (20). IR ($CHCl_3$) cm^{-1}: 1651. ^1H NMR δ: 1.52–1.71 (2H, m), 1.75–1.92 (3H, m), 2.04–2.17 (2H, m), 2.21–2.42 (4H, m), 2.71 (1H, ddd, *J*=18.5, 13, 7 Hz, H7), 2.86 (1H, dd, *J*=12, 6 Hz, H5), 3.40–3.54 (1H, m), 3.63–3.87 (4H, m), 3.91–4.01 (2H, m), 4.03–4.14 (1H, m), 5.20 (1H, d, *J*=7 Hz, H12), 5.51 (1H, s), 5.52 (1H, s, H14). ^{13}C NMR δ: 19.9 (CH_2), 24.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 32.9 (CH_2), 36.0 (CH_2), 45.9 (C), 50.2 (CH), 62.7 (CH_2), 63.5 (CH_2), 64.4 (CH_2), 65.9 (CH_2), 88.0 (C, C9), 95.0 (CH, C12), 103.9 (CH), 106.9 (CH, C14), 110.0 (C, C4), 164.5 (C, C8), 199.1 (C).

4.2.5. NaOMe treatment of 22 in the presence of Me_2S. NaOMe (40 mg, 0.741 mmol) was added to a cooled (0 °C) slurry of **22** (210 mg, 0.629 mmol) and Me_2S (0.23 ml, 3.14 mmol) in MeOH (8 ml) and the mixture was stirred at 0 °C for 0.5 h and at 18 °C for 14 h. The same work-up as above afforded recovered **22** (28 mg, 13%), **23** (122 mg, 58%), and **26** (31 mg, 14%) in order of increasing polarity. **26**: Colorless needles, mp 234–235 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.75; H, 7.35. DI-HRMS Calcd for $C_{19}H_{26}O_6$: 350.1728. Found: 350.1737. DI-MS *m/z*: 350 (M^+, 8), 288 (11), 260 (11), 165 (11), 99 (100), 73 (83), 55 (19), 45 (35). IR ($CHCl_3$) cm^{-1}: 1660. ^1H NMR δ: 1.39–1.51 (1H, m), 1.57–1.91 (6H, m), 1.97–2.05 (1H, m), 2.12–2.18 (1H, m), 2.16 (1H, br s, OH), 2.26–2.69 (6H, m), 3.67–4.04 (8H, m), 5.51 (1H, s), 5.66 (1H, br d, *J*=2 Hz, H14). ^{13}C NMR δ: 19.1 (CH_2), 19.3 (CH_2), 26.3 (CH_2), 30.0 (CH_2), 31.2 (CH_2), 33.5 (CH_2, C12), 35.3 (CH_2), 43.8 (CH), 48.9 (C, C10), 62.7 (CH_2), 64.0 (CH_2), 64.3 (CH_2), 65.5 (CH_2), 71.5 (C, C9), 104.0 (CH), 110.6 (C), 122.9 (CH, C14), 165.2 (C, C8), 199.3 (C, C13).

4.2.6. DBU treatment of 22 to form hydroperoxide 25 and 26. A solution of **22** (10 mg, 29.9 μmol) and DBU (9 μl, 60.3 mmol) in benzene (2.5 ml) was refluxed with stirring for 4 h. Addition of H_2O, extraction with EtOAc, successive washing with $CuSO_4$–H_2O and saturated $NaHCO_3$–H_2O, and PTLC [benzene–EtOAc (4:1)] gave recovered **22** (4 mg, 40%), **25** (2 mg, 18%), and **26** (2 mg, 19%) in order of increasing polarity. **25**: Colorless glass. DI-HRMS Calcd for $C_{19}H_{26}O_7$: 366.1677. Found: 366.1695. DI-MS *m/z*: 366 (M^+, 2), 350 (3), 293 (3), 277 (3), 251 (4), 99 (62), 73 (100), 55 (17), 45 (25). IR ($CHCl_3$) cm^{-1}: 1653. ^1H NMR δ: 1.43 (1H, ddd, *J*=12.5, 12.5, 5.5 Hz, H1), 1.49–1.92 (6H, m), 2.17 (1H, br d, *J*=12.5 Hz, H1), 2.24–2.89 (7H, m), 3.64–4.03 (8H, m), 5.52 (1H, s), 5.95 (1H, d, *J*=2 Hz, H14), 7.59 (1H, br s, OOH).

4.2.7. Alternative preparation of 26 and 27 by *m*-CPBA oxidation of 22. *m*-CPBA (26 mg, 0.151 mmol) was added to a solution of **22** (18 mg, 53.9 μmol) in CH_2Cl_2 (3 ml) and the mixture was stirred at 0 °C for 1 h, and at 20 °C for 2.5 h. Saturated $Na_2S_2O_3$–H_2O and saturated $NaHCO_3$–H_2O were added and the whole was extracted with CH_2Cl_2. Usual work-up and rough separation by PTLC [hexane–EtOAc (1:1)] afforded a mixture of products (20 mg), which were treated with DBU (40 μl, 0.292 mmol) in refluxing benzene (3 ml) for 30 min. The same work-up as in Section 4.2.5 and purification by PTLC [1.5% MeOH–CH_2Cl_2] furnished **26** (11.5 mg, 61%) and **27** (6.5 mg, 34%) in order of decreasing polarity. **27**: Colorless prisms, mp 194–196 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.85; H, 7.38. DI-HRMS Calcd for $C_{19}H_{26}O_6$: 350.1728. Found: 350.1724. DI-MS *m/z*: 350 (M^+, 3), 260 (2), 133 (7), 99 (100), 73 (23), 55 (11), 45 (14). IR ($CHCl_3$) cm^{-1}: 1665, 1620. ^1H NMR δ: 1.34 (1H, ddd, *J*=12.5, 12.5, 5 Hz, H1), 1.45–1.71 (4H, m), 1.77–2.02 (3H, m), 2.03 (1H, dddd, *J*=13, 13, 4.5, 1.5 Hz, H12), 2.17 (1H, ddd, *J*=13, 4.5, 2.5 Hz, H12), 2.19–2.39 (3H, m), 2.90 (1H, ddd, *J*=17, 13, 4.5 Hz, H11), 3.32 (1H, dddd, *J*=15.5, 12, 7, 2.5 Hz, H7), 3.76–3.87 (2H, m), 3.89–4.07 (5H, m), 4.08–4.17 (1H, m), 4.55 (1H, d, *J*=1.5 Hz, OH), 5.53 (1H, s). ^{13}C NMR δ: 18.1 (CH_2, C6), 19.7 (CH_2, C2), 28.3 (CH_2), 31.5 (CH_2), 33.2 (CH_2, C12), 34.0 (CH_2, C11), 35.7 (CH_2), 44.4 (CH, C5), 46.7 (C), 62.6 (CH_2), 64.2 (CH_2), 65.0 (CH_2), 65.7 (CH_2), 74.9 (C, C9), 106.1 (CH), 110.0 (C), 126.6 (CH), 166.4 (C, C8), 199.4 (C).

4.2.8. Reduction of 23 to form allylalcohol 28. $CeCl_7 \cdot H_2O$ (408 mg, 1.10 mmol) and $NaBH_4$ (43 mg, 1.13 mmol) were added to a cooled (0 °C) solution of **23** (330 mg, 0.988 mmol) in MeOH (25 ml) and the mixture was stirred at that temperature for 30 min. Quenching by successive addition of saturated NH_4Cl–H_2O and saturated $NaHCO_3$–H_2O followed by extraction with CH_2Cl_2, usual work-up, and PTLC [benzene–EtOAc (2:1)] provided **28** as colorless prisms, mp 191–192 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{19}H_{28}O_5 \cdot 1/4H_2O$: C, 66.93; H, 8.43. Found: C, 67.08; H, 8.37. DI-HRMS Calcd for $C_{19}H_{28}O_5$: 336.1935. Found: 336.1936. DI-MS *m/z*: 336 (M^+, 1), 318 (8), 184 (22), 99 (100), 73 (98), 45 (28). ^1H NMR δ: 0.93–1.05 (1H, m), 1.11–1.28 (1H, m), 1.38–1.50 (1H, m), 1.55–1.94 (10H, m, including OH), ca. 2.01–2.14 (1H, m), ca. 2.12–2.25 (1H, m), 2.41 (1H, ddd, *J*=15, 3, 3 Hz, H7), 2.46 (1H, br dddd, *J*=13, 3, 3, 1.5 Hz, H1), 3.65–3.73 (1H, m), 3.77–3.96 (6H, m), 3.97–4.03 (1H, m), 4.14–4.23 (1H, m, $W_{1/2}$=19 Hz, H13), 5.21–5.25 (1H, m, $W_{1/2}$=5.5 Hz, H14), 5.45 (1H, s).

^{13}C NMR δ: 19.7 (CH_2), 19.8 (CH_2), 22.1 (CH_2, C11), 33.9 (CH_2), 34.3 (CH_2), 34.5 (CH_2), 35.8 (CH_2), 44.4 (C), 48.9 (CH, C9), 52.8 (CH), 62.6 (CH_2), 64.1 (CH_2), 65.1 (CH_2), 65.4 (CH_2), 67.9 (CH, C13), 105.7 (CH), 110.0 (C), 122.3 (CH, C14), 141.3 (C, C8).

4.2.9. Claisen rearrangement of 28 under neutral conditions to form 29. A solution of **28** (500 mg, 1.49 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (1.53 ml, 10.48 mmol) in toluene (20 ml) was heated with stirring at 160 °C (bath temperature) in a sealed tube for 4 h. The volatile materials were removed in vacuo and resulting residue was purified by SiO_2 column chromatography [25 g, benzene–EtOAc (4:1)] to yield **29** (418 mg, 69%) as colorless needles, mp 140.5–141.5 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45. Found: C, 68.04; H, 8.62; N, 3.48. DI-HRMS Calcd for $C_{23}H_{35}NO_5$: 405.2513. Found: 405.2521. DI-MS *m*/*z*: 405 (M^+, 4), 360 (6), 332 (20), 319 (15), 245 (56), 99 (82), 73 (100), 45 (34). IR ($CHCl_3$) cm^{-1}: 1622. ^{1}H NMR δ: 1.09 (1H, ddd, *J*=13, 13, 4.5 Hz, H1), 1.48 (1H, ddd, *J*=13, 13, 5 Hz, H3), 1.52–2.02 (12H, m), 2.08–2.19 (1H, m), 2.32 (1H, d, *J*=14 Hz, CH_2CON), 2.51 (1H, br dddd, *J*=13, 3, 3, 1 Hz, H1), 2.56 (1H, d, *J*=14 Hz, CH_2CON), 2.91 (3H, s), 2.98 (3H, s), 3.65–4.07 (8H, m), 5.34 (1H, s), 5.45 (1H, br dd, *J*=10, 1.5 Hz, H14), 5.67 (1H, ddd, *J*=10, 5, 2.5 Hz, H13). ^{13}C NMR δ: 16.9 (CH_2), 20.0 (CH_2), 20.7 (CH_2), 23.6 (CH_2), 34.3 (CH_2), 34.5 (CH_3), 35.9 (CH_2), 38.1 (C), 38.2 (CH_2), 38.5 (CH_3), 43.8 (C, C8), 46.2 (CH_2, *C*H_2CON), 49.7 (CH), 50.6 (CH), 62.3 (CH_2), 63.9 (CH_2), 64.0 (CH_2), 65.6 (CH_2), 104.9 (CH), 110.5 (C), 126.3 (CH, C13), 136.6 (CH, C14), 171.5 (C).

4.2.10. Acetylation of 28 to form diene 30. Ac_2O (0.10 ml, 1.06 mmol) was added to a solution of **28** (5.5 mg, 16.4 μmol) and pyridine (0.30 ml, 3.71 mmol) in CH_2Cl_2 (1 ml) and the mixture was stirred at 20 °C for 2 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–CH_2Cl_2 (1:2)] gave **30** (4.5 mg, 86%) as a labile colorless syrup. GC–HRMS Calcd for $C_{19}H_{26}O_4$: 318.1830. Found: 318.1818. GC–MS *m*/*z*: 318 (M^+, 8), 245 (11), 211 (10), 184 (24), 99 (84), 73 (100), 45 (35). ^{1}H NMR δ: 0.96–1.08 (1H, m), 1.41–1.71 (4H, m), 1.85–2.26 (8H, m), 2.59 (1H, dddd, *J*=13, 3, 3, 1.5 Hz, H1), 3.67–3.86 (4H, m), 3.90–4.06 (4H, m), 5.43 (1H, s), 5.50–5.55 (1H, m, H7), 5.61–5.69 (1H, m, H13), 5.99 (1H, dd, *J*=9.5, 1.5 Hz, H14). ^{13}C NMR δ: 19.6, 22.0, 24.1, 27.3, 35.4, 36.0, 41.9, 48.6, 48.7, 62.1, 64.1, 65.46, 65.52, 105.3, 109.9, 122.6, 126.4, 129.7, 136.0.

4.2.11. Claisen rearrangement of 28 under acidic conditions to form 31. A solution of **28** (20 mg, 59.5 μmol) and pivalic acid (2 mg, 19.6 μmol) in triethyl orthoacetate (1.50 ml, 8.19 mmol) was heated with stirring at 160 °C (bath temperature) in a sealed tube for 15 h. After the mixture had been cooled, saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–CH_2Cl_2 (1:1)] gave **31** (5 mg, 21%) as a colorless syrup. DI-HRMS Calcd for $C_{23}H_{34}O_6$: 406.2353. Found: 406.2342. DI-MS *m*/*z*: 406 (M^+, 7), 361 (12), 344 (6), 333 (16), 319 (15), 245 (21), 99 (79), 73 (100), 45 (37). IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H NMR δ: 1.03 (1H, ddd, *J*=13, 13, 4.5 Hz, H1), 1.24 (3H, dd, *J*=7, 7 Hz, OCH_2CH_3), 1.42–1.94 (13H, m), 2.12 (1H, ddd, *J*=13.5, 6.5, 6.5 Hz, H7), 2.29 (1H, d, *J*=13.5 Hz, CH_2COO), 2.51 (1H, d, *J*=13.5 Hz, CH_2COO), 2.52 (1H, br d, *J*=13 Hz, H1), 3.63–4.04 (8H, m), 4.02–4.14 (2H, m, OCH_2CH_3), 5.34 (1H, s), 5.40 (1H, br d, *J*=10 Hz, H14), 5.69 (1H, ddd, *J*=10, 5, 2.5 Hz, H13). ^{13}C NMR δ: 14.3 (CH_3), 16.8 (CH_2), 20.0 (CH_2), 20.6 (CH_2), 23.6 (CH_2), 34.1 (CH_2), 35.9 (CH_2), 37.6 (C), 38.4 (CH_2), 43.8 (C), 49.5 (CH), 49.7 (CH_2, *C*H_2COO), 50.4 (CH), 59.8 (CH_2, O*C*H_2CH$_3$), 62.3 (CH_2), 63.9 (CH_2), 64.1 (CH_2), 65.7 (CH_2), 104.9 (CH), 110.4 (C), 126.4 (CH, C13), 136.1 (CH, C14), 171.8 (C).

4.2.12. Reduction of acetamide 29 to form 32. *n*-BuLi (1.5 M in hexane, 5.57 ml, 8.36 mmol) was added to a cooled (0 °C) slurry of $BH_3 \cdot NH_3$ (90%, 307 mg, 8.97 mmol) in THF (12 ml) in a round bottom flask (300 ml). The mixture was stirred under an Ar atmosphere at that temperature for 5 min and at 20 °C for 10 min, and then was allowed to cool again to 0 °C. A THF (8 ml) solution of **29** (480 mg, 1.19 mmol) was added dropwise to this and the mixture was stirred for 10 min. The cooling bath was removed and the mixture was further stirred at 22 °C for 19 h. After the mixture had been cooled in an ice bath again, saturated NH_4Cl–H_2O (25 ml) and NH_4Cl powder (ca. 2 g) were gradually added to this with efficient stirring. SiO_2 (15 g) and CH_2Cl_2 (30 ml) were further added and the whole was vigorously stirred at 20 °C for 3 h. The whole was filtered under reduced pressure and filtered SiO_2 was washed thoroughly with CH_2Cl_2. Usual work-up followed by SiO_2 column chromatography [30 g, 1% MeOH–CH_2Cl_2] yielded **32** (404 mg, 94%) as a colorless viscous syrup. DI-HRMS Calcd for $C_{21}H_{32}O_5$: 364.2248. Found: 364.2247. DI-MS *m*/*z*: 364 (M^+, 6), 319 (27), 291 (17), 185 (6), 112 (21), 99 (99), 73 (100), 55 (21), 45 (46). ^{1}H NMR δ: 1.00 (1H, ddd, *J*=13, 13, 4.5 Hz, H1), 1.31 (1H, ddd, *J*=13.5, 13, 6.5 Hz, H7), 1.46 (1H, ddd, *J*=13, 13, 5 Hz, H3), 1.48–1.81 (9H, m, including OH), 1.81–2.01 (5H, m), 2.09 (1H, ddd, *J*=13.5, 7, 7 Hz, H7), 2.53 (1H, dddd, *J*=13, 3, 3, 1.5 Hz, H1), 3.66–3.83 (4H, m), 3.87–3.97 (3H, m), 3.99–4.07 (1H, m), 5.33 (1H, s), 5.37 (1H, dd, *J*=10, 1.5 Hz, H14), 5.70 (1H, ddd, *J*=10, 5, 2.5 Hz, H13). ^{13}C NMR δ: 16.7 (CH_2), 20.0 (CH_2), 21.0 (CH_2), 26.4 (CH_2), 34.2 (CH_2), 36.0 (CH_2), 36.9 (C, C8), 38.7 (CH_2), 43.7 (C), 49.0 (CH_2, *C*H_2CH$_2$OH), 49.3 (CH), 51.8 (CH), 59.9 (CH_2, CH_2*C*H_2OH), 62.3 (CH_2), 63.9 (CH_2), 64.2 (CH_2), 65.7 (CH_2), 104.9 (CH), 110.4 (C), 126.4 (CH), 137.2 (CH).

4.2.13. Pivaloylation of 32 to form 5. Piv_2O (1.22 ml, 6.02 mmol) was slowly added to a cooled (0 °C) solution of Et_3N (3.30 ml, 23.7 mmol) in CH_2Cl_2 (3 ml) under an Ar atmosphere and the mixture was stirred at that temperature for 15 min. The resulting solution was slowly added dropwise to a cooled (−18 °C) solution of **32** (560 mg, 1.54 mmol) and 4-DMAP (28 mg, 0.230 mmol) in CH_2Cl_2 (2 ml). The whole was stirred at −18 to 23 °C for five days. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and SiO_2 column chromatography [40 g, hexane–EtOAc (8:1)] afforded **5** (674 mg, 98%) as a colorless needles, mp 93–94 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.40; H, 9.02. DI-HRMS Calcd for $C_{26}H_{40}O_6$: 448.2823. Found: 448.2832. DI-MS *m*/*z*: 448 (M^+, 3), 403 (3), 375

(8), 319 (5), 99 (61), 73 (100), 57 (35), 45 (24), 41 (17). IR ($CHCl_3$) cm^{-1}: 1719. ^1H NMR δ: 1.01 (1H, ddd, J=13.5, 13, 4.5 Hz, H1), 1.18 (9H, s), 1.34 (1H, ddd, J=13.5, 13.5, 6.5 Hz, H7), 1.47 (1H, ddd, J=13, 13, 5 Hz, H3), 1.48–1.80 (8H, m), 1.81–2.00 (1H, m), 2.10 (1H, ddd, J=13.5, 7, 7 Hz, H7), 2.53 (1H, br d, J=13 Hz, H1), 3.66–3.84 (4H, m), 3.87–3.97 (3H, m), 4.00–4.12 (3H, m), 5.31 (1H, br dd, J=9.5, 1.5 Hz, H14), 5.34 (1H, s), 5.70 (1H, ddd, J=9.5, 5, 2.5 Hz, H13). ^{13}C NMR δ: 16.7 (CH_2), 20.0 (CH_2), 21.0 (CH_2), 23.9 (CH_2), 27.2 ($CH_3\times3$), 34.1 (CH_2), 36.0 (CH_2), 36.8 (C, C8), 38.6 (C, CO*C*Me$_3$), 38.7 (CH_2), 43.8 (C), 44.1 (CH_2, *C*H_2CH$_2$OPiv), 49.4 (CH), 51.5 (CH), 62.0 (CH_2, *C*H_2OPiv), 62.3 (CH_2), 63.9 (CH_2), 64.2 (CH_2), 65.7 (CH_2), 104.9 (CH), 110.4 (C), 126.4 (CH, C13), 136.4 (CH, C14), 178.4 (C).

4.3. Acetal–ene reactions of 29, 31, and 5 (Scheme 5)

4.3.1. BF_3 treatment of 29 and 31 to form 33 and 34 (35) (Table 1). The procedure for Table 1, run b was described as a representative example. $BF_3\cdot OEt_2$ (105 μl, 0.828 mmol) was added to a cooled (−18 °C) solution of **29** (56 mg, 0.138 mmol) in toluene (5 ml) under an Ar atmosphere with stirring. After stirring for 2 h at −18 °C, saturated $NaHCO_3$–H_2O (8 ml) and EtOAc (10 ml) were added and resulting mixture was vigorously stirred for 2 h at an ambient temperature. Extraction with EtOAc followed by usual work-up gave a residue (66 mg). The residue was dissolved in benzene (6 ml) and to this were added ethylene glycol (0.40 ml, 7.18 mmol) and *p*-TsOH·H_2O (4 mg, 21.1 μmol). The mixture was stirred under reflux using a Dean–Stark apparatus for 2 h. After the mixture had been cooled, saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC (1.8% MeOH–CH_2Cl_2) afforded **33** (23 mg, 41%) and **34** (25 mg, 48%) in order of decreasing polarity. **33**: Colorless glass. DI-HRMS Calcd for $C_{23}H_{35}NO_5$: 405.2513. Found: 405.2522. DI-MS *m/z*: 405 (M^+, 19), 360 (20), 343 (12), 318 (9), 273 (9), 257 (14), 99 (100), 87 (58), 72 (33), 55 (19), 45 (34). IR ($CHCl_3$) cm^{-1}: 1627. ^1H NMR δ: 1.06 (1H, ddd, J=13, 12, 5 Hz, H1), 1.19–1.31 (1H, m), 1.46 (1H, br d, J=5 Hz, H9), 1.50–1.80 (7H, m), 1.85–1.98 (1H, m), 2.07 (1H, br d, J=13 Hz, H1), 2.18 (1H, d, J=15.5 Hz, C*H*$_2$CON), 2.20 (1H, dddd, J=19, 5, 2.5, 2.5 Hz, H11), 2.38 (1H, br d, J=19 Hz, H11), 2.48 (1H, d, J=15.5 Hz, C*H*$_2$CON), 2.89 (1H, br s, OH), 2.91 (1H, ddd, J=7, 6.5, 1.5 Hz, H14), 2.93 (3H, s), 3.00 (3H, s), 3.38 (1H, ddd, J=11, 6, 3.5 Hz), 3.57 (1H, ddd, J=11, 6, 3 Hz), 3.62–3.76 [2H, m, changed with D_2O to 3.66 (1H, ddd, J=12, 6, 3 Hz) and 3.72 (1H, ddd, J=12, 6, 3.5 Hz)], 3.74–3.86 (1H, m), 3.86–4.00 (3H, m), 4.44 (1H, d, J=6.5 Hz, H20), 5.59 (1H, ddd, J=9.5, 3, 2.5 Hz, H12), 5.70 (1H, dddd, J=9.5, 7, 2, 1.5 Hz, H13). ^{13}C NMR δ: 18.3 (CH_2, C6), 21.3 (CH_2, C2), 27.1 (CH_2, C11), 28.8 (CH_2, C1), 33.8 (CH_2, C7), 34.8 (CH_2, C3), 35.3 (CH_3, N*C*H$_3$), 37.4 (CH_2, *C*H_2CON), 37.8 (CH_3, N*C*H$_3$), 43.6 (C, C8), 48.1 (CH, C14), 48.2 (C, C10), 50.5 (CH, C5), 54.5 (CH, C9), 62.2 (CH_2, *C*H_2OH), 63.9 (CH_2), 65.4 (CH_2), 69.6 (CH_2, *C*H_2CH$_2$OH), 80.3 (CH, C20), 110.5 (C, C4), 125.7 (CH, C12), 128.7 (CH, C13), 172.5 (C, *C*ON). **34**: Colorless prisms, mp 206–207 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.36; H, 8.02. DI-HRMS Calcd for $C_{21}H_{30}O_6$: 378.2041. Found: 378.2043. DI-MS *m/z*: 378 (M^+, 3), 333 (25), 318 (6), 113 (16), 112 (14), 99 (100), 86 (10), 55 (10), 45 (17). IR ($CHCl_3$) cm^{-1}: 1767. ^1H NMR δ: 0.94–0.97 (1H, m), 1.25–1.92 (13H, m), 2.04 (1H, ddddd, J=14, 14, 14, 4, 4 Hz, H2), 2.28 (1H, d, J=19 Hz, C*H*$_2$COO), 2.29–2.37 (2H, m), 2.69 (1H, d, J=19 Hz, C*H*$_2$COO), 3.33–3.41 (1H, m), 3.35 (1H, br s, OH), 3.61–3.79 (2H, m, sharpened with D_2O), 3.71–3.77 (1H, m), 3.81–3.89 (1H, m), 3.85 (1H, d, J=3 Hz, H corresponding to H20), 3.90–4.03 (3H, m), 4.26 (1H, d, J=4 Hz, C*H*OCO). ^{13}C NMR δ: 9.8 (CH_2, C corresponding to C12), 15.3 (CH_2, C corresponding to C11), 17.1 (CH_2, C6), 22.1 (CH_2, C2), 31.9 (CH_2, C1), 33.1 (CH, C corresponding to C13), 34.6 (CH_2, C3), 37.9 (CH_2, C7), 38.9 (C, C8), 40.6 (CH_2, *C*H_2COO), 40.9 (C, C10), 47.4 (CH, C9), 50.5 (CH, C5), 61.9 (CH_2, *C*H_2OH), 64.2 (CH_2), 65.4 (CH_2), 70.6 (CH_2, *C*H_2CH$_2$OH), 75.5 (CH, C corresponding to C20), 84.1 (CH, C corresponding to C14), 110.1 (C, C4), 176.3 (C, *C*OO). Another by-product **35** with polarity between **33** and **34** was obtained as a colorless glass employing cyclohexene–toluene (6:1) as the reaction solvent (run a). DI-HRMS Calcd for $C_{21}H_{30}O_6$: 378.2041. Found: 378.2027. DI-MS *m/z*: 378 (M^+, 5), 333 (42), 317 (4), 289 (2), 99 (100), 55 (13), 45 (20). IR ($CHCl_3$) cm^{-1}: 1719. ^1H NMR δ: 0.82–0.91 (1H, m), 1.07–2.07 (12H, m), 2.23 (1H, d, J=19.5 Hz, C*H*$_2$COO), 2.24–2.38 (2H, m), 2.47–2.58 (3H, m), 2.70 (1H, d, J=19.5 Hz, C*H*$_2$COO), 3.58–3.65 (1H, m), 3.68–3.85 (4H, m), 3.89–4.01 (3H, m), 4.58 (1H, br dd, J=4.5, 4 Hz, H13), 4.68 (1H, d, J=6.5 Hz, H20).

4.3.2. HCl treatment of 29 to form 34 and 36 (Table 1, run h). HCl–H_2O (2.5% 0.5 ml) was added to a cooled (0 °C) solution of **29** (30 mg, 74.1 μmol) in THF (2 ml) and the mixture was stirred for 1 h. Saturated $NaHCO_3$–H_2O (5 ml) and EtOAc (5 ml) were added and resulting mixture was vigorously stirred for 2 h at an ambient temperature. Extraction with EtOAc followed by usual work-up and PTLC (0.8% MeOH–CH_2Cl_2) afforded **34** (18 mg, 64%) and **36** (7 mg, 26%) in order of increasing polarity. **36**: Colorless glass. DI-HRMS Calcd for $C_{21}H_{31}NO_4$: 361.2251. Found: 361.2264. DI-MS *m/z*: 361 (M^+, 1), 333 (2), 288 (7), 274 (11), 261 (7), 246 (19), 218 (8), 201 (18), 91 (21), 87 (85), 73 (100), 45 (38). IR ($CHCl_3$) cm^{-1}: 1704, 1631. ^1H NMR δ: 1.19–1.39 (2H, m), 1.72 (1H, ddd, J=13, 13, 4 Hz), 1.80–2.11 (8H, m), 2.14–2.24 (2H, m), 2.24 (1H, d, J=15 Hz), 2.29–2.45 (2H, m), 2.53 (1H, d, J=15 Hz), 2.65 (1H, br ddd, J=13, 3.5, 3.5 Hz, H1), 2.92 (3H, s), 2.99 (3H, s), 3.59–3.77 (3H, m), 3.96–4.06 (1H, m), 5.29 (1H, s), 5.71 (1H, ddd, J=10, 3.5, 2.5 Hz), 5.59 (1H, br d, J=10 Hz). ^{13}C NMR δ: 17.4 (CH_2), 17.5 (CH_2), 21.3 (CH_2), 22.4 (CH_2), 33.3 (CH_2), 35.4 (CH_3), 37.3 (C), 37.9 (CH_2), 38.1 (CH_3), 39.2 (CH_2, C3), 45.3 (CH_2), 45.9 (CH), 47.9 (C), 57.8 (CH, C5), 62.7 (CH_2), 65.2 (CH_2), 105.0 (CH), 129.5 (CH), 136.1 (CH), 170.8 (C), 209.8 (C, C4).

4.3.3. Acetal–ene reaction of 5 to form 6 (37, 38) (Table 2). The procedure for Table 2, run d was described as a representative example. $BF_3\cdot OEt_2$ (392 μl, 3.09 mmol) was added to a cooled (−18 °C) solution of **5** (231 mg, 0.516 mmol) in toluene (10 ml) under an Ar atmosphere with stirring. After stirring for 1 h at −18 °C, saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. After usual work-up, obtained residue (260 mg) was dissolved in acetone

(10 ml) and to this was added *p*-TsOH·H_2O (21 mg, 0.111 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and at 19 °C for 3.5 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (2:1)] yielded crude **38** (12 mg), **6** (138 mg, 66%), and crude **37** (18 mg) in order of increasing polarity. The crude **37** was further purified by PTLC (0.3% MeOH–CH_2Cl_2) to give **37** (6 mg, 3%). The crude-**38** was also separated by PTLC [hexane-1,2-dimethoxyethane (DME) (19:1)] to provide **38** (6 mg, 3%). **6**: Colorless glass. DI-HRMS Calcd for $C_{24}H_{36}O_5$: 404.2561. Found: 404.2569. DI-MS *m*/*z*: 404 (M^+, 3), 369 (5), 302 (5), 275 (8), 240 (31), 91 (39), 73 (36), 57 (100), 45 (41), 41 (47). IR ($CHCl_3$) cm^{-1}: 1717, 1705. ^1H NMR δ: 1.18 (9H, s), 1.45–1.98 (8H, m, including OH), 1.68 (1H, ddd, J=13.5, 8.5, 6 Hz, CH_2CH$_2$OPiv), 1.98–2.09 (1H, m), 2.04 (1H, ddd, J=13, 5, 8.5, 6.5 Hz, CH_2CH$_2$OPiv), 2.21–2.36 (5H, m), 2.42 (1H, br d, J=19 Hz, H11), 2.56 (1H, ddd, J=6.5, 6.5, 1.5 Hz, H14), 3.25 (1H, ddd, J=9, 5, 4.5, 3 Hz, CH_2CH$_2$OH), 3.35 (1H, ddd, J=9.5, 7.5, 3 Hz, CH_2CH$_2$OH), 3.54–3.72 [2H, m, changed with D_2O to 3.58 (1H, ddd, J=11.5, 4.5, 3 Hz) and 3.66 (1H, ddd, J=11.5, 7.5, 3 Hz)], 3.62 (1H, d, J=6.5 Hz, H20), 4.00 (1H, ddd, J=11, 8.5, 6.5 Hz, CH_2OPiv), 4.14 (1H, ddd, J=11, 8.5, 6 Hz, CH_2OPiv), 5.60 (1H, ddd, J=9.5, 3, 3 Hz, H12), 5.69 (1H, dddd, J=9.5, 6.5, 2, 1.5 Hz, H13). ^{13}C NMR δ: 19.1 (CH_2, C6), 25.6 (CH_2, C2), 27.17 ($CH_3\times3$), 27.23 (CH_2, C11), 28.6 (CH_2, C1), 33.6 (CH_2, *C*H$_2$CH$_2$OPiv), 33.8 (CH_2, C7), 38.6 (C, *C*Me$_3$), 41.5 (CH_2, C3), 42.6 (C, C8), 47.7 (CH, C14), 53.8 (CH, C9), 54.0 (C, C10), 56.5 (CH, C6), 62.0 (CH_2, *C*H$_2$OH), 62.5 (CH_2, *C*H$_2$OPiv), 69.8 (CH_2, *C*H$_2$CH$_2$OH), 81.2 (CH, C20), 126.2 (CH, C12), 126.9 (CH, C13), 178.4 (C), 212.1 (C). **37**: Colorless glass. DI-HRMS Calcd for $C_{24}H_{36}O_5$: 404.2561. Found: 404.2580. DI-MS *m*/*z*: 404 (M^+, 3), 342 (16), 302 (8), 275 (14), 240 (28), 213 (39), 91 (37), 73 (32), 57 (100), 45 (49), 41 (48). IR ($CHCl_3$) cm^{-1}: 1708. ^1H NMR δ: 1.18 (9H, s), 1.40–1.73 (6H, m), 1.41 (1H, br d, J=4.5 Hz, H9), 1.62 (1H, br s, OH), 1.98–2.42 (8H, m), 2.53 (1H, br d, J=6 Hz, H5), 2.55 (1H, ddd, J=7, 6, 1.5 Hz, H14), 3.41 (1H, ddd, J=9.5, 5, 3.5 Hz), 3.46 (1H, ddd, J=9.5, 6.5, 3.5 Hz), 3.62–3.79 [2H, m, changed with D_2O to 3.66 (1H, ddd, J=11.5, 5, 3.5 Hz) and 3.73 (1H, ddd, J=11.5, 6.5, 3.5 Hz)], 3.96 (1H, d, J=6 Hz), 4.00 (1H, ddd, J=10.5, 8, 6.5 Hz), 4.09 (1H, ddd, J=10.5, 8.5, 6 Hz), 5.60 (1H, ddd, J=9.5, 3, 3 Hz), 5.69 (1H, dddd, J=9.5, 7, 2, 1.5 Hz). ^{13}C NMR δ: 17.8 (CH_2), 23.7 (CH_2), 25.9 (CH_2), 27.2 ($CH_3\times3$), 28.4 (CH_2), 32.3 (CH_2), 33.5 (CH_2), 38.6 (C), 41.3 (CH_2), 43.3 ($\times2$, CH and C, C8 and C9), 46.4 (CH), 53.1 (C), 57.3 (CH, C5), 61.9 (CH_2), 62.4 (CH_2), 70.3 (CH_2), 87.6 (CH), 126.2 (CH), 126.7 (CH), 178.4 (C), 210.7 (C). **38**: Colorless glass. DI-HRMS Calcd for $C_{22}H_{30}O_3$: 342.2193. Found: 342.2201. DI-MS *m*/*z*: 342 (M^+, 2), 240 (56), 212 (20), 129 (25), 91 (31), 57 (100), 41 (64). IR ($CHCl_3$) cm^{-1}: 1709. ^1H NMR δ: 1.06–1.15 (2H, m, H14 and H20), 1.18 (9H, s), 1.32–1.42 (1H, m), 1.37–1.52 (2H, m), 1.52–1.73 (5H, m), 1.80–2.06 (3H, m), 1.99 (1H, dd, J=7, 1.5 Hz), 2.20–2.39 (3H, m), 3.94–4.09 (2H, m), 5.67 (1H, ddd, J=8, 7, 2 Hz, H11), 6.11 (1H, ddd, J=8, 5.5, 1.5 Hz, H12). ^{13}C NMR δ: 16.4 (CH, C13), 18.8 (CH, C20), 19.8 (CH_2, C6), 23.7 (CH_2, C2), 24.0 (CH, C14), 27.2 ($CH_3\times3$), 29.3 (CH_2), 31.9 (CH_2), 32.8 (CH_2), 38.6 (C), 39.2 (C), 41.8 (CH_2), 48.7 (C), 53.2 (CH), 54.0 (CH), 62.2 (CH_2), 124.3 (CH, C11), 125.7 (CH, C12), 178.3 (C), 212.4 (C).

4.3.4. Acetal–ene reaction, reacetalization of 5 to form 39, 40, and 41. The crude ene reaction product (592 mg) prepared as above from **5** (582 mg, 1.30 mmol) and $BF_3\cdot OEt_2$ (0.80 ml, 6.50 mmol) was dissolved in benzene (40 ml). Ethylene glycol (3.60 ml, 64.6 mmol) and *p*-TsOH·H_2O (30 mg, 0.16 mmol) were added to the solution and the mixture was heated under reflux for 1.5 h with Dean–Stark apparatus. The same work-up as before followed by separation by PTLC [benzene–EtOAc (8:1)] furnished crude-**40** (42 mg), **39** (408 mg, 70%), and crude **41** (35 mg) in order of increasing polarity. The crude-**40** was purified by PTLC [hexane–CH_2Cl_2 (1:1)] to yield **40** (25 mg, 3%). Crude **41** was also separated by PTLC [benzene–EtOAc (3:1)] to afford **41** (18 mg, 3%). **39**: Colorless glass. DI-HRMS Calcd for $C_{26}H_{40}O_6$: 448.2823. Found: 448.2831. DI-MS *m*/*z*: 448 (M^+, 5), 403 (11), 386 (3), 363 (2), 319 (3), 285 (3), 284 (3), 257 (4), 112 (16), 99 (100), 57 (50), 45 (23), 41 (20). IR ($CHCl_3$) cm^{-1}: 1711. ^1H NMR δ: 1.00–1.11 (1H, m), 1.17–1.28 (2H, m), 1.18 (9H, s), 1.51–1.89 (9H, m), 2.06 (1H, ddd, J=13.5, 8.5, 6.5 Hz), 2.07 (1H, br d, J=13.5 Hz, H1), 2.18 (1H, dddd, J=19, 5, 2.5, 2.5 Hz, H11), 2.36 (1H, br d, J=19 Hz, H11), 2.50 (1H, ddd, J=6.5, 6, 1 Hz, H14), 2.85 (1H, t, J=6.5 Hz, OH), 3.33–3.41 (1H, m), 3.51–3.59 (1H, m), 3.66–3.73 (2H, m), 3.77–3.87 (1H, m), 3.87–4.00 (3H, m), 4.00 (1H, ddd, J=10.5, 8.5, 6.5 Hz), 4.13 (1H, ddd, J=10.5, 8.5, 6 Hz), 4.42 (1H, d, J=6.5 Hz), 5.59 (1H, br ddd, J=9.5, 2.5, 2.5 Hz, H12), 5.66 (1H, br dd, J=9.5, 6.5 Hz, H13). ^{13}C NMR δ: 18.3 (CH_2), 21.2 (CH_2), 26.9 (CH_2), 27.2 ($CH_3\times3$), 28.8 (CH_2), 33.5 (CH), 34.1 (CH_2), 34.7 (CH_2, C3), 38.5 (C), 42.3 (C), 47.6 (CH), 48.4 (C), 50.6 (CH, C5), 54.8 (CH), 62.3 (CH_2), 62.6 (CH_2), 63.9 (CH_2), 65.4 (CH_2), 69.7 (CH_2), 80.6 (CH), 110.4 (C, C5), 125.9 (CH), 127.4 (CH), 178.4 (C). **40**: Colorless glass. DI-HRMS Calcd for $C_{24}H_{34}O_4$: 386.2455. Found: 386.2460. DI-MS *m*/*z*: 386 (M^+, 4), 284 (27), 257 (5), 195 (6), 99 (100), 57 (38), 41 (17). IR ($CHCl_3$) cm^{-1}: 1712. ^1H NMR δ: 0.82–0.96 (1H, m), 1.07 (1H, ddd, J=7, 5, 1 Hz, H14), 1.17 (9H, s), 1.19–1.82 (15H, m), 3.80–4.05 (6H, m), 5.57 (1H, ddd, J=8, 6.5, 2 Hz, H11), 6.08 (1H, ddd, J=8, 5.5, 1.5 Hz, H12). ^{13}C NMR δ: 16.1 (CH, C13), 18.8 (CH_2), 19.1 (CH, C20), 20.4 (CH_2), 24.2 (CH, C14), 27.2 ($CH_3\times3$), 29.8 (CH_2), 32.6 (CH_2), 32.9 (CH), 35.5 (CH_2), 38.5 (C), 39.2 (C), 43.8 (C), 48.7 (CH), 54.0 (CH), 62.4 (CH_2), 64.4 (CH_2), 65.4 (CH_2), 110.5 (C, C4), 123.8 (CH), 125.8 (CH), 178.4 (C). **41**: Colorless glass. DI-HRMS Calcd for $C_{26}H_{42}O_7$: 466.2928. Found: 466.2924. DI-MS *m*/*z*: 466 (M^+, 2), 421 (18), 405 (2), 364 (11), 319 (7), 302 (6), 112 (30), 99 (100), 73 (16), 57 (84), 45 (15), 41 (21). IR ($CHCl_3$) cm^{-1}: 1713. ^1H NMR δ: 0.76 (1H, dd, J=2.5, 2.5 Hz, H9), 0.80 (1H, ddd, J=13, 13, 4.5 Hz, H1), 1.21–1.41 (4H, m), 1.23 (9H, s), 1.41–1.89 (11H, m, including secondary OH), 1.90–2.03 (2H, m), 2.33 (1H, br ddd, J=13, 3, 3 Hz, H1), 3.24 (1H, br dd, J=5.5, 5.5 Hz, primary OH), 3.35–3.44 (1H, m), 3.56–3.65 (2H, m), ca. 3.63–3.74 (3H, m), 3.79–3.99 (5H, m), 4.70 (1H, d, J=2.5 Hz, C*H*OH). ^{13}C NMR δ: 10.5 (CH_2, C corresponding to C12), 14.8 (CH_2, C corresponding to C11), 16.6 (CH_2), 22.2 (CH_2), 27.2 ($CH_3\times3$), 32.2 (CH_2), 33.8 (CH, C corresponding to C13), 34.9 (CH_2), 35.0 (CH_2), 36.9 (CH_2), 37.1 (C), 39.1 (C), 40.6 (C), 46.7 (CH), 50.8 (CH), 59.9 (CH_2), 61.9

(CH_2), 64.3 (CH_2), 65.4 (CH_2), 70.2 (CH_2), 74.6 (CH, *C*HOH), 75.8 (CH), 110.4 (C), 177.8 (C).

4.4. Model deprotection of 2-hydroxyethyl group and allylic oxidation of 33 (Scheme 7)

4.4.1. Bromination of 33 to form 42. Ph_3P (33 mg, 0.143 mmol) and CBr_4 (33 mg, 99.4 μmol) were added to a cooled (0 °C) solution of **33** (20 mg, 49.4 μmol) in CH_2Cl_2 (4 ml) and the mixture was stirred at 20 °C for 1 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [CH_2Cl_2–EtOAc (19:1)] gave **42** (20 mg, 87%) as a colorless glass. DI-HRMS Calcd for $C_{23}H_{34}BrNO_4$: 469.1650, 467.1670. Found: 469.1654, 467.1671. DI-MS *m*/*z*: 469, 467 (M^+, 10, 10), 424, 422 (3, 2), 388 (16), 360 (23), 344 (8), 273 (11), 257 (11), 99 (100), 87 (67), 72 (27), 45 (28). IR ($CHCl_3$) cm^{-1}: 1632. ^1H NMR δ: 1.02 (1H, ddd, J=13, 13, 4 Hz, H1), 1.22 (1H, ddd, J=13.5, 12.5, 4 Hz, H3), 1.42 (1H, br d, J=5.5 Hz, H9), 1.50–1.79 (7H, m), 1.86–1.96 (1H, m), 2.04 (1H, br dddd, J=13, 3, 3, 1.5 Hz, H1), 2.17 (1H, dddd, J=18, 5.5, 2.5, 2 Hz, H11), 2.36 (1H, br d, J=18.5 Hz, H11), 2.45 (1H, d, J=15.5 Hz), 2.69 (1H, d, J=15.5 Hz), 2.90 (1H, ddd, J=6.5, 6.5, 1.5 Hz), 2.92 (3H, s), 3.00 (3H, s), 3.38–3.54 (2H, m, C*H*$_2$Br), 3.55–3.64 (1H, m), 3.67–3.81 (2H, m), 3.85–3.98 (3H, m), 4.33 (1H, d, J=6.5 Hz), 5.55 (1H, ddd, J=9.5, 3, 2.5 Hz), 5.68 (1H, dddd, J=9.5, 6.5, 2, 2 Hz). ^{13}C NMR δ: 18.2 (CH_2), 21.0 (CH_2), 27.0 (CH_2), 28.7 (CH_2), 30.4 (CH_2, *C*H_2Br), 33.9 (CH_2), 34.9 (CH_2), 35.3 (CH_3), 37.5 (CH_2), 37.8 (CH_3), 43.7 (C), 48.3 (CH), 48.4 (C), 50.6 (CH), 54.6 (CH), 63.9 (CH_2), 65.4 (CH_2), 69.6 (CH_2, *C*H_2CH$_2$Br), 81.3 (CH), 110.3 (C), 125.3 (CH), 129.0 (CH), 172.5 (C).

4.4.2. Reductive deprotection of 42 to form 43. Zn dust (252 mg, 3.85 mg atom) and NH_4Cl (10 mg, 0.187 mmol) were added to a solution of **42** (18 mg, 38.5 μmol) in 2-propanol–H_2O (14:1, 5 ml) and the mixture was refluxed with stirring for 3 h. Saturated NH_4Cl–H_2O was added and the whole was filtered under reduced pressure. Extraction with CH_2Cl_2 followed by PTLC [hexane-DME (2:1)] afforded **43** (13 mg, 94%) as a colorless glass. DI-HRMS Calcd for $C_{21}H_{34}NO_4$: 361.2251. Found: 361.2240. DI-MS *m*/*z*: 361 (M^+, 56), 332 (24), 316 (41), 274 (15), 245 (22), 183 (23), 99 (87), 87 (100), 72 (46), 55 (29), 45 (50). IR ($CHCl_3$) cm^{-1}: 1626. ^1H NMR δ: 1.09 (1H, ddd, J=13, 13, 4 Hz), 1.23 (1H, ddd, J=13, 12.5, 4 Hz), 1.51 (1H, br d, J=5 Hz), 1.54–1.94 (9H, m), 2.12 (1H, br d, J=11.5 Hz, OH), 2.28 (1H, dd, J=19.5, 5 Hz), 2.38 (1H, br d, J=19.5 Hz), 2.49 (1H, d, J=15.5 Hz), 2.59 (1H, d, J=15.5 Hz), 2.85–2.92 (1H, m), 2.93 (3H, s), 3.01 (3H, s), 3.73–3.81 (1H, m), 3.84–4.00 (3H, m), 4.70 (1H, br dd, J=11.5, 7 Hz, changed to d, J=7 Hz with D_2O, H20), 5.72–5.83 (2H, m). ^{13}C NMR δ: 18.0 (CH_2), 21.1 (CH_2), 27.5 (CH_2), 29.1 (CH_2), 33.9 (CH_2), 34.9 (CH_2), 35.3 (CH_3), 37.6 (CH_2), 37.9 (CH_3), 43.7 (C), 48.4 (C, C10), 50.0 (CH), 50.5 (CH, C14), 53.8 (CH), 63.9 (CH_2), 65.5 (CH_2), 72.6 (CH, C20), 110.1 (C), 128.6 (CH), 129.6 (CH), 172.4 (C).

4.4.3. Dess–Martin oxidation of 43 to form 44. A solution of **43** (12 mg, 33.2 μmol) and Dess–Martin periodinane (70 mg, 0.165 mmol) in CH_2Cl_2 (4 ml) was refluxed with stirring for 8 h. Saturated $NaHCO_3$–H_2O and saturated $Na_2S_2O_3$–H_2O were added and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [hexane–DME (3:2)] provided **44** (11 mg, 92%) as colorless prisms, mp 195–196 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.19; H, 8.13; N, 3.90. Found: C, 70.03; H, 8.23; N, 3.94. DI-HRMS Calcd for $C_{21}H_{29}NO_4$: 359.2095. Found: 359.2084. DI-MS *m*/*z*: 359 (M^+, 3), 331 (27), 244 (21), 129 (27), 99 (100), 91 (24), 87 (67), 72 (34), 55 (25), 45 (37). IR ($CHCl_3$) cm^{-1}: 1727, 1635. ^1H NMR δ: 1.25 (1H, ddd, J=13, 13, 4 Hz), 1.34 (1H, ddd, J=13.5, 13.5, 4.5 Hz), 1.51–1.66 (2H, m), 1.69–1.92 (6H, m), 2.09 (1H, br dd, J=5.5, 3 Hz), 2.22–2.40 (3H, m), 2.47 (1H, d, J=16 Hz), 2.52 (1H, d, J=16 Hz), 2.94 (1H, dd, J=7.5, 2.5 Hz, H14), 2.94 (3H, s), 3.02 (3H, s), 3.73–3.81 (1H, m), 3.83–4.02 (3H, m), 5.70 (1H, ddd, J=9.5, 3, 2.5 Hz), 5.80 (1H, dddd, J=9.5, 7.5, 2, 1.5 Hz). ^{13}C NMR δ: 19.5 (CH_2), 20.0 (CH_2), 26.1 (CH_2), 29.8 (CH_2), 34.0 (CH_2), 34.8 (CH_2), 35.4 (×2, CH_3 and CH_2), 37.8 (CH_3), 41.1 (C), 51.1 (CH), 52.7 (CH), 54.9 (C, C10), 56.7 (CH, C14), 64.0 (CH_2), 66.0 (CH_2), 109.2 (C), 126.8 (CH), 128.1 (CH), 171.5 (C), 211.7 (C, C20).

4.4.4. Oxidation of 42 with CrO_3 and 3,5-dimethylpyrazole. To a cooled (−18 °C) slurry of CrO_3 (49 mg, 0.490 mmol) in CH_2Cl_2 was added 3,5-dimethylpyrazole (55 mg, 0.573 mmol) and the mixture was stirred for 15 min. A solution of **42** (19 mg, 40.6 μmol) in CH_2Cl_2 (2 ml) was added to this and the resulting mixture was stirred at −18 to 27 °C for 38 h. Saturated $NaHCO_3$–H_2O and saturated $Na_2S_2O_3$–H_2O were added and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC (0.5% MeOH–CH_2Cl_2) provided recovery of **42** (5.5 mg, 29%) and a mixture of **45** and **46** (15 mg) in order of increasing polarity. The latter was further purified by PTLC [hexane–2-propanol (6:1)] and yielded **45** (5.5 mg, 28%) and **46** (5.5 mg, 28%) in order of decreasing polarity. **45**: Colorless glass. DI-HRMS Calcd for $C_{23}H_{32}BrNO_5$: 483.1443, 481.1463. Found: 483.1434, 481.1461. DI-MS *m*/*z*: 483, 481 (M^+, 6, 6), 402 (16), 397, 395 (6, 6), 271 (84), 109, 107 (17, 17), 99 (100), 87 (84), 72 (41), 55 (25), 45 (32). IR ($CHCl_3$) cm^{-1}: 1661, 1639. ^1H NMR δ: 1.20–1.38 (3H, m), 1.47–1.82 (7H, m), 2.08 (1H, br dd, J=1.5, 1.5 Hz, H9), 2.19 (1H, ddd, J=13.5, 6.5, 2 Hz), 2.25 (1H, d, J=16 Hz), 2.57 (1H, d, J=16 Hz), 2.89 (3H, s), 2.91 (3H, s), 3.39 (1H, dt, J=10, 6.5 Hz), 3.45 (1H, dt, J=10, 6.5 Hz), 3.72 (2H, dd, J=6.5, 6.5 Hz), 3.76–3.85 (2H, m), 3.88–4.00 (3H, m), 4.66 (1H, d, J=6.5 Hz), 6.11 (1H, dd, J=9.5, 1.5 Hz, H12), 7.16 (1H, dd, J=9.5, 7.5 Hz, H13). ^{13}C NMR δ: 18.0 (CH_2), 20.7 (CH_2), 29.5 (CH_2), 30.2 (CH_2), 34.5 (CH_2), 34.9 (CH_2), 35.3 (CH_3), 37.6 (CH_3), 38.0 (CH_2), 47.7 (C), 49.6 (CH), 50.0 (CH), 51.8 (C), 64.0 (CH_2), 65.5 (CH_2), 70.1 (CH_2), 74.6 (CH, C9), 79.6 (CH, C20), 109.6 (C), 129.4 (CH, C12), 153.7 (CH, C13), 170.8 (C), 202.0 (C, C11). **46**: Colorless glass. DI-HRMS Calcd for $C_{23}H_{32}BrNO_5$: 483.1443, 481.1463. Found: 483.1418, 481.1461. DI-MS *m*/*z*: 483, 481 (M^+, 13, 10), 402 (11), 374 (16), 358 (11), 271 (12), 109, 107 (14, 14), 99 (100), 87 (33), 72 (32), 55 (11), 45 (17). IR ($CHCl_3$) cm^{-1}: 1677, 1638. ^1H NMR δ: 1.19–1.89 (10H, m), 2.01 (1H, br d, J=13 Hz), 2.32 (1H, d, J=15.5 Hz), 2.39 (1H, d, J=15.5 Hz), 2.66 (1H, dd, J=7, 1.5 Hz, H9), 2.89 (3H, s), 2.92 (3H, s), 3.18 (1H, ddd, J=7, 1.5, 1.5 Hz, H14), 3.32 (2H, dd, J=6.5, 6.5 Hz), 3.56 (1H, dt, J=10.5, 6.5 Hz),

3.75 (1H, dt, J=10.5, 6.5 Hz), 3.76–3.85 (1H, m), 3.88–4.01 (3H, m), 4.61 (1H, d, J=7 Hz), 6.10 (1H, dd, J=9.5, 1.5 Hz, H12), 7.08 (1H, dd, J=9.5, 7 Hz, H11). ^{13}C NMR δ: 17.9 (CH_2), 20.7 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 33.9 (CH_2), 35.0 (CH_2), 35.3 (CH_3), 36.3 (CH_2), 37.7 (CH_3), 49.4 (CH), 51.5 (C), 53.1 (C), 56.7 (CH, C9), 64.0 (CH_2), 65.4 (CH_2), 66.1 (CH, C14), 70.8 (CH_2), 77.5 (CH), 109.7 (C), 131.1 (CH, C12), 151.1 (CH, C11), 170.8 (C), 200.4 (C, C13).

4.4.5. Zn reduction of 45 to form 47. In a similar manner as for the preparation of **43** from **42** (Section 4.4.2), **45** (6.5 mg, 13.5 μmol) was treated with Zn (220 mg, 3.36 mg atom) and NH_4Cl (11 mg, 0.206 mmol) for 3 h. The same work-up and PTLC (2% MeOH–CH_2Cl_2) gave **47** (4.5 mg, 89%) as a colorless glass. DI-HRMS Calcd for $C_{21}H_{31}NO_5$: 377.2200. Found: 377.2209. DI-MS m/z: 377 (M^+, 22), 332 (6), 276 (7), 180 (10), 99 (100), 87 (61), 72 (41), 55 (17), 46 (23), 45 (21). IR ($CHCl_3$) cm^{-1}: 1689, 1640. ^{1}H NMR δ: 1.06–1.21 (2H, m), 1.32 (1H, ddd, J=12.5, 12.5, 5 Hz, H3), 1.46–1.74 (6H, m), 1.66 (1H, br s, OH), 1.75–1.84 (3H, m), 2.15 (1H, d, J=16.5 Hz), 2.15–2.32 (3H, m), 2.28 (1H, d, J=16.5 Hz), 2.64 (1H, ddd, J=19, 10, 10 Hz, H12), 2.92 (3H, s), 2.94 (3H, s), 2.98–3.05 (1H, m), 3.77–3.85 (1H, m), 3.86–4.01 (3H, m), 4.95 (1H, br d, J=7 Hz, H20). ^{13}C NMR δ: 17.9 (CH_2), 20.8 (CH_2), 20.9 (CH_2, C13), 27.0 (CH_2), 34.4 (CH_2), 35.2 (CH_2), 35.3 (CH_3), 36.9 (CH_2, C12), 37.6 (CH_3), 38.5 (CH_2), 45.5 (CH, C14), 46.3 (C), 48.7 (C), 49.7 (CH), 64.0 (CH_2), 65.5 (CH_2), 70.2 (CH), 74.2 (CH, C9), 109.7 (C), 170.2 (C), 215.0 (C).

4.4.6. Zn reduction of 46 to form 48, 49, 50. In the same manner as for the procedure of Section 4.4.5, **46** (6.5 mg, 13.5 μmol) was treated with Zn (220 mg, 3.36 mg atom) and NH_4Cl (11 mg, 0.206 mmol) for 4 h. The same work-up and PTLC (2% MeOH–CH_2Cl_2) gave **48** (2.5 mg, 49%), **50** (2 mg, 39%), and **49** (0.5 mg, 9%) in order of decreasing polarity. **48**: Colorless glass. DI-HRMS Calcd for $C_{21}H_{29}NO_5$: 375.2044. Found: 375.2057. DI-MS m/z: 375 (M^+, 25), 347 (8), 330 (4), 289 (9), 271 (22), 227 (11), 99 (100), 87 (76), 72 (28), 45 (22). IR ($CHCl_3$) cm^{-1}: 1675, 1634. ^{1}H NMR δ: 1.25–1.92 (11H, m, including OH), 2.12 (1H, br d, J=13 Hz, H1), 2.34 (1H, d, J=15.5 Hz), 2.41 (1H, d, J=15.5 Hz), 2.71 (1H, br d, J=7 Hz), 2.89 (3H, s), 2.92 (3H, s), 3.11 (1H, ddd, J=7, 1.5, 1.5 Hz, H14), 3.77–3.85 (1H, m), 3.87–3.98 (3H, m), 5.05 (1H, br d, J=7 Hz, H20), 6.12 (1H, dd, J=9.5, 1.5 Hz), 7.14 (1H, dd, J=9.5, 7 Hz). ^{13}C NMR δ: 17.8 (CH_2), 20.9 (CH_2), 29.6 (CH_2), 33.9 (CH_2), 35.1 (CH_2), 35.3 (CH_3), 36.3 (CH_2), 37.7 (CH_3), 49.5 (CH), 51.6 (C), 52.1 (C), 56.9 (CH), 64.1 (CH_2), 65.4 (CH_2), 68.2 (CH, C14), 69.3 (CH, C20), 109.7 (C), 170.9 (C), 130.9 (CH), 151.8 (CH), 201.5 (C). **49**: Colorless glass. DI-HRMS Calcd for $C_{23}H_{33}NO_5$: 403.2357. Found: 403.2367. DI-MS m/z: 403 (M^+, 25), 374 (15), 358 (7), 317 (21), 99 (100), 87 (22), 72 (33). IR ($CHCl_3$) cm^{-1}: 1672, 1633. ^{1}H NMR δ: 1.04 (3H, dd, J=7, 7 Hz, OCH_2CH_3), 1.20–1.88 (10H, m), 2.00 (1H, br d, J=13 Hz), 2.32 (1H, d, J=15.5 Hz), 2.39 (1H, d, J=15.5 Hz), 2.64 (1H, br d, J=7 Hz), 2.89 (3H, s), 2.92 (3H, s), 3.16 (1H, ddd, J=7, 1.5, 1.5 Hz), 3.30 (1H, dq, J=9, 7 Hz, OCH_2CH_3), 3.49 (1H, dq, J=9, 7 Hz, OCH_2CH_3), 3.74–3.85 (1H, m), 3.87–3.99 (3H, m), 4.54 (1H, d, J=7 Hz), 6.09 (1H, dd, J=9.5, 1.5 Hz), 7.06 (1H, dd, J=9.5, 7 Hz). **50**: Colorless glass. DI-HRMS Calcd for $C_{21}H_{31}NO_5$: 377.2200. Found: 377.2197. DI-MS m/z: 377 (M^+, 19), 332 (10), 192 (7), 168 (12), 99 (100), 87 (40), 72 (32), 55 (15), 46 (22). IR ($CHCl_3$) cm^{-1}: 1701, 1640. ^{1}H NMR δ: 1.23 (1H, ddd, J=13.5, 13.5, 4.5 Hz), 1.32 (1H, ddd, J=13, 13, 4 Hz), 1.42–2.27 (14H, m, including OH), 2.08 (1H, d, J=15.5 Hz), 2.30 (1H, d, J=15.5 Hz), 2.67 (1H, ddd, J=18, 10, 10 Hz, H12), 2.83 (1H, d, J=7.5 Hz, H14), 2.92 (3H, s), 2.96 (3H, s), 3.76–3.85 (1H, m), 3.86–4.00 (3H, m), 4.94 (1H, br d, J=7.5 Hz, H20). ^{13}C NMR δ: 17.9 (CH_2), 19.5 (CH_2, C11), 20.9 (CH_2), 27.7 (CH_2), 33.3 (CH_2), 34.8 (CH_2), 35.4 (CH_3), 36.2 (CH_2, C12), 36.6 (CH_2), 37.8 (CH_3), 47.2 (C), 47.7 (C), 50.0 (CH), 52.5 (CH), 63.9 (CH_2), 65.4 (CH_2), 67.9 (CH, C14), 68.8 (CH, C20), 110.1 (C), 170.4 (C), 212.4 (C).

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