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Synthetic study of hetisine-type aconite alkaloids. Part 3: Total synthesis of (±)-nominine

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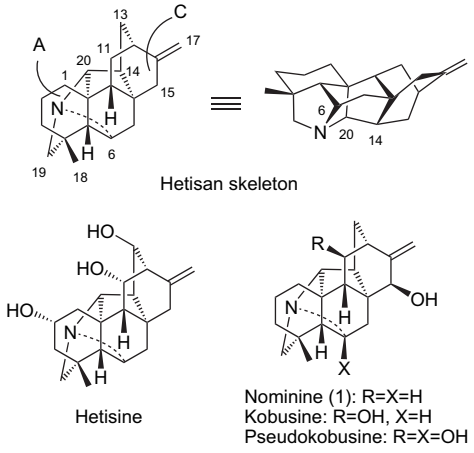
Abstract—Completion of the total synthesis of (±)-nominine (**1**) is described in detail. Based on the results of the preceding two papers, total synthesis of (±)-nominine was accomplished diverging from the intermediate **7**. Thus, following pyrrolidine ring formation through transformation from **7** to **8**, the C-ring was constructed by radical cyclization to form **10** from the enyne precursor **9**. Subsequent elaboration of the C-ring, followed by formation of the azabicyclic ring system, completed a total synthesis of (±)-**1**. Single-crystal X-ray analysis of (±)-**1** unambiguously confirmed its molecular structure and racemic crystal structure.

1. Introduction

1.1. The hetisine-type aconite alkaloid nominine

The term aconite alkaloid is applied to the diterpene alkaloids isolated from *Aconitum*, *Delphinium*, *Consolida*, *Thalictrum*, and *Spiraea*. These alkaloids are generally classified into five skeletons, atidane, veatchane, cycloveatchane, aconitane, and hetisan (the name of which is derived from hetisine) based on their fundamental frameworks.[1,2] Extensive synthetic efforts over the last 40 years have resulted in total syntheses of several alkaloids belonging to the first four of the above five groups. However, the synthesis of even the basic skeleton of the hetisine-type alkaloids, which include hetisine, nominine, kobusine, etc. had remained elusive until we recently reported a total synthesis of (±)-nominine (**1**) (Scheme 1).[3]



Scheme 1. Hetisan skeleton and representative hetisine-type aconite alkaloids.

Nominine (**1**) is structurally the simplest hetisine-type aconite alkaloid. Ochiai et al. first isolated **1** as 'Nomi-base I' from *Aconitum sanyoense* Nakai, collected at Nomi, Sakyo-ku, Kyoto prefecture, Japan in 1956.[4] Sakai et al. gave it the name nominine in 1982 and determined the absolute structure by chemical correlation with kobusine, whose structure was established unequivocally by single crystal X-ray analysis.[5] The name nominine was redundantly given to an insecticidal indole diterpene in 1989.[6]

1.2. Synthetic background

Discovery of the palladium-catalyzed intramolecular α-arylation reaction of aliphatic ketone, formyl, and nitro groups[7] triggered our synthetic studies leading toward the total synthesis of aconite alkaloids with the hetisan skeleton.[8] Our synthetic efforts culminated in a total synthesis of **1**, which was reported in a preliminary communication.[3] In the preceding two papers,[9,10] we have presented full details of the preparation of compound **2** lacking the C-ring of the hetisan framework, starting from **3** by way of the intermediates **4**–**7**. We employed the acetal ene-reaction to form **6**, stereoselective hydrocyanation to form **7**, and azabicyclic ring formation to form **2**, as well as the above Pd-catalyzed cyclization reaction (**4**→**5**), as the key reactions (Scheme 2). Here, we present full details of the synthesis of **1**, diverging from the above-mentioned intermediate **7**.

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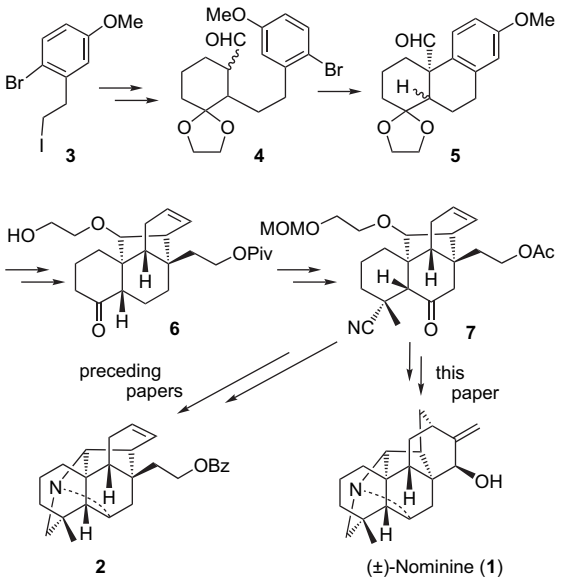
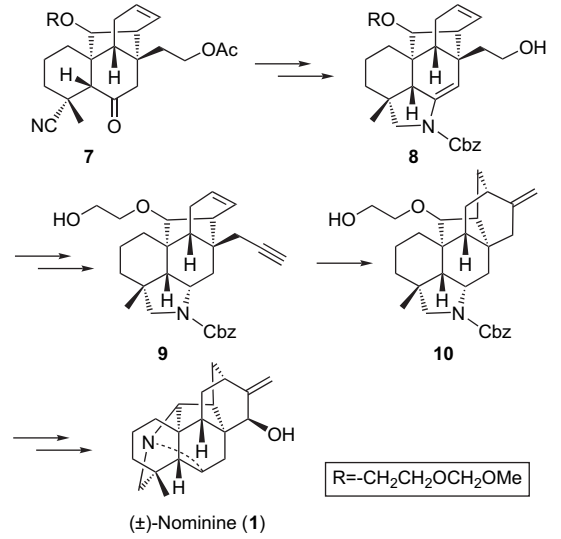


Scheme 2. Outline of the synthetic pathways in the three papers.

We had initially considered synthesizing **1** from **2** through C-ring construction followed by functionalization at C15 with a β-hydroxy substituent. However, taking into consideration that the strong basicity of **2** seriously restricts its versatility as a synthetic intermediate, we decided to construct the bicyclo[2.2.2]octane ring (C-ring) from the intermediate **7**, keeping the nitrogen protected as a carbamate, prior to the creation of the azabicyclic ring system for completion of the total synthesis of **1**.

2. Results and discussion

An outline of the reaction sequence described in this paper is shown in Scheme 3. Compound **7** was transformed to a pentacyclic intermediate **8** according to the method reported in the preceding paper.[10] Compound **8** was led to an enyne derivative **9**, which was then subjected to radical cyclization reaction to secure the hexacyclic intermediate **10**. C-ring elaboration followed by *O*- and *N*-deprotections and azabicyclic ring formation completed the total synthesis of (±)-nominine (**1**). These results constitute the first total synthesis of a hetisine-type aconite alkaloid. We present below full details of not only the reactions along Scheme 3, but also reaction procedures that were ultimately not employed for the total synthesis.

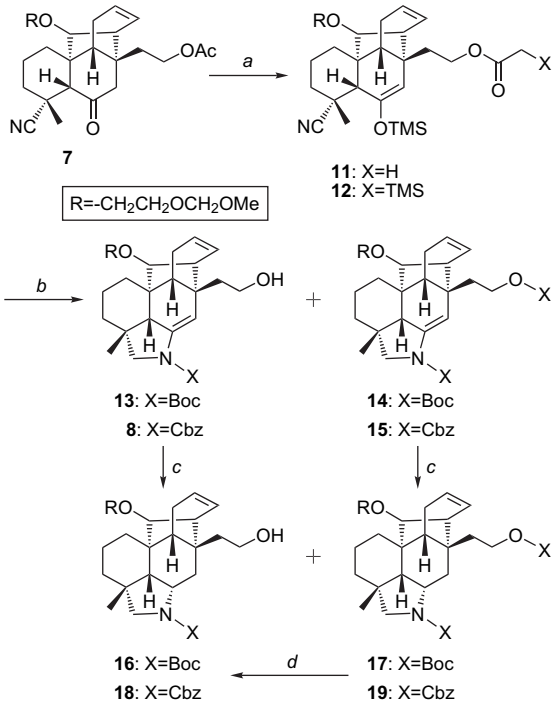


Scheme 3. Outline of the synthesis of **1** from **7**.

2.1. Preparation of pentacyclic intermediates 16 and 18 from 7 by way of 13 and 8

In the preceding paper,[10] we formed the pyrrolidine ring after deprotection of the C20 hydroxy group. In this paper, this protecting group was retained until the final stage of the synthesis with a change of the functional group at the primary hydroxy part of the 2-hydroxyethyl protecting group. The protecting group played a pivotal role in this total synthesis in that it prevented a possible retro-ene reaction with the bond fission of C14 and C20, and it was extremely stable under a wide variety of reaction conditions encountered in the synthetic procedures.

Kinetic enolate formation from **7** with lithium diisopropylamide (LDA) and simultaneous trapping with chlorotrimethylsilane (TMSCl) afforded two products, **11** and **12** (Scheme 4). The latter was a trimethylsilylated compound at the methyl carbon of the acetyl group. Compound **11** was the product derived from the corresponding O-silylated intermediate, which was hydrolyzed during extractive isolation. Of the two products, **11** was subjected, as before,[10] to



Scheme 4. Preparation of **16** and **18** from **7** by way of **13** and **8**: (a) TMSCl, LDA, THF, **11** (79%), **12** (12%); (b) $LiAlH_4$, THF, then Boc_2O or ClCbz, Et_3N, CH_2Cl_2, **13** (62%) from **11**, **14** (16%) from **11**, **13** (55%) overall from **7**, **14** (10%) overall from **7**, **8** (63%) overall from **7**, **15** (4%) overall from **7**; (c) $NaBH_3CN$, 2.5% HCl–H_2O, MeOH, **16** (91%) from **13**, **17** (93%) from **14**, **18** (90%) from **8**, **19** (91%) from **15** and (d) K_2CO_3, MeOH, **16** (quant.) from **17**, **18** (quant.) from **19**.

the lithium aluminum hydride (LAH) reduction followed by protection with di-*tert*-butyl dicarbonate (Boc_2O) to afford **13** (62%) and **14** (16%). As the desired compounds were obtained, the above three operations [enol silylation, LAH reduction, protection with Boc_2O or benzyl chloroformate (ClCbz)] were carried out on **7** without isolation of **11** and **12** to yield **13** (55%) and **14** (10%) or **8** (63%) and **15** (4%), respectively, overall from **7**. Compounds **8** and **15** with the Cbz group functioned as intermediates leading toward **1** in the event, since we could not find suitable reaction conditions to cleave the Boc group after C-ring formation (vide infra).

These four compounds **13**, **14**, **8**, and **15** were separately reduced with sodium cyanoborohydride ($NaBH_3CN$) in a weak acid solvent to afford **16**, **17**, **18**, and **19** in high yields, respectively. Then the carbonates **17** and **19** were converged to **16** and **18**, respectively, by treatment with potassium carbonate (K_2CO_3) in methanol (MeOH).

2.2. Some trials of C-ring formation from 16

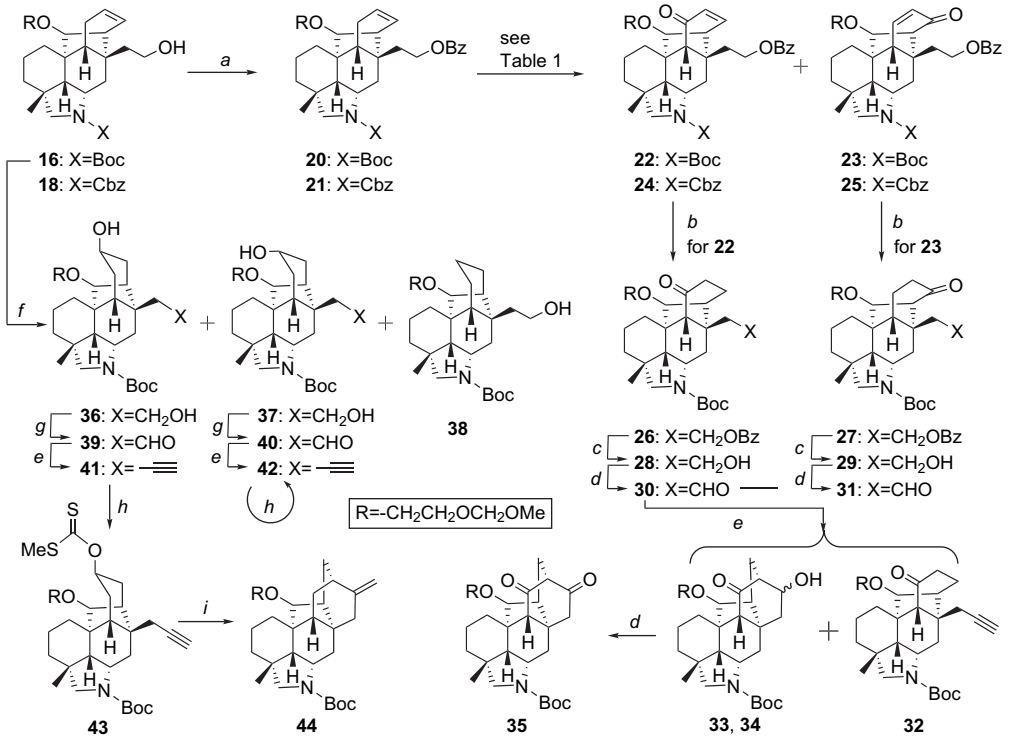
Before description of the C-ring formation by radical cyclization from the enyne precursor **9** to form **10** (Scheme 3), we report here some other attempts to achieve the C-ring formation.

2.2.1. C-ring formation by aldol reaction. Compounds **16** and **18** were led to the benzoates **20** and **21**, respectively, then oxidized with chromium oxide (CrO_3) according to the preceding paper (Scheme 5).[10] Different from the previous case, where the pyrrolidine ring had not yet been formed, the oxidation with CrO_3 and 3,5-dimethylpyrazole did not afford satisfactory results (Table 1). Various amounts of the oxidant were tested (runs a–d), and 6 equiv of CrO_3 (run b) was found to give the best yields of **22** (45%) and **23** (28%). Nevertheless, this condition could not adapted to **21** with the Cbz group, since **24** (12%) and **25** (6%) were obtained only in low yields with 50% recovery of **21** (run e). Further excess of the oxidant resulted in decreased yields of **24**, **25**, and as well as recovery of **21**. Although various conditions[11–14] for the allylic oxidation of **21** were attempted, the only condition affording better results than run e was oxidation with CrO_3 and *tert*-butyl hydroperoxide (*t*-BuOOH),[14] which still gave unsatisfactory yields of **24** (22%) and **25** (16%), along with recovery of **21** in 44% (run f). Since oxidation of **21** gave only disappointing results, we employed **22** and **23** for further transformation in this route.

Table 1. Allylic oxidation of **20** and **21** with CrO_3 (yield: %)

Run[a]	Sub.	CrO_3 (equiv)	Additive[b] (equiv)	**22**	**23**	**24**	**25**	Recovery
a	**20**	4	DP (4.3)	29	20			30
b	**20**	6	DP (6.7)	45	28			4
c	**20**	8	DP (8.7)	34	20			0
d	**20**	12	DP (13)	24	15			0
e	**21**	6.3	DP (7.4)			12	6	50
f	**21**	1.75	BH (10)			22	16	44

[a] All reactions were carried out in CH_2Cl_2.
[b] Additive, DP: 3,5-dimethylpyrazole; BH: *t*-BuOOH.



Scheme 5. Some trials for the C-ring formation: (a) BzCl, Et_3N, CH_2Cl_2, **20** (99%) from **16**, **21** (97%) from **18**; (b) H_2, Pd/C, MeOH, **26** (quant.) from **22**, **27** (quant.) from **23**; (c) K_2CO_3, MeOH, **28** (quant.) from **26**, **29** (quant.) from **27**; (d) PCC–Al_2O_3, CH_2Cl_2, **30** (90%) from **28**, **31** (75%) from **29**, **35** (quant.) from **33**, **35** (quant.) from **34**; (e) dimethyl (1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, **32** (34%), **33** (33%), **34** (22%), **41** (96%) from **39**, **42** (91%) from **40**; (f) $BH_3{\cdot}SMe_2$, THF then H_2O_2, NaOH, **36** (48–17%), **37** (26–9%), **38** (18–62%); (g) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, **39** (75%) from **36**, **40** (75%) from **37**; (h) NaH, imidazole, THF, then CS_2, then MeI, **43** (85%) and (i) Bu_3SnH, AIBN, toluene, **44** (85%).

The enones **22** and **23** were converted to ketoaldehydes **30** and **31** in three steps with conventional methods [(i) hydrogenation on palladium for **26** and **27**, (ii) alcoholysis with potassium carbonate (K_2CO_3) for **28** and **29**, and (iii) oxidation with pyridinium chlorochromate (PCC)–aluminum oxide (Al_2O_3) for **30** and **31**]. Treatment of **30** with dimethyl (1-diazo-2-oxopropyl)phosphonate[15] and K_2CO_3 as before[10] provided the desired compound **32**, but in only 34% yield, together with 33 and 22% yields of the two isomeric aldol products **33** and **34**, whose stereochemistry at the C16 hydroxy group remains unclear. While these aldols **33** and **34** were readily converted to diketone **35** with PCC–Al_2O_3, reaction of the compound **35** with methylenetriphenylphosphorane gave no desired product but recovery in a preliminary experiment.

2.2.2. C-ring formation by radical cyclization from xanthate. As the attempted route of allylic oxidation followed by aldol reaction proved tricky, we next explored the route by way of the radical intermediate generated from xanthate. The hydroboration–oxidation reaction of **16** provided three products, **36**, **37**, and **38**. We could not find suitable reaction conditions to prevent the formation of the dihydro derivative **38**, and its yield varied from 18 to 62% even though the same equivalent ratio of borane–dimethyl sulfide complex ($BH_3 \cdot SMe_2$) was used, with a corresponding yield variation of **36** (48–17%) and **37** (26–9%). The direction of the hydroxy group of **36** and **37** was determined by the fact that H12 of the major product **36** (equatorial OH) appeared at δ4.22 (ddd, J=10, 10, 7.5, 7.5 Hz) in the ^{1}H NMR spectrum.

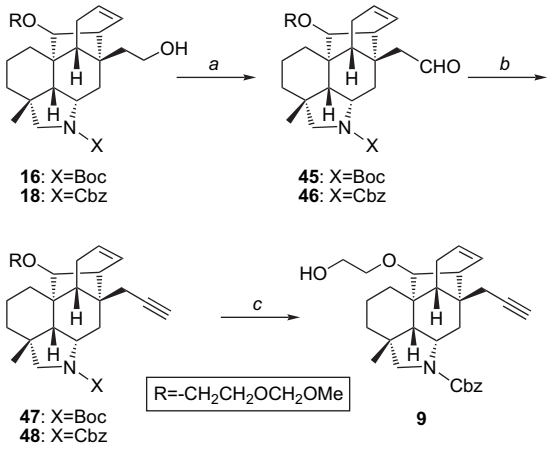
The primary alcohol of the obtained diols **36** and **37** was selectively oxidized with iodobenzene diacetate [PhI(OAc)$_2$] and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to yield **39** and **40**, respectively.[16] These products were led to the alkynes **41** and **42** in high yields. Our choice of method to cyclize the C-ring from the alkyne-alcohols **41** and **42** was the intramolecular radical cyclization reaction via thioimidazolide or xanthate ester.[17] As the attempted formation of thioimidazolide from **41** or **42** with thiocarbonyldiimidazole in refluxing 1,2-dichloroethane resulted in an intractable mixture from the former or recovery of the starting material from the latter, we next tried to form a xanthate ester as the radical precursor. According to the literature,[18] the equatorial alcohol **41** was easily converted to the corresponding xanthate **43** by successive treatment with sodium hydride (NaH)–imidazole in boiling tetrahydrofuran (THF), carbon disulfide (CS_2), and then iodomethane (MeI). On the other hand, the axial alcohol **42** did not afford the xanthate at all under the same or modified [in THF–dimethylformamide (DMF)] conditions. Radical reaction of **43** with tributyltin hydride (Bu_3SnH) in the presence of 2,2′-azobisisobutyronitrile (AIBN) readily provided the desired hexacyclic compound **44** in a high yield. However, all attempts to remove the methoxymethyl (MOM) or Boc group from **44** failed due to the instability of the newly formed methylenebicyclo[2.2.2]octane ring of **44** under acidic conditions.

Thus, we could acquire the desired compound **44** from **16**. This route, however, suffered from the following three drawbacks: (1) the reproducibility of the hydroboration–oxidation used to form **36** from **16** was poor; (2) the xanthate could not be obtained from the axial alcohol **37**; (3) the MOM and Boc groups could not be removed after the formation of the methylenebicyclo[2.2.2]octane ring. Therefore, we decided to explore another C-ring formation method starting from **16** and **18** in a more straightforward manner.

2.3. C-ring formation from 16 and 18 by radical cyclization of enyne precursor

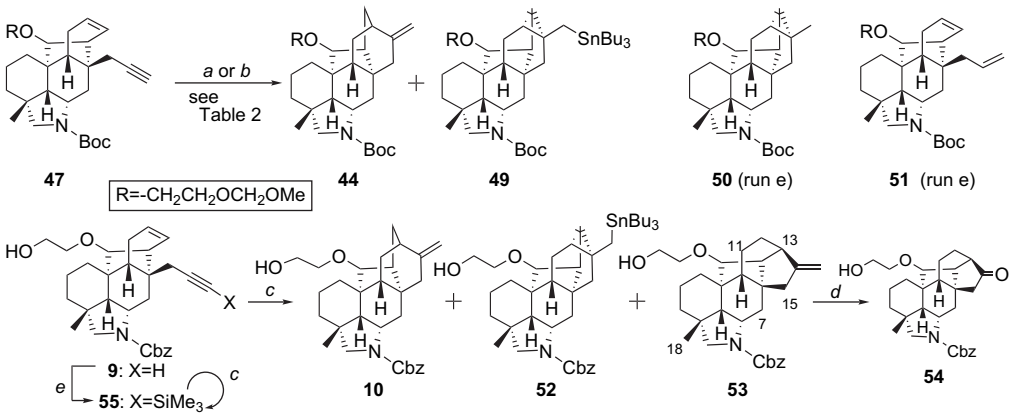
As described above, it turned out that (1) the methylenebicyclo[2.2.2]octane framework was more sensitive than expected to acidic conditions, and (2) the radical cyclization method was effective for construction of this framework, but the examined xanthate route was problematic. Taking these points into consideration, we decided to construct the C-ring by the radical cyclization of an enyne precursor prepared from **16** and **18**.

2.3.1. Preparation of enyne radical cyclization precursors. Compounds **16** and **18** were oxidized separately with PCC–Al_2O_3 as usual to get the aldehydes **45** and **46**, respectively (Scheme 6). These were led to the enyne derivatives **47** and **48**, respectively, with dimethyl (1-diazo-2-oxopropyl)-phosphonate[15] and K_2CO_3 as before. The MOM group of **48** was cleaved at this stage to yield **9**, which was finally employed as the radical cyclization precursor. This is because of the instability of the methylenebicyclo[2.2.2]octane framework under acidic conditions, as noted above. Compounds **47** and **9** were the precursors of choice for the next radical cyclization reaction.



Scheme 6. Preparation of enyne radical cyclization precursors: (a) PCC–Al_2O_3, CH_2Cl_2, **45** (91%) from **16**, **46** (84%) from **18**; (b) dimethyl (1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, **47** (96%) from **45**, **48** (98%) from **46** and (c) 5% HCl, DME–H_2O (3:1), **9** (96%) from **48**.

2.3.2. C-ring formation from 47 and 9. At first, compound **47** was subjected to radical cyclization reaction (Scheme 7, Table 2). The reactions with Bu_3SnH in the presence of AIBN in refluxing benzene or toluene (runs a–d) according to the protocol of Stork[18] afforded the desired compound **44** and a stannylcyclopropane derivative **49** as a by-product after destannylation of the vinyl stannane products with silica gel. Compound **44** was identical with an authentic specimen obtained via the xanthate route from **43** (Scheme 5). The reactions with 10 equiv of Bu_3SnH gave comparable results in either benzene (run a) or toluene (run b). The



Scheme 7. C-ring formation from **47** and **9** by radical reaction or reductive palladium catalyst: (a) Bu_3SnH, AIBN (20 mol %), benzene or toluene under reflux, then SiO_2, CH_2Cl_2 (for yields see Table 2); (b) $Pd_2(dba)_3 \cdot CHCl_3$, poly(methylhydrosiloxane) (PMHS), *N*,*N*′-bis(benzylidene)-1,2-ethylenediamine, HOAc, benzene under reflux (for yields see Table 2); (c) slow addition of Bu_3SnH in toluene into dilute solution of **9** and AIBN in toluene under reflux, then SiO_2, CH_2Cl_2, **10** (57%), **52** (31%), **53** (8%); (d) cat. OsO_4, $NaIO_4$, THF–H_2O, **54** (quant.) and (e) TMSCl, $(TMS)_2NLi$, THF, then aq HCl–THF, **55** (81%).

Table 2. C-ring formation from **47** to form **44**

Run	Bu_3SnH (equiv)	Solvent	Time (h)	**44** (%)	**49** (%)	Recovery (%)
a	10	Benzene	2	40	50	—
b	10	Toluene	0.5	43	49	—
c	5	Benzene	2	33	52	—
d	1.3	Toluene	3	50	18	29
e[a]	—	Benzene	0.5	19	—	—

[a] Reaction was carried out with $Pd_2(dba)_3 \cdot CHCl_3$, PMHS, *N*,*N*′-bis(benzylidene)-1,2-ethylenediamine, and HOAc; **50** (19%) and **51** (25%) were also isolated.

reaction in benzene with 5 equiv of Bu_3SnH resulted in lowering of the yield of **44** (run c). The use of a slight excess amount (1.3 equiv) of Bu_3SnH brought about a better result, giving rise to **44** in 50% yield along with **49** in 18% yield and a recovery of **47** in 29% yield (run d). Although the palladium-catalyzed reductive cyclization[19] was adopted for **47**, **44** was obtained in only 19% yield, and the cyclopropane derivative **50** (19%) and simply reduced compound **51** (25%) were isolated as by-products (run e).

These results indicated that coexistence of an excess amount of Bu_3SnH with **47** increased the formation of the by-product **49**. With this in mind, we executed the radical cyclization of **9** as follows so as to allow the substrate **9** to react with small amounts of Bu_3SnH at a time (Scheme 7). A solution of Bu_3SnH (70 mM) in toluene was slowly added dropwise (over 1.5 h) to a solution of **9** (5.5 mM) and a catalytic amount of AIBN (22 mol %) in toluene at reflux to secure the desired compound **10** in 57% yield, together with by-products **52** (31%) and **53** (8%). The structure of **53** was confirmed by transformation to the corresponding cyclopentanone derivative **54** (IR: ν_{max}=1730 cm^{-1}) through the Lemieux oxidation. The formation of the by-product **52** was attributable to radical trapping with Bu_3SnH at C17 after two radical cyclizations, 6-*exo* (*endo*)-*trig* and 3-*exo-trig* (vide infra). Therefore **9** was led to the trimethylsilyl derivative **55**, and this was subjected to the radical reaction for the purpose of avoiding formation of **52**. This attempt, however, resulted in complete recovery of **55**, probably due to failure of formation of the initial vinyl radical.

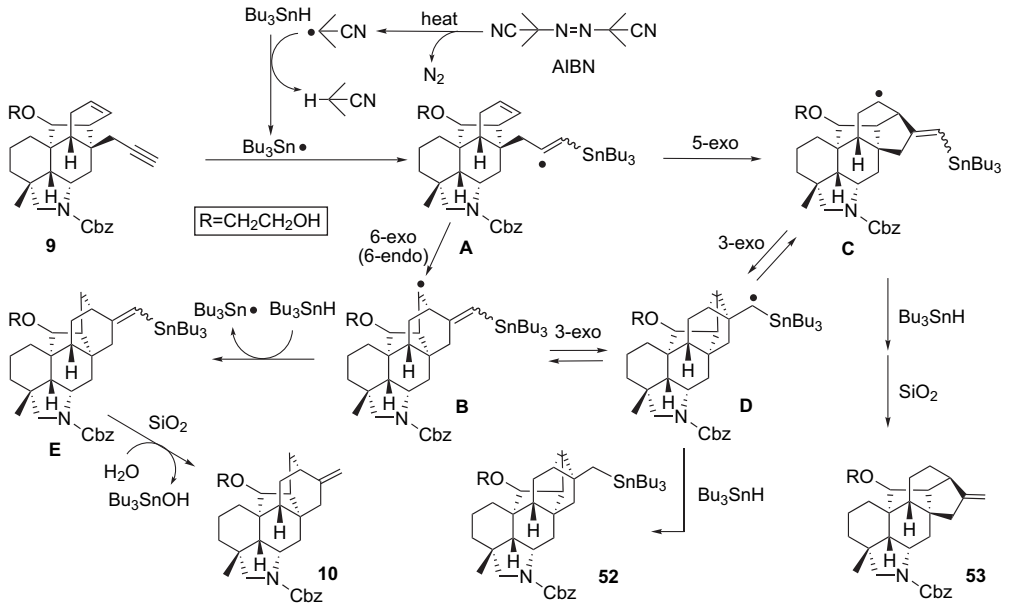
2.3.3. Reaction mechanism of the radical cyclization. A likely reaction mechanism for the radical cyclization is shown in Scheme 8, taking the reaction from **9** as an example. The reaction starts with the pyrolysis of AIBN to generate isobutyronitrile radical by elimination of molecular nitrogen. The radical abstracts hydrogen radical from the gradually dropped Bu_3SnH to give tributyltin radical. Then the tin radical adds to the alkyne of **9** to form radical intermediate **A**. There are two modes for the radical cyclization from **A**, i.e., 6-*exo-trig* mode giving radical intermediate **B** and 5-*exo-trig* mode giving **C**. The desired former mode is also conceivable as 6-*endo-trig*, as the olefin $\Delta_{12,13}$ was originally involved in a six-membered ring. Although formation of the undesired **C** is in danger of taking precedence over that of **B** in accordance with the Baldwin rule,[20] in practice, we were able to get **10** as the main product.

The intermediate **B** could plausibly be derived from **C** by way of the cyclopropane-radical intermediate **D** through homoallyl–homoallyl radical rearrangement.[21] But the facts shown in Table 2, runs a–d, suggest that the intermediate **B** is directly generated from **A**, because the compound corresponding to **53** derived from a **C**-type intermediate was not isolated in runs a–d, where **47** and AIBN was simply heated with a coexisting excess amount of Bu_3SnH from the start.

The radicals **B** and **C** were trapped by Bu_3SnH to form **10** and **53**, respectively, after destannylation from vinyl stannane by stirring with SiO_2 in CH_2Cl_2. The intermediate **D**, generated from **B** and/or **C** in 3-*exo-trig* mode, abstracts a hydrogen radical to yield the by-product **52**. There appears to be fast equilibration between **B** (thermodynamically favored) and **D** (kinetically favored), judging from the results that **49** was the main product in runs a–d (Table 2), while the desired **10** became the main product from **9** when Bu_3SnH was slowly added.

2.4. Completion of the total synthesis of (±)-nominine (1) from 10

The remaining requirements to obtain **1** from **10** are: (i) introduction of 15β-OH and (ii) construction of the azabicyclic ring system after deprotections of oxygen and nitrogen.

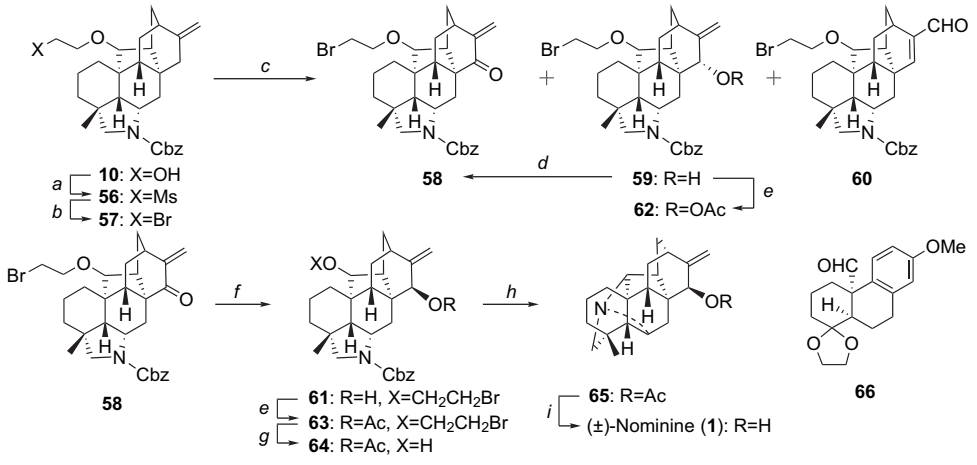


Scheme 8. Reaction mechanism for the radical cyclization of **9** to form **10**, **52**, and **53**.

2.4.1. Introduction of 15β-OH. Prior to the oxidation at C15, the hydroxy group was transformed to a bromide **57** by way of a mesylate **56** (Scheme 9). The 2-bromoethyl group is a convenient precursor for the unprotected 20-hydroxy derivative, as reported in the preceding paper.[9] Attempted direct conversion of **10** to **57** with Br_4C and Ph_3P as before, however, failed due to instability of the methylenebicyclo[2.2.2]octane framework of **10** under the slightly acidic reaction conditions.

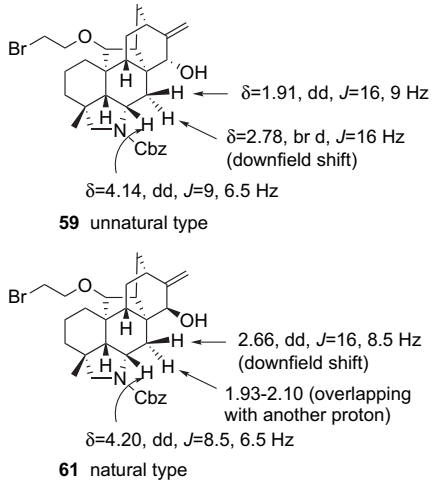
The high reactivity of the framework turned out to be favorable in the next oxidation, as follows. Exposure of **57** to *tert*-butyl hydroperoxide (*t*-BuOOH) and selenium dioxide (SeO_2) readily afforded the enone **58** (77%), allyl alcohol **59** (14%), and enal **60** (trace amount). The 15α-hydroxy compound **59**, with unnatural C15 configuration, was oxidized quantitatively to **58** with manganese dioxide (MnO_2). The desired 15β-hydroxy compound **61** was secured by the reduction of **58** with sodium borohydride ($NaBH_4$) and cerium chloride ($CeCl_3 \cdot 7H_2O$) in MeOH. The stereochemistry of **59** and **61** is described below. These results mean that both oxidizing agent for **57** and reducing agent for **58** attack C15 exclusively from the α side. We cannot give a satisfactory explanation for such stereoselectivity in spite of the symmetric nature of the surroundings of C15 of **57** and **58** in the methylenebicyclo[2.2.2]octane framework.

2.4.2. Stereoconfiguration of 59 and 61. The stereochemistries of **59** and **61** were determined on the basis of the rule reported by Kawazoe et al. (Scheme 10).[22] Thus, in the ^1H NMR spectra, the signals for 7α-H of **59** and 7β-H of **61** are shifted downfield by the influence of the vicinal *syn* 15-hydroxy group (the signals due to the 7α- and 7β-protons of **59**, **61** are easily discriminable by their *J* values with H6). Furthermore, the signals due to the corresponding hydrogen atom of the acetylated compounds **62** and **63** are shifted



Scheme 9. Completion of the total synthesis of (±)-nominine (**1**) from **10**: (a) MsCl, Et_3N, CH_2Cl_2, **56** (97%); (b) LiBr, acetone, **57** (90%); (c) *t*-BuOOH, SeO_2, CH_2Cl_2–H_2O, **58** (77%), **59** (14%), **60** (trace); (d) MnO_2, CH_2Cl_2, **58** (quant.) from **59**; (e) Ac_2O, pyridine, CH_2Cl_2, **62** (93%) from **59**, **63** (93%) from **61**; (f) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, **61** (quant.); (g) Zn, NH_4Cl in *i*-PrOH–H_2O (14:1), **64** (97%); (h) Et_3SiH, cat. $Pd(OAc)_2$, cat. Et_3N, CH_2Cl_2, then $SOCl_2$, pyridine, CH_2Cl_2, **65** (80%) overall from **64** and (i) K_2CO_3 in MeOH, (±)-nominine (**1**) (95%).

upfield in accordance with the rule [δ=2.38–2.58 ppm for 7α-H of **62** and $\delta \approx$ 2.0–2.2 ppm for 7β-H of **63** (overlapping with other signals)]. Consequently, it was clarified that the 15-hydroxy group of **59** has the unnatural α-configuration, while **61** has the natural β-configuration. In the ^{1}H NMR spectrum of **62**, the fact that a weak NOE enhancement (ca. 2.1%) was observed at δ 7.24–7.39 (phenyl protons of the Cbz group) on irradiation of the singlet at δ 1.48 (methyl protons of the acetyl group) also gave support to the above assignment.



Scheme 10. Structure assignments of **59** and **61**.

2.4.3. The final stage of the total synthesis. Now the synthesis reached its final stage. The 2-bromoethyl group of **63** was readily removed to provide **64** in a high yield by the method reported before,[9] i.e., stirring with zinc (Zn) and ammonium chloride (NH_4Cl) in refluxing 2-propanol/H_2O (14:1) (Scheme 9). The protecting group of the 20-hydroxy group, originating from ethylene glycol, had been retained for 21 steps, since it was first introduced at the ene reaction in the preceding paper.[9] The next task is removal of the Cbz group. Hydrogenation or Birch reduction, generally used for this purpose, cannot be employed for **64**, as it contains olefin and ester groups. The cleavage of the Cbz group was executed with triethylsilane (Et_3SiH) in the presence of palladium acetate [$Pd(OAc)_2$] and triethylamine (Et_3N) according to the literature method.[23] The resulting amino-alcohol was then subjected, without purification other than extractive isolation, to azabicyclo ring formation with thionyl chloride ($SOCl_2$) and pyridine[24] to furnish *O*-acetylnominine (**65**) in good yield. The target alkaloid, (±)-nominine (**1**) was easily obtained from **65** by conventional alcoholysis with K_2CO_3 in MeOH.

2.4.4. Identity with the natural alkaloid and single-crystal X-ray analysis. The spectral data (MS, IR, ^{1}H NMR, and ^{13}C NMR) of the synthesized (±)-**1** were indistinguishable with those of natural nominine (see the Section 4). However, these data do not verify the synthesized specimen to be a racemate. Therefore, we carried out a single-crystal X-ray analysis. The molecular structure of (±)-**1** was proved to be identical with that of nominine (Fig. 1). This provides a direct demonstration of the β-configuration of the 15-hydroxy group, which had been assigned by chemical correlation[5] of

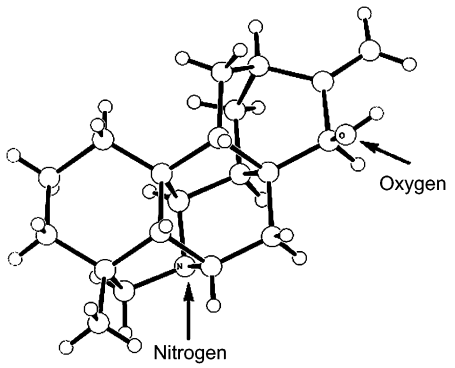


Figure 1. Molecular structure of (±)-nominine (**1**).

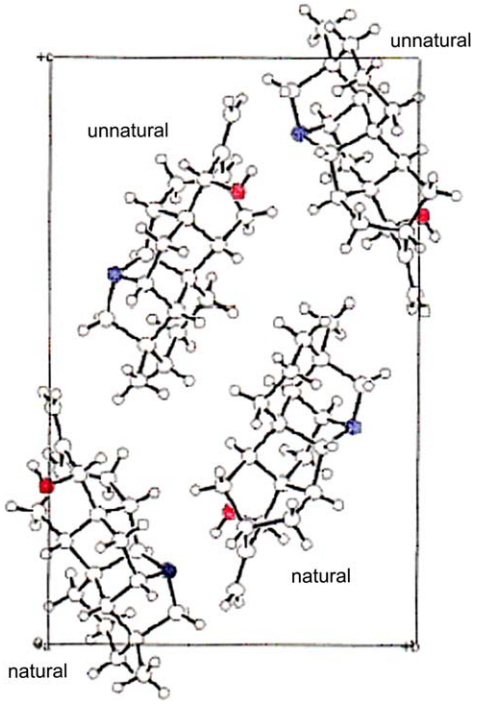


Figure 2. Crystal structure of (±)-nominine (**1**).

natural nominine with kobusine. Furthermore, the crystal structure of (±)-**1** revealed that the analyzed single crystal is racemic (Fig. 2). Thus, the X-ray analysis confirmed the validity of the total synthesis executed according to the schemes described in this and the preceding two papers.[9,10] It was fortunate that recrystallization of (±)-**1** gave a racemic crystal, since spontaneous resolution occurs occasionally during recrystallization. A single crystal of the intermediate **66**, incidentally, was proved to be optically active by X-ray analysis.[7c,9]

3. Conclusion

In summary, a synthetic route to (±)-nominine (**1**) from **7** was established, involving radical cyclization for the C-ring formation (**9**→**10**), stereoselective introduction of the 15β-hydroxy group into **10**, as well as azabicyclic ring construction to afford (±)-**1**. The work described in this and the two preceding reports[9,10] constitutes a 40-step total

synthesis of (±)-**1** starting from 1-bromo-2-(2-iodoethyl)-4-methoxybenzene in 0.15% overall yield (ca. 85% yield per step). This is the first total synthesis of a hetisine-type aconite alkaloid, of which nearly 100 have been isolated up to now. Over 60 years have elapsed since hetisine was isolated[25] as the first example of an aconite alkaloid with the hetisan skeleton, and over 40 years since its structure was elucidated by X-ray analysis.[26]

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 direct inlet mode at an ionizing voltage of 70 eV, and figures in parentheses indicate the relative intensities. IR spectra were measured on a Shimadzu IR-460 spectrophotometer. ^{1}H 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). ^{13}C NMR of compound **16** and subsequently synthesized compounds with a Boc or Cbz group on the nitrogen could not be determined due to the presence of rotational isomers at ambient temperature. The NMR signals were assigned using proton decoupling techniques, as well as gCOSY, DEPT, gHSQC, gHMBC and/or NOESY spectra. Some characteristic signals for ^{1}H and ^{13}C NMR 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) or aluminum oxide (Merck, aluminum oxide 90), and the weight of SiO_2 or Al_2O_3 and the eluting solvent are 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. Preparation of 16 and 18 from 7 (Scheme 4)

4.1.1. Preparation of 11 and 12 from 7. Butyl lithium (BuLi, 1.57 M in hexane, 0.56 ml, 0.879 mmol) was added to a cooled (−18 °C) solution of diisopropylamine (*i*-Pr_2NH, 164 μl, 1.17 mmol) in THF (2 ml) under an Ar atmosphere and the mixture was stirred at that temperature for 10 min. The resulting solution was cooled to −78 °C and to this were added TMSCl (0.28 ml, 2.21 mmol) and a THF (2 ml) solution of **7** (13 mg, 29.2 μmol) in this order. After the mixture had been stirred at −78 °C for 30 min, Et_3N (0.61 ml, 4.38 mmol) was added and the resulting mixture was stirred for 5 min. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. The organic layer was successively washed with saturated $CuSO_4$–H_2O, saturated $NaHCO_3$–H_2O, and H_2O, and then treated as usual. Separation by SiO_2 column chromatography [8 g, hexane–EtOAc (3:1)] afforded **11** (12 mg, 79%) and **12** (2 mg, 12%) in order of decreasing polarity. **11**: Colorless glass. HRMS Calcd for $C_{28}H_{43}NO_6Si$: 517.2857. Found: 518.2853. MS *m/z*: 517 (M^+, 3), 472 (2), 428 (2), 351 (16), 247 (81), 148 (14), 105 (13), 89 (17), 73 (59), 45 (100). IR ($CHCl_3$) cm^{-1}: 2225, 1726, 1635. ^{1}H NMR δ: 0.30 (9H, s), 1.05 (1H, ddd, J=12.5, 12.5, 4 Hz, H1), 1.25 (1H, ddd, J=14.5, 14.5, 3.5 Hz, H3), 1.51–1.77 (3H, m), 1.60 (3H, s, H18), 1.92–2.15 (4H, m), 2.04 (3H, s), 2.21 (1H, dd, J=19, 5 Hz, H11), 2.29 (1H, d, J=2 Hz, H5), 2.30 (1H, br d, J=19 Hz, H11), 2.54–2.61 (1H, m, H14), 3.35 (3H, s), 3.48–3.75 (4H, m), 4.03–4.18 (2H, m, CH_2OAc), 4.54 (1H, d, J=6 Hz, H20), 4.63 (1H, d, J=6.5 Hz, CH_2OMe), 4.67 (1H, d, J=6.5 Hz, CH_2OMe), 4.82 (1H, d, J=2 Hz, H7), 5.47–5.62 (2H, m). ^{13}C NMR δ: 0.3 (CH_3×3, $SiMe_3$), 20.4 (CH_2, C2), 21.1 (CH_3), 26.7 (CH_2, C11), 29.6 (CH_2, C1), 30.8 (CH_3, C18), 31.2 (CH_2, CH_2CH$_2$OAc), 33.3 (C, C4), 40.5 (CH_2, C3), 41.4 (C, C8), 49.1 (CH, C14), 48.7 (C, C10), 50.9 (CH, C9), 55.0 (CH_3, CH_2OCH_3), 58.5 (CH, C5), 62.3 (CH_2, CH_2OAc), 66.6 (CH_2, CH_2OMOM), 68.4 (CH_2, CH_2CH$_2$OMOM), 83.9 (CH, C20), 96.2 (CH_2, OCH_2OMe), 111.9 (CH, C7), 124.0 (C, CN), 125.1 (CH, C12 or C13), 126.4 (CH, C12 or C13), 149.8 (C, C6), 170.8 (C, O*C*OCH$_3$). **12**: Colorless glass. HRMS Calcd for $C_{31}H_{51}NO_6Si_2$: 589.3252. Found: 589.3241. MS *m/z*: 589 (M^+, 3), 574 (1), 558 (1), 544 (1), 500 (2), 351 (22), 247 (100), 148 (13), 105 (18), 89 (19), 75 (15), 73 (87), 59 (18), 45 (81). IR ($CHCl_3$) cm^{-1}: 2230, 1705, 1638. ^{1}H NMR δ: 0.11 (9H, s, $COCH_2Si$*Me*$_3$), 0.30 (9H, s, $OSiMe_3$), 1.04 (1H, ddd, J=12.5, 12.5, 4 Hz), 1.19–1.31 (1H, m), 1.53–1.74 (3H, m), 1.88 (2H, s, $COCH_2Si$), 1.92–2.15 (4H, m), 1.60 (3H, s), 2.17–2.36 (2H, m), 2.78 (1H, d, J=2 Hz, H5), 2.54–2.60 (1H, m), 3.35 (3H, s), 3.48–3.75 (4H, m), 3.99–4.13 (2H, m), 4.53 (1H, d, J=6 Hz, H20), 4.63 (1H, d, J=6.5 Hz), 4.67 (1H, d, J=6.5 Hz), 4.81 (1H, d, J=2 Hz, H7), 5.47–5.62 (2H, m).

4.1.2. Preparation of 13 and 14 from 11. LAH (40 mg, 1.05 mmol) was added to a solution of **11** (11 mg, 21.3 μmol) in THF (4 ml) and the mixture was refluxed with stirring under an Ar atmosphere for 2 h. The mixture was allowed to cool in an ice bath, and water–saturated Et_2O (2 ml) was slowly added dropwise to it to decompose excess LAH. Volatile materials were evaporated off and the residue was dried over P_2O_5 in vacuo for 3 h. To a slurry of the residue in CH_2Cl_2 (1.5 ml) and Et_3N (0.44 ml, 3.16 mmol) was added Boc_2O (150 μl, 0.640 mmol) at 0 °C under an Ar atmosphere, and the resulting mixture was stirred at 0 °C for 10 min and at 19 °C for 18 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [benzene–EtOAc (4:1)] afforded **13** (6.5 mg, 62%), and **14** (2 mg, 16%) in order of decreasing polarity. **13**: Colorless glass. HRMS Calcd for $C_{28}H_{43}NO_6$: 489.3088. Found: 489.3079. MS *m/z*: 489 (M^+, 4), 389 (3), 344 (7), 317 (10), 300 (18), 282 (13), 261 (70), 246 (15), 57 (100), 45 (92), 41 (33). IR ($CHCl_3$) cm^{-1}: 1682. ^{1}H NMR δ: 1.12 (3H, s), 1.12–1.22 (1H, m), 1.33–1.49 (2H, m), 1.52 (9H, s), 1.53–1.64 (2H, m, including OH), 1.67 (1H, ddd, J=13.5, 7.5, 6.5 Hz, CH_2CH$_2$OH), 1.75–1.90 (1H, m), 1.94–1.99 (1H, m), ca. 1.97–2.04 (1H, m), 2.07 (1H, ddd, J=13.5, 7.5, 6 Hz, CH_2CH$_2$OH), 2.21 (1H, br dddd, J=19,

5, 2.5, 2.5 Hz, H11), 2.32 (1H, br d, *J*=19 Hz, H11), 2.42 (1H, ddd, *J*=6.5, 6, 1.5 Hz, H14), 2.49 (1H, d, *J*=3 Hz, H5), 3.09 (1H, d, *J*=11 Hz, H19), 3.29 (1H, ddd, *J*=10.5, 5.5, 5 Hz, CH_2CH$_2$OMOM), 3.36 (3H, s), 3.48 (1H, ddd, *J*=10.5, 5, 4.5 Hz, CH_2CH$_2$OMOM), 3.57 (1H, d, *J*=11 Hz, H19), ca. 3.60–3.67 (2H, m), 3.68–3.86 (2H, m), 3.77 (1H, d, *J*=6 Hz, H20), 4.62 (1H, d, *J*=6.5 Hz, OCH_2OMe), 4.65 (1H, d, *J*=6.5 Hz, OCH_2OMe), 5.37 (1H, br s, H7), 5.51 (1H, dddd, *J*=9.5, 6.5, 1.5, 1.5 Hz, H13), 5.58 (1H, ddd, *J*=9.5, 3.5, 2.5 Hz, H12). ^{13}C NMR *δ*: 17.6 (CH$_2$), 22.0 (CH$_2$), 26.7 (CH$_2$), 28.4 (CH$_3$×3), 30.6 (CH$_3$, C18), 31.4 (CH$_2$), 34.5 (C, C4), 35.2 (CH$_2$), 45.2 (C), 48.4 (C), 50.2 (CH, C14), 51.2 (CH, C9), 55.1 (CH$_3$), 61.1 (CH$_2$), 61.4 (CH), 64.4 (CH$_2$, C19), 66.9 (CH$_2$), 68.8 (CH$_2$), 80.4 (C, O*C*Me$_3$), 88.1 (CH, C20), 96.5 (CH$_2$), 110.5 (CH, C7), 125.4 (CH), 126.0 (CH), 139.8 (C, C6), 152.6 (C). **14**: Colorless glass. HRMS Calcd for $C_{33}H_{51}NO_8$: 589.3612. Found: 589.3593. MS *m*/*z*: 589 (M$^+$, 3), 489 (2), 433 (2), 417 (5), 400 (4), 344 (15), 317 (12), 282 (10), 261 (53), 57 (100), 45 (59), 41 (29). IR (CHCl$_3$) cm^{-1}: 1731, 1682. ^{1}H NMR *δ*: 1.11 (3H, s), 1.12–1.21 (1H, m), 1.30–1.63 (3H, m), 1.47 (9H, s), 1.52 (9H, s), 1.74 (1H, ddd, *J*=13.5, 9, 6 Hz), 1.79–1.89 (1H, m), 1.93–1.97 (1H, m), 1.97–2.06 (1H, m), 2.14 (1H, ddd, *J*=13.5, 9, 6.5 Hz), 2.21 (1H, br dddd, *J*=19, 5, 2.5, 2.5 Hz, H11), 2.32 (1H, br d, *J*=19 Hz, H11), 2.41 (1H, br dd, *J*=6.5, 6 Hz, H14), 2.44 (1H, d, *J*=3 Hz, H5), 3.09 (1H, d, *J*=11 Hz, H19), 3.29 (1H, ddd, *J*=10.5, 5.5, 5.5 Hz), 3.35 (3H, s), 3.47 (1H, ddd, *J*=10.5, 5, 5 Hz), 3.57 (1H, d, *J*=11 Hz, H19), 3.60–3.66 (2H, m), 3.76 (1H, d, *J*=6 Hz, H20), 4.07–4.24 (2H, m, CH_2OBoc), 4.62 (1H, d, *J*=6.5 Hz), 4.65 (1H, d, *J*=6.5 Hz), 5.34 (1H, br s, H7), 5.49 (1H, br dd, *J*=9.5, 6.5 Hz, H13), 5.57 (1H, ddd, *J*=9.5, 2.5, 2.5 Hz, H12). ^{13}C NMR *δ*: 17.6 (CH$_2$), 21.9 (CH$_2$), 26.7 (CH$_2$), 27.8 (CH$_3$×3), 28.4 (CH$_3$×3), 30.6 (CH$_3$, C18), 31.2 (CH$_2$), 31.4 (CH$_2$), 34.4 (C, C4), 45.0 (C), 48.4 (C), 50.2 (CH, C14), 51.1 (CH, C9), 55.1 (CH$_3$), 61.4 (CH), 64.4 (CH$_2$, C19), 65.3 (CH$_2$, *C*H$_2$OBoc), 66.9 (CH$_2$), 68.9 (CH$_2$), 80.4 (C, O*C*Me$_3$), 81.5 (C, O*C*Me$_3$), 88.1 (CH, C20), 96.5 (CH$_2$), 109.8 (CH, C7), 125.2 (CH), 126.1 (CH), 139.9 (C, C6), 152.6 (C, N*C*OO*t*-Bu), 153.3 (C, O*C*OO*t*-Bu).

4.1.3. Sequential preparation of 13 and 14 from 7 by way of a mixture of 11 and 12. In the same manner as described in Section 4.1.1, a mixture of **11** and **12** was prepared from **7** (52 mg, 0.117 mmol). It was allowed to react with LAH (111 mg, 2.92 mmol) as before and then treated as above. The residue was dissolved in CH_2Cl_2 (4 ml) and Et_3N (0.98 ml, 7.04 mmol) and then the solution was stirred with Boc_2O (0.41 ml, 1.75 mmol) under an Ar atmosphere at 0 °C for 1 h, and at 20 °C for 15 h. The same work-up and separation by PTLC [benzene–EtOAc (6:1)] afforded **13** (38 mg, 55% overall), and **14** (7 mg, 10% overall).

4.1.4. Sequential preparation of 8 and 15 from 7 by way of a mixture of 11 and 12. In the same manner as above (Section 4.1.3), **7** (142 mg, 0.319 mmol) was treated with LDA, TMSCl, and then with LAH to give a residue after having been dried over P_2O_5 in vacuo overnight. To the residue in CH_2Cl_2 (6 ml) and Et_3N (1.33 ml, 9.56 mmol) was added dropwise a solution of ClCbz (0.46 ml, 3.22 mmol) in CH_2Cl_2 (2 ml) during 15 min at −18 °C and the mixture was stirred under an Ar atmosphere at −18 °C for 10 min, at 0 °C for 0.5 h, and at 22 °C for 17 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by PTLC [benzene–EtOAc (9:1) for **15** and then benzene–EtOAc (5:2) for **8**] afforded **15** (8 mg, 4%) and **8** (105 mg, 63%) in order of increasing polarity. **8**: Colorless glass. HRMS Calcd for $C_{31}H_{41}NO_6$: 523.2932. Found: 523.2941. MS *m*/*z*: 523 (M$^+$, 2), 479 (2), 434 (2), 417 (2), 390 (5), 351 (23), 216 (5), 91 (100), 45 (32). IR (CHCl$_3$) cm^{-1}: 1693. ^{1}H NMR (at 50 °C) *δ*: 1.11 (3H, s, H18), ca. 1.12–1.23 (1H, m, H1), 1.30–1.48 (3H, m, including OH), 1.50–1.63 (1H, m), 1.65 (1H, ddd, *J*=14, 7.5, 6.5 Hz, CH_2CH$_2$OH), 1.76–1.92 (1H, m), 1.93–1.98 (1H, m), ca. 2.00–2.09 (1H, m), 2.05 (1H, ddd, *J*=14, 7, 7 Hz, CH_2CH$_2$OH), 2.22 (1H, dddd, *J*=19, 5, 2.5, 2.5 Hz, H11), 2.31 (1H, br d, *J*=19 Hz, H11), 2.39 (1H, ddd, *J*=7, 6, 1.5 Hz, H14), 2.49 (1H, d, *J*=2.5 Hz, H5), 3.16 (1H, d, *J*=10.5 Hz, H19), 3.26 (1H, ddd, *J*=10.5, 5, 5 Hz, CH_2CH$_2$OMOM), 3.34 (3H, s), 3.46 (1H, ddd, *J*=10.5, 5, 4.5 Hz, CH_2CH$_2$OMOM), 3.59–3.64 (2H, m, CH_2OMOM), 3.67 (1H, d, *J*=10.5 Hz, H19), 3.68–3.78 (2H, m, CH_2OH), 3.75 (1H, d, *J*=6 Hz, H20), 4.60 (1H, d, *J*=6.5 Hz, CH_2OMe), 4.62 (1H, d, *J*=6.5 Hz, CH_2OMe), 5.16 (1H, d, *J*=12.5 Hz, COOCH_2Ph), 5.21 (1H, d, *J*=12.5 Hz, COOCH_2Ph), ca. 5.43–5.52 (1H, m, H7), 5.49 (1H, dddd, *J*=9.5, 7, 1.5, 1.5 Hz, H13), 5.56 (1H, ddd, *J*=9.5, 3, 2.5 Hz, H12), 7.27–7.42 (5H, m, COOCH$_2$*Ph*). *^{13}C NMR of this and subsequently synthesized compounds containing the Cbz group could not be determined due to the presence of rotational isomers*. **15**: Colorless glass. HRMS Calcd for $C_{39}H_{47}NO_8$: 657.3299. Found: 657.3316. MS *m*/*z*: 657 (M$^+$, 1), 568 (1), 524 (3), 485 (11), 333 (4), 198 (4), 91 (100), 45 (33). IR (CHCl$_3$) cm^{-1}: 1734, 1693. ^{1}H NMR *δ*: 1.11 (3H, s), 1.11–1.21 (1H, m), 1.30–1.65 (3H, m), 1.66–1.90 (2H, m), 1.92–1.98 (1H, m), 2.01 (1H, ddd, *J*=13, 11, 1 Hz, H1), 2.11–2.25 (2H, m), 2.30 (1H, br d, *J*=19 Hz, H11), 2.39 (1H, br dd, *J*=6, 6 Hz, H14), 2.48 (1H, d, *J*=3 Hz, H5), 3.17 (1H, d, *J*=11 Hz, H19), 3.25 (1H, ddd, *J*=10.5, 5, 5 Hz), 3.34 (3H, s), 3.45 (1H, ddd, *J*=10.5, 5, 4.5 Hz), 3.59–3.64 (2H, m), 3.66 (1H, d, *J*=11 Hz, H19), 3.76 (1H, d, *J*=6 Hz, H20), 4.18–4.29 (2H, m, CH_2OCbz), 4.61 (1H, d, *J*=6.5 Hz), 4.63 (1H, d, *J*=6.5 Hz), 5.15 (2H, s, OCOOCH_2Ph), 5.16 (1H, d, *J*=12 Hz), 5.21 (1H, d, *J*=12 Hz), ca. 5.36–5.50 (1H, m), 5.46 (1H, br dd, *J*=9.5, 6.5 Hz, H13), 5.55 (1H, ddd, *J*=9.5, 3, 2.5 Hz, H12), 7.30–7.42 (10H, m).

4.1.5. Reduction of 13, 14, 8, and 15 with $NaBH_3CN$. The procedure for the preparation of **16** from **13** is described as a representative example. $NaBH_3CN$ (34 mg, 0.540 mmol) and HCl–H_2O (2.5%, 0.51 ml, 0.349 mmol) were added in this order to a cooled (0 °C) solution of **13** (22 mg, 45.0 μmol) in MeOH (5 ml) and the mixture was stirred at that temperature for 30 min and at 21 °C for 1 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [benzene–EtOAc (3:2)] provided **16** (20 mg, 91%) as a colorless glass. HRMS Calcd for $C_{28}H_{45}NO_6$: 491.3244. Found: 491.3246. MS *m*/*z*: 491 (M$^+$, 2), 402 (3), 390 (12), 346 (18), 302 (25), 284 (36), 57 (100), 45 (69), 41 (26). IR (CHCl$_3$) cm^{-1}: 1673. ^{1}H NMR (at 50 °C) *δ*: 0.94 (3H, s, H18), 0.99 (1H, ddd, *J*=10, 7.5, 5.5 Hz, H1), 1.18–1.23 (1H, m, H9), 1.23–1.32 (1H, m, H3), 1.38–1.47 (1H, m,

H2), 1.47 (9H, s), 1.51 (1H, br s, OH), 1.59–1.70 (2H, m), 1.62 (1H, d, *J*=7 Hz, H5), 1.79–2.30 (7H, m), 2.39 (1H, dd, *J*=6, 5.5 Hz, H14), 3.18–3.32 (2H, m, H19×2), 3.35 (3H, s), 3.48 (1H, ddd, *J*=10.5, 6, 5 Hz, C*H*$_2$CH$_2$OMOM), 3.52 (1H, ddd, *J*=10.5, 5, 4.5 Hz, C*H*$_2$CH$_2$OMOM), 3.61–3.68 (2H, m, C*H*$_2$OMOM), ca. 3.62–3.81 (2H, m, C*H*$_2$OH), 4.02 (1H, d, *J*=6 Hz, H20), 4.06–4.16 (1H, m, H6), 4.62 (1H, d, *J*=6.5 Hz, OC*H*$_2$OMe), 4.64 (1H, d, *J*=6.5 Hz, OC*H*$_2$OMe), 5.46–5.61 (2H, m, H12 and H13). *^{13}C NMR of this and subsequently synthesized compounds containing the Boc group could not be determined due to the presence of rotational isomers*. In the same manner, **17** (13 mg, 93%) was obtained from **14** (14 mg, 23.8 μmol) after PTLC [hexane–EtOAc (3:1)] as a colorless glass. HRMS Calcd for $C_{33}H_{53}NO_8$: 591.3768. Found: 591.3761. MS *m*/*z*: 591 (M^+, 1), 502 (1), 491 (3), 434 (9), 402 (10), 390 (5), 346 (45), 284 (10), 89 (8), 57 (100), 45 (40), 41 (26). IR ($CHCl_3$) cm^{-1}: 1732, 1674. ^{1}H NMR (at 50 °C) *δ*: 0.93 (3H, s, H18), 0.98 (1H, ddd, *J*=12.5, 10, 5.5 Hz, H1), 1.23 (1H, d, *J*=4.5 Hz, H9), 1.27 (1H, ddd, *J*=13.5, 11, 5 Hz, H3), ca. 1.39–1.50 (1H, m), 1.47 (18H, s), ca. 1.60–1.70 (1H, m, H3), 1.62 (1H, d, *J*=7.5 Hz, H5), 1.74 (1H, ddd, *J*=13.5, 9, 6 Hz, C*H*$_2$CH$_2$OBoc), 1.79–1.92 (1H, m, H2), 1.92–2.24 (4H, m), 2.24 (1H, dd, *J*=16.5, 9 Hz, H7), 2.25 (1H, br d, *J*=20 Hz, H11), 2.39 (1H, br dd, *J*=6, 6 Hz, H14), ca. 3.11–3.28 (1H, m, H19), 3.28 (1H, br d, *J*=9.5 Hz, H19), 3.35 (3H, s), 3.38 (1H, dt, *J*=10, 5 Hz, C*H*$_2$CH$_2$OMOM), 3.52 (1H, dt, *J*=10, 5 Hz, C*H*$_2$CH$_2$OMOM), 3.64 (2H, dd, *J*=5, 5 Hz, C*H*$_2$OMOM), 4.03 (1H, d, *J*=6 Hz, H20), 4.01–4.23 (3H, m), 4.62 (1H, d, *J*=6.5 Hz, C*H*$_2$OMe), 4.64 (1H, d, *J*=6.5 Hz, C*H*$_2$OMe), 5.50 (1H, br dd, *J*=9.5, 3 Hz, H12), 5.55 (1H, br dd, *J*=9.5, 6 Hz, H13). In the same manner, **18** (77 mg, 90%) was obtained from **8** (85 mg, 0.163 mmol) after PTLC [hexane–EtOAc (3:2)] as a colorless glass. HRMS Calcd for $C_{31}H_{43}NO_6$: 525.3088. Found: 525.3062. MS *m*/*z*: 525 (M^+, 1), 480 (1), 436 (8), 420 (2), 392 (13), 390 (12), 300 (4), 284 (4), 91 (100), 45 (39). IR ($CHCl_3$) cm^{-1}: 1683. ^{1}H NMR (at 50 °C) *δ*: 0.94 (3H, s), 0.98 (1H, ddd, *J*=12.5, 10, 6 Hz, H1), 1.17–1.24 (1H, m), 1.28 (1H, ddd, *J*=13.5, 11, 5 Hz, H3), 1.38–1.50 (2H, m, including OH), 1.55–1.71 (2H, m), 1.64 (1H, d, *J*=7 Hz, H5), 1.80–2.07 (4H, m), 2.10–2.33 (4H, m), 2.32–2.44 (1H, m, H14), ca. 3.21–3.40 (2H, m), 3.33 (3H, s), 3.38 (1H, d, *J*=11 Hz, H19), 3.50 (1H, ddd, *J*=10.5, 5, 4.5 Hz, C*H*$_2$CH$_2$OMOM), ca. 3.55–3.80 (2H, m), 3.60–3.65 (2H, m), 4.00 (1H, d, *J*=6 Hz, H20), 4.19 (1H, dd, *J*=9, 7 Hz, H6), 4.59 (1H, d, *J*=6.5 Hz, C*H*$_2$OMe), 4.62 (1H, d, *J*=6.5 Hz, C*H*$_2$OMe), 5.09 (1H, d, *J*=12.5 Hz, OC*H*$_2$Ph), 5.19 (1H, d, *J*=12.5 Hz, OC*H*$_2$Ph), 5.48–5.60 (2H, m, H12 and H13), 7.26–7.38 (5H, m). In the same manner, **19** (5.5 mg, 91%) was obtained from **15** (6 mg, 9.13 μmol) after PTLC [hexane–EtOAc (4:1)] as a colorless glass. HRMS Calcd for $C_{39}H_{49}NO_8$: 659.3455. Found: 659.3434. MS *m*/*z*: 659 (M^+, 0.8), 614 (0.5), 570 (4), 526 (12), 524 (8), 436 (3), 91 (100), 45 (27). IR ($CHCl_3$) cm^{-1}: 1735, 1684. ^{1}H NMR (at 50 °C) *δ*: 0.94 (3H, s), 0.97 (1H, ddd, *J*=12.5, 9.5, 5.5 Hz, H1), 1.18–1.25 (1H, m), 1.27 (1H, ddd, *J*=13.5, 11, 5 Hz, H3), 1.39–1.51 (1H, m), ca. 1.60–1.71 (1H, m), 1.79–1.92 (1H, m), 1.63 (1H, d, *J*=7.5 Hz, H5), 1.98 (1H, ddd, *J*=12.5, 4.5, 4.5 Hz, H1), 2.10 (1H, ddd, *J*=13.5, 9, 6.5 Hz), 2.13–2.32 (5H, m), 2.32–2.43 (1H, m), 3.22–3.41 (3H, m), 3.32 (3H, s), 3.48 (1H, ddd, *J*=10.5, 4.5, 4.5 Hz), 3.59–3.65 (2H, m), 4.00 (1H, d, *J*=6 Hz, H20), 4.04–4.34 (3H, m, H6 and C*H*$_2$OCbz), 4.59 (1H, d, *J*=6.5 Hz), 4.61 (1H, d, *J*=6.5 Hz), 5.09 (1H, d, *J*=12.5 Hz), 5.14 (2H, s, OCOOC*H*$_2$Ph), 5.19 (1H, br d, *J*=12.5 Hz), 5.45–5.55 (2H, m), 7.27–7.40 (10H, m).

4.1.6. Alcoholysis of 17 and 19 to form 16 and 18, respectively. The procedure for the preparation of **16** from **17** was typical. A solution of **17** (6 mg, 10.2 μmol) in K_2CO_3 in MeOH (1% w/v, 2 ml) was stirred under reflux for 2.5 h. After the mixture had been cooled, saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [benzene–EtOAc (3:2)] gave **16** (5 mg, quant.) as a colorless glass. In the same manner, **18** (4 mg, quant.) was obtained from **19** (5 mg, 7.59 μmol).

4.2. Attempts at C-ring formation (Scheme 5)

4.2.1. Benzoylation of 16 and 18 to form 20 and 21, respectively. The procedure for the preparation of **20** from **16** is described as a representative example. Benzoyl chloride (98 μl, 0.819 mmol) was added to a cooled (0 °C) solution of **16** (20 mg, 40.7 μmol) in CH_2Cl_2 (1.5 ml) and Et_3N (0.56 ml, 4.03 mmol). Stirring was continued at 0 °C for 15 min and at 20 °C for 16 h, then the mixture was cooled again in an ice bath. MeOH (66 μl, 1.63 mmol) was added to it and the whole was stirred at that temperature for 1 h. Addition of saturated $NaHCO_3$–H_2O followed by extraction with CH_2Cl_2, usual work-up, and separation by PTLC [hexane–EtOAc (4:1)] afforded **20** (24 mg, 99%) as a colorless glass. HRMS Calcd for $C_{35}H_{49}NO_7$: 595.3506. Found: 595.3512. MS *m*/*z*: 595 (M^+, 1), 495 (7), 494 (9), 406 (45), 390 (10), 389 (10), 346 (7), 284 (17), 105 (33), 69 (31), 57 (100), 45 (62), 41 (39). IR ($CHCl_3$) cm^{-1}: 1706, 1674. ^{1}H NMR (at 50 °C) *δ*: 0.95 (3H, s), 0.95–1.05 (1H, m), 1.22–1.34 (2H, m), 1.41–1.54 (1H, m), 1.47 (9H, s), 1.61–1.70 (1H, m), 1.64 (1H, d, *J*=7 Hz, H5), 1.80–1.96 (2H, m), 2.00 (1H, ddd, *J*=13, 5, 5 Hz, H1), 2.12–2.34 (4H, m), 2.35 (1H, dd, *J*=16, 9 Hz, H7), 2.46 (1H, br dd, *J*=6, 5 Hz, H14), 3.13–3.33 (2H, m), 3.35 (3H, s), 3.35–3.43 (1H, m), 3.47–3.56 (1H, m), 3.61–3.68 (2H, m), 4.06 (1H, d, *J*=6 Hz, H20), 4.09–4.21 (1H, m), 4.35 (1H, ddd, *J*=10.5, 8.5, 7 Hz, C*H*$_2$OBz), 4.44 (1H, ddd, *J*=10.5, 8.5, 6 Hz, C*H*$_2$OBz), 4.62 (1H, d, *J*=6.5 Hz), 4.64 (1H, d, *J*=6.5 Hz), 5.48–5.62 (2H, m), 7.39–7.46 (2H, m), 7.50–7.57 (1H, m), 8.00–8.06 (2H, m). In the same manner, **21** (73 mg, 97%) was obtained from **18** (63 mg, 0.120 mmol) as a colorless glass after PTLC [hexane–EtOAc (3:1)]. HRMS Calcd for $C_{38}H_{47}NO_7$: 629.3350. Found: 629.3338. MS (*m*/*z*): 629 (M^+, 3), 540 (10), 496 (20), 494 (15), 480 (5), 404 (5), 336 (6), 105 (21), 91 (100), 59 (11), 45 (38). IR ($CHCl_3$) cm^{-1}: 1684. ^{1}H NMR (at 50 °C) *δ*: 0.95 (3H, s), 1.00 (1H, ddd, *J*=13, 10, 5.5 Hz, H1), 1.22–1.35 (2H, m), 1.39–1.52 (1H, m), 1.61–1.72 (1H, m), 1.67 (1H, d, *J*=7 Hz, H5), 1.77–1.96 (2H, m), 2.01 (1H, ddd, *J*=13, 4.5, 4.5 Hz, H1), 2.13–2.42 (5H, m), 2.39–2.51 (1H, m), ca. 3.25–3.42 (3H, m), 3.32 (3H, s), 3.50 (1H, dt, *J*=10, 5 Hz), 3.63 (2H, dd, *J*=5, 5 Hz), 4.04 (1H, d, *J*=5.5 Hz, H20), 4.23 (1H, br dd, *J*=8, 7 Hz, H6), 4.26–4.48 (2H, m, C*H*$_2$OBz), 4.60 (2H, s), 5.10 (1H, d, *J*=12.5 Hz), 5.18 (1H, d, *J*=12.5 Hz), 5.50–5.60 (2H, m), 7.26–7.38 (5H, m), 7.38–7.46 (2H, m), 7.50–7.57 (1H, m), 8.00–8.07 (2H, m).

4.2.2. Allylic oxidation of 20 and 21 for respective formation of 22, 23 and 24, 25. The procedure for the preparation of **22**, **23** from **20** (Table 1, run b) is described as a representative example. 3,5-Dimethylpyrazole (13 mg, 0.135 mmol) was added to a cooled (−18 °C) slurry of CrO_3 (12 mg, 0.120 mmol) in CH_2Cl_2 (1.5 ml) under an Ar atmosphere and the mixture was stirred at that temperature for 15 min. A CH_2Cl_2 (2 ml) solution of **20** (12 mg, 20.2 μmol) was added to it, and the resulting mixture was stirred at −18 to 23 °C for 48 h. Successive addition of saturated $NaHCO_3$–H_2O and saturated $Na_2S_2O_3$–H_2O followed by extraction with CH_2Cl_2, usual work-up, and separation by PTLC [hexane–EtOAc (3:1)] afforded **22** (5.5 mg, 45%) and **23** (3.5 mg, 28%) in order of decreasing polarity. **22**: Colorless glass. HRMS Calcd for $C_{35}H_{47}NO_8$: 609.3299. Found: 609.3291. MS (*m*/*z*): 609 (M^+, 1), 509 (18), 420 (29), 360 (14), 105 (53), 89 (11), 77 (18), 57 (100), 45 (85), 41 (25). IR ($CHCl_3$) cm^{-1}: 1709, 1665. ^1H NMR (at 50 °C) *δ*: 0.98 (3H, s), 1.17 (1H, ddd, *J*=13, 10, 5 Hz), 1.25–1.81 (5H, m), 1.47 (9H, s), 1.82 (1H, d, *J*=7 Hz), 1.83 (1H, ddd, *J*=14, 7, 7 Hz), 2.07 (1H, ddd, *J*=14, 7, 7 Hz), 2.13 (1H, s, H9), 2.20–2.38 (2H, m), 3.08 (1H, ddd, *J*=7, 6, 1.5 Hz, H14), 3.21–3.37 (2H, m), 3.33 (3H, s), 3.47–3.58 (2H, m), 3.59–3.65 (2H, m), 4.10–4.19 (1H, m), 4.27–4.34 (2H, m), 4.41 (1H, d, *J*=6 Hz), 4.58 (1H, d, *J*=6.5 Hz), 4.60 (1H, d, *J*=6.5 Hz), 6.19 (1H, dd, *J*=9.5, 1.5 Hz, H12), 6.99 (1H, dd, *J*=9.5, 7 Hz, H13), 7.40–7.47 (2H, m), 7.51–7.58 (1H, m), 7.99–8.03 (2H, m). **23**: Colorless glass. HRMS Calcd for $C_{35}H_{47}NO_8$: 609.3299. Found: 609.3292. MS (*m*/*z*): 609 (M^+, 0.6), 509 (20), 464 (9), 420 (47), 404 (5), 298 (6), 105 (51), 89 (7), 77 (16), 57 (100), 45 (72), 41 (23). IR ($CHCl_3$) cm^{-1}: 1708, 1676. ^1H NMR (at 50 °C) *δ*: 1.00 (3H, s), 1.09 (1H, ddd, *J*=12.5, 11.5, 4 Hz, H1), 1.35 (1H, ddd, *J*=13.5, 3, 4 Hz), 1.47 (9H, s), 1.62–1.79 (3H, m), 1.75 (1H, d, *J*=6.5 Hz, H5), 1.82 (1H, dt, *J*=14, 7 Hz), 1.91 (1H, dt, *J*=14, 7 Hz), 2.01 (1H, ddd, *J*=12.5, 4, 4 Hz, H1), 2.06 (1H, dd, *J*=7, 1.5 Hz, H9), 2.20 (1H, dd, *J*=16.5, 8.5 Hz, H7), 2.39 (1H, br d, *J*=16.5 Hz, H7), 3.11 (1H, ddd, *J*=7, 1.5, 1.5 Hz, H14), 3.21 (1H, br d, *J*=11 Hz, H19), 3.32 (3H, s), 3.32–3.42 (1H, m), 3.38 (1H, d, *J*=11 Hz, H19), 3.50–3.55 (2H, m), 3.60–3.67 (1H, m), 4.07–4.16 (1H, m), 4.28 (2H, dd, *J*=7, 7 Hz), 4.40 (1H, d, *J*=7 Hz, H20), 4.55 (1H, d, *J*=6.5 Hz), 4.57 (1H, d, *J*=6.5 Hz), 6.15 (1H, dd, *J*=9.5, 1.5 Hz, H12), 6.93 (1H, dd, *J*=9.5, 7 Hz, H11), 7.39–7.46 (2H, m), 7.51–7.58 (1H, m), 7.99–8.04 (2H, m). In the same manner, **24** (1 mg, 12%) and **25** (0.5 mg, 6%) were obtained along with a recovery of unchanged starting material (4 mg, 50%) from **21** (8 mg, 12.7 μmol), in order of decreasing polarity (Table 1, run e) after separation by PTLC [hexane–EtOAc (3:1)]. **24**: Colorless glass. HRMS Calcd for $C_{38}H_{45}NO_8$: 643.3143. Found: 643.3142. MS (*m*/*z*): 643 (M^+, 8), 554 (2), 510 (15), 507 (7), 418 (3), 105 (20), 91 (100), 89 (7), 77 (6), 45 (36). IR ($CHCl_3$) cm^{-1}: 1706, 1687, 1666. ^1H NMR (at 50 °C) *δ*: 0.99 (3H, s), 1.11–1.84 (7H, m), 1.84 (1H, d, *J*=7 Hz, H5), 2.06 (1H, ddd, *J*=14, 7, 7 Hz), 2.13 (1H, s, H9), 2.24–2.38 (2H, m), 3.01–3.10 (1H, m, H14), 3.30 (3H, s), 3.30–3.69 (6H, m), 4.18–4.33 (3H, m), 4.38 (1H, d, *J*=6 Hz, H20), 4.56 (2H, s), 5.11 (1H, d, *J*=12.5 Hz), 5.19 (1H, d, *J*=12.5 Hz), 6.11 (1H, dd, *J*=9.5, 1 Hz, H12), 6.98 (1H, dd, *J*=9.5, 7 Hz, H13), 7.26–7.39 (5H, m), 7.40–7.47 (2H, m), 7.51–7.58 (1H, m), 7.98–8.04 (2H, m). **25**: Colorless glass. HRMS Calcd for $C_{38}H_{45}NO_8$: 643.3143. Found: 643.3144. MS (*m*/*z*): 643 (M^+, 3), 554 (3), 510 (18), 508 (9), 476 (6), 420 (4), 105 (27), 91 (100), 59 (7), 45 (46). IR ($CHCl_3$) cm^{-1}: 1702 (sh), 1680. ^1H NMR (at 50 °C) *δ*: 1.01 (3H, s), 1.01 (1H, ddd, *J*=12, 12, 4 Hz), 1.20–1.75 (4H, m), 1.78 (1H, d, *J*=6.5 Hz, H5), 1.81 (1H, dt, *J*=15, 6.5 Hz), 1.89 (1H, dt, *J*=15, 6.5 Hz), 2.01 (1H, br ddd, *J*=12, 3.5, 3.5 Hz), 2.06 (1H, br d, *J*=7 Hz, H9), 2.22 (1H, dd, *J*=16.5, 8.5 Hz), ca. 2.28–2.50 (1H, br m), 3.09 (1H, br d, *J*=7 Hz, H14), 3.25–3.38 (2H, m), 3.29 (3H, s), 3.44–3.53 (3H, m), 3.61 (1H, ddd, *J*=10, 4, 4 Hz), 4.19 (1H, br dd, *J*=8.5, 6.5 Hz), 4.26 (2H, dd, *J*=6.5, 6.5 Hz), 4.37 (1H, d, *J*=7 Hz), 4.54 (2H, s), 5.12 (1H, d, *J*=12.5 Hz), 5.18 (1H, d, *J*=12.5 Hz), 6.15 (1H, dd, *J*=9.5, 1.5 Hz, H12), 6.93 (1H, dd, *J*=9.5, 7 Hz, H11), 7.26–7.38 (5H, m), 7.39–7.47 (2H, m), 7.50–7.58 (1H, m), 7.99–8.05 (2H, m).

4.2.3. Allylic oxidation of 21 with CrO_3 and *t*-BuOOH (Table 1, run f). *t*-BuOOH (70%, 20 μl, 0.146 mmol) was added to a slurry of CrO_3 (2.5 mg, 25 μmol) in CH_2Cl_2 (1.5 ml) and the mixture was stirred at 25 °C for 10 min under an Ar atmosphere. The mixture was allowed to cool in an ice bath, and to this was added a CH_2Cl_2 (1.5 ml) solution of **21** (9 mg, 14.3 μmol). Stirring was continued at 0–25 °C for 42 h and the reaction was quenched by addition of saturated $NaHCO_3$–H_2O and saturated $Na_2S_2O_3$–H_2O. Extraction with CH_2Cl_2, usual work-up, and PTLC [hexane–EtOAc (3:1)] gave **24** (2 mg, 22%), **25** (1.5 mg, 16%), and recovered **21** (4 mg, 44%) in order of decreasing polarity.

4.2.4. Hydrogenation of 22 and 23 to form 26 and 27, respectively. The procedure for the preparation of **26** from **22** was typical. A slurry of **22** (6 mg, 9.85 μmol) and 10% Pd/C (1.5 mg, 1.4 μg atom) in MeOH (3 ml) was stirred under a hydrogen atmosphere (1 atm) at 21 °C for 2 h. The mixture was filtered through a Celite pad and the pad was rinsed with CH_2Cl_2. Evaporation of the combined organic layers followed by separation by PTLC [hexane–EtOAc (7:4)] provided **26** (6 mg, quantitative) as a colorless glass. HRMS Calcd for $C_{35}H_{49}NO_8$: 611.3455. Found: 611.3448. MS (*m*/*z*): 611 (M^+, 1), 510 (10), 422 (57), 377 (16), 349 (4), 328 (6), 300 (14), 105 (49), 89 (7), 77 (12), 57 (100), 45 (63), 41 (19). IR ($CHCl_3$) cm^{-1}: 1706, 1681. ^1H NMR (at 50 °C) *δ*: 0.95–1.07 (1H, m), 0.98 (3H, s), 1.31–1.42 (1H, m), 1.43–1.54 (1H, m), 1.47 (9H, s), 1.62–2.02 (7H, m), 1.64 (1H, d, *J*=7 Hz, H5), 1.84 (1H, s, H9), 2.10 (1H, dd, *J*=16, 8.5 Hz), 2.28 (1H, dd, *J*=18, 7 Hz, H12), 2.40–2.52 (2H, m), 2.50 (1H, ddd, *J*=18, 10, 10 Hz, H12), 3.28 (1H, br d, *J*=11 Hz, H19), 3.35 (3H, s), 3.37 (1H, d, *J*=11 Hz, H19), 3.52–3.62 (1H, m), 3.65–3.74 (3H, m), 4.10 (1H, dd, *J*=8.5, 7 Hz, H6), 4.25 (1H, d, *J*=6.5 Hz), 4.35 (1H, ddd, *J*=11, 9, 6 Hz), 4.46 (1H, ddd, *J*=11, 9, 6.5 Hz), 4.62 (2H, s), 7.39–7.46 (2H, m), 7.51–7.57 (1H, m), 7.99–8.04 (2H, m). In the same manner as above, **27** (4 mg, quantitative) was obtained from **23** (4 mg, 6.57 mmol) as a colorless glass after PTLC [hexane–EtOAc (2:1)]. HRMS Calcd for $C_{35}H_{49}NO_8$: 611.3455. Found: 611.3478. MS (*m*/*z*): 611 (M^+, 1), 510 (10), 466 (9), 450 (7), 422 (51), 328 (7), 300 (7), 105 (38), 57 (100), 45 (61), 41 (23). IR ($CHCl_3$) cm^{-1}: 1704, 1679. ^1H NMR (at 50 °C) *δ*: 0.99 (3H, s), 1.11 (1H, ddd, *J*=13, 11, 4.5 Hz), 1.35 (1H, ddd, *J*=13.5, 12, 5.5 Hz), 1.44–1.58 (2H, m), 1.46 (9H, s), 1.65–2.17 (7H, m), 1.68 (1H, d, *J*=6.5 Hz, H5), 2.17 (1H, dd,

J=16.5, 8.5 Hz), 2.25 (1H, dd, J=17.5, 8.5 Hz, H12), 2.33 (1H, br d, J=16.5 Hz), 2.58 (1H, ddd, J=17.5, 10.5, 10.5 Hz, H12), 2.90 (1H, d, J=7 Hz, H14), 3.22 (1H, br d, J=10.5 Hz, H19), 3.33 (3H, s), 3.36 (1H, d, J=10.5 Hz, H19), 3.38–3.46 (1H, m), 3.51–3.59 (3H, m), 4.12 (1H, dd, J=8.5, 6.5 Hz, H6), 4.28 (1H, d, J=7 Hz), 4.33 (1H, ddd, J=11, 8, 6.5 Hz), 4.43 (1H, ddd, J=11, 8, 6 Hz), 4.58 (2H, s), 7.39–7.46 (2H, m), 7.50–7.57 (1H, m), 8.01–8.07 (2H, m).

4.2.5. Alcoholysis of 26 and 27 to form 28 and 29, respectively. In a similar manner to that described for the preparation of **16** from **17** (Section 4.1.6), **26** (6 mg, 9.82 μmol) and **27** (5 mg, 8.18 μmol) were separately heated in K_2CO_3–MeOH (0.5% w/v, 2.5 ml each) for 2 h to afford, respectively, **28** (5 mg, quantitative) and **29** (4 mg, quantitative) after purification by PTLC [hexane–EtOAc (3:2)]. **28**: Colorless glass. HRMS Calcd for $C_{28}H_{45}NO_7$: 507.3193. Found: 507.3188. MS (*m*/*z*): 507 (M^+, 2), 418 (2), 406 (10), 362 (33), 345 (7), 318 (23), 300 (12), 273 (20), 270 (9), 59 (11), 57 (100), 45 (72), 41 (22). IR ($CHCl_3$) cm^{-1}: 1679. ^1H NMR (at 50 °C) δ: 0.97 (3H, s), 0.99 (1H, ddd, J=12.5, 9.5, 5 Hz, H1), 1.35 (1H, ddd, J=13, 10.5, 4.5 Hz, H3), 1.39–1.89 (8H, m, including OH), 1.49 (9H, s), 1.62 (1H, d, J=7.5 Hz, H5), 1.81 (1H, s, H9), 1.87–1.97 (1H, m), 2.05 (1H, dd, J=16, 9 Hz, H7), 2.25 (1H, dd, J=18, 7.5 Hz, H12), 2.26–2.43 (2H, m), 2.48 (1H, ddd, J=18, 10, 10 Hz, H12), 3.27 (1H, br d, J=11 Hz, H19), 3.35 (3H, s), 3.36 (1H, d, J=11 Hz, H19), 3.51–3.60 (1H, m), 3.65–3.79 (5H, m), 4.07 (1H, dd, J=9, 7.5 Hz, H6), 4.21 (1H, d, J=6.5 Hz, H20), 4.63 (2H, s). **29**: Colorless glass. HRMS Calcd for $C_{28}H_{45}NO_7$: 507.3193. Found: 507.3170. MS (*m*/*z*): 507 (M^+, 2), 434 (2), 406 (9), 362 (21), 318 (35), 300 (17), 270 (13), 57 (100), 45 (79), 41 (27). IR ($CHCl_3$) cm^{-1}: 1679. ^1H NMR (at 50 °C) δ: 0.98 (3H, s), 1.10 (1H, ddd, J=12.5, 11.5, 4.5 Hz, H1), 1.35 (1H, ddd, J=13.5, 12, 5 Hz, H3), 1.44–2.16 (10H, m, including OH), 1.47 (9H, s), 1.67 (1H, d, J=6.5 Hz, H5), 2.03 (1H, dd, J=16, 8.5 Hz, H7), 2.21 (1H, dd, J=17.5, 8.5 Hz, H12), 2.33 (1H, br d, J=16 Hz, H7), 2.57 (1H, ddd, J=17.5, 10.5, 10.5 Hz, H12), 2.90 (1H, d, J=7 Hz, H14), 3.21 (1H, br d, J=10.5 Hz, H19), 3.33 (3H, s), 3.39 (1H, d, J=10.5 Hz, H19), 3.35–3.45 (1H, m), 3.50–3.58 (3H, m), 3.68–3.76 (2H, m, CH_2OH), 4.09 (1H, dd, J=8.5, 6.5 Hz, H6), 4.25 (1H, d, J=7 Hz, H20), 4.58 (2H, s).

4.2.6. Oxidation of 28 and 29 to form 30 and 31, respectively. The procedure for the preparation of **30** from **28** was typical. PCC–Al_2O_3 (20 wt %, 32 mg, 29.7 μmol) was added in one-portion to a cooled (0 °C) solution of **28** (5 mg, 9.86 mmol) in CH_2Cl_2 (3 ml) and the mixture was stirred at 0 °C for 10 min and at 24 °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 [hexane–EtOAc (1:1)] provided **30** (4.5 mg, 90%) as a colorless glass. HRMS Calcd for $C_{28}H_{43}NO_7$: 505.3037. Found: 505.3042. MS (*m*/*z*): 505 (M^+, 2), 416 (2), 404 (12), 360 (31), 316 (25), 299 (16), 298 (14), 271 (17), 57 (100), 45 (75), 41 (31). IR ($CHCl_3$) cm^{-1}: 1715, 1680. ^1H NMR (at 50 °C) δ: 0.99 (3H, s), 1.02 (1H, ddd, J=13, 9.5, 5 Hz), 1.37 (1H, ddd, J=13.5, 10.5, 5 Hz), 1.44–1.54 (1H, m), 1.47 (9H, s), 1.59 (1H, d, J=7 Hz), 1.59–2.04 (5H, m), 1.93 (1H, s, H9), 2.03 (1H, dd, J=16, 9 Hz, H7), 2.25 (1H, dd, J=18, 7.5 Hz), 2.42 (2H, d, J=2 Hz, CH_2CHO), 2.53 (1H, ddd, J=18, 10, 10 Hz), ca. 2.61–2.69 (1H, m), 2.65 (1H, d, J=16 Hz, H7), 3.28 (1H, br d, J=11 Hz), 3.35 (3H, s), 3.38 (1H, d, J=11 Hz), 3.54–3.63 (1H, m), 3.66–3.74 (3H, m), 4.07 (1H, dd, J=9, 7 Hz, H6), 4.27 (1H, d, J=6.5 Hz), 4.62 (2H, s), 9.78 (1H, t, J=2 Hz, CHO). In the same manner as above, **31** (3 mg, 75%) was obtained from **29** (4 mg, 7.89 μmol) as a colorless glass after separation by PTLC [hexane–EtOAc (2:1)]. HRMS Calcd for $C_{28}H_{43}NO_7$: 505.3037. Found: 505.3034. MS (*m*/*z*): 505 (M^+, 1), 432 (2), 404 (11), 360 (28), 316 (25), 298 (13), 288 (7), 57 (100), 45 (81), 41 (28). IR ($CHCl_3$) cm^{-1}: 1714, 1680. ^1H NMR (at 50 °C) δ: 0.99 (3H, s), 1.13 (1H, ddd, J=13, 11, 4.5 Hz), 1.36 (1H, ddd, J=13.5, 12, 5 Hz), 1.46 (9H, s), ca. 1.46–1.57 (1H, m), 1.64–2.28 (7H, m), 1.72 (1H, d, J=7 Hz), 2.17 (1H, dd, J=16, 8 Hz), 2.28 (1H, dd, J=17, 2 Hz, CH_2CHO), 2.34 (1H, br d, J=16 Hz), 2.44 (1H, dd, J=17, 1.5 Hz, CH_2CHO), 2.61 (1H, ddd, J=17.5, 10.5, 10.5 Hz), 2.93 (1H, d, J=6.5 Hz), 3.22 (1H, br d, J=11 Hz), 3.33 (3H, s), 3.36 (1H, d, J=11 Hz), 3.39–3.47 (1H, m), 3.51–3.58 (3H, m), 4.29 (1H, d, J=6.5 Hz), 4.58 (2H, s), 9.76 (1H, dd, J=2, 1.5 Hz, CHO).

4.2.7. Preparation of 32, 33, and 34 from 30. K_2CO_3 (7.5 mg, 54.3 μmol) was added to a solution of **30** (4.5 mg, 8.91 μmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (15 mg, 78.1 μmol) in MeOH (1.5 ml) and the mixture was stirred at 24 °C under an Ar atmosphere for 3 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [hexane–EtOAc (5:1)] furnished **32** (1.5 mg, 34%) and a mixture of **33** and **34** (4 mg) in order of increasing polarity. The latter was purified by PTLC [hexane–EtOAc (1:1)] to give **33** (1.5 mg, 33%) and **34** (1 mg, 22%) in order of decreasing polarity. **32**: Colorless glass. HRMS Calcd for $C_{29}H_{43}NO_6$: 501.3088. Found: 501.3106. MS (*m*/*z*): 501 (M^+, 2), 400 (10), 356 (30), 312 (15), 295 (9), 294 (14), 267 (15), 57 (100), 45 (64), 41 (27). IR ($CHCl_3$) cm^{-1}: 2120, 1680. ^1H NMR (at 50 °C) δ: 0.95–1.06 (1H, m), 0.99 (3H, s), 1.30–1.50 (2H, m), 1.49 (9H, s), 1.61 (1H, d, J=7 Hz, H5), 1.61–1.88 (4H, m), 1.82 (1H, br s), 1.96 (1H, ddd, J=13.5, 10, 3 Hz, H13), 1.98 (1H, dd, J=2.5, 2.5 Hz, C≡CH), 2.08 (1H, br dd, J=16.5, 8 Hz, H7), 2.12 (1H, dd, J=16.5, 2.5 Hz, CH_2C≡CH), 2.19 (1H, dd, J=16.5, 2.5 Hz, CH_2C≡CH), 2.25 (1H, dd, J=18, 7.5 Hz, H12), 2.45–2.52 (1H, m), 2.51 (1H, ddd, J=18, 10, 10 Hz, H12), 2.67 (1H, d, J=16.5 Hz, H7), 3.28 (1H, br d, J=11 Hz, H19), 3.35 (3H, s), 3.38 (1H, d, J=11 Hz, H19), 3.54–3.62 (1H, m), 3.66–3.74 (3H, m), 4.08 (1H, dd, J=8, 7 Hz, H6), 4.25 (1H, d, J=7 Hz, H20), 4.62 (2H, s). **33**: Colorless glass. HRMS Calcd for $C_{28}H_{43}NO_7$: 505.3037. Found: 505.3028. MS (*m*/*z*): 505 (M^+, 1), 404 (11), 360 (28), 316 (16), 299 (32), 298 (23), 271 (14), 254 (8), 59 (10), 57 (100), 45 (67), 41 (23). IR ($CHCl_3$) cm^{-1}: 1706, 1678. ^1H NMR (at 50 °C) δ: 0.99 (3H, s), 1.19–1.72 (8H, m, including OH), 1.38 (1H, d, J=14.5 Hz, H15), 1.47 (9H, s), 1.60 (1H, d, J=5.5 Hz, H5), 1.83 (1H, dd, J=16, 8 Hz, H7), 1.85–1.94 (1H, m), 1.97 (1H, dd, J=13.5, 5 Hz, H13), 2.16 (1H, dd, J=14.5, 8 Hz, H15), 2.17–2.24 (1H, m, H14), 2.32 (1H, dd, J=5, 5 Hz, H12), 2.60 (1H, br d, J=16 Hz, H7), 3.17 (1H, br d, J=11.5 Hz), 3.31–3.39 (1H, m), 3.33 (3H, s), 3.40 (1H, d, J=11.5 Hz), 3.44–3.52 (1H, m), 3.60–3.65 (2H, m), 4.03 (1H, dd, J=8, 5.5 Hz, H6), 4.04 (1H, d,

J=7 Hz, H20), 4.14 (1H, dd, J=8, 5 Hz, H16), 4.59 (2H, s). **34**: Colorless glass. HRMS Calcd for $C_{28}H_{43}NO_7$: 505.3037. Found: 505.3022. MS (*m/z*): 505 (M^+, 1), 404 (13), 360 (24), 316 (19), 299 (34), 298 (25), 271 (9), 254 (9), 59 (12), 57 (100), 45 (60), 41 (21). IR ($CHCl_3$) cm^{-1}: 1706, 1678. ^1H NMR (at 50 °C) δ: 0.99 (3H, s), 1.16–1.96 (9H, m, including OH), 1.42 (1H, d, J=1.5 Hz, H9), 1.48 (9H, s), 1.57 (1H, d, J=6.5 Hz, H5), 1.61 (1H, dd, J=14.5, 5.5 Hz, H15), 1.77 (1H, dd, J=16, 8 Hz, H7), 1.90 (1H, dd, J=14.5, 9.5 Hz, H15), 2.26–2.30 (1H, m, H12), 2.59 (1H, br d, J=16 Hz, H7), 3.18 (1H, br d, J=10.5 Hz, H19), 3.31–3.39 (1H, m), 3.33 (3H, s), 3.40 (1H, d, J=10.5 Hz, H19), 3.46–3.55 (1H, m), 3.61–3.66 (2H, m), 4.01 (1H, dd, J=8, 6.5 Hz, H6), 4.02 (1H, d, J=7 Hz, H20), 4.04–4.12 (1H, m, H16), 4.60 (2H, s).

4.2.8. Oxidation of 33 and 34 to form 35. The procedure from **33** was typical. To a cooled (0 °C) solution of **33** (1.5 mg, 2.97 μmol) in CH_2Cl_2 (2 ml) was added PCC–Al_2O_3 (20 wt %, 16 mg, 14.8 μmol) and the mixture was stirred at 0 °C for 5 min and at 25 °C for 1.5 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [hexane–EtOAc (2:1)] yielded **35** (1.5 mg, quantitative) as a colorless glass. HRMS Calcd for $C_{28}H_{41}NO_7$: 503.2881. Found: 503.2875. MS (*m/z*): 503 (M^+, 2), 447 (1), 402 (8), 358 (23), 314 (14), 297 (18), 269 (10), 57 (100), 45 (64), 41 (24). IR ($CHCl_3$) cm^{-1}: 1734, 1698, 1680. ^1H NMR (at 50 °C) δ: 1.02 (3H, s), 1.23–1.74 (6H, m), 1.49 (9H, s), 1.65 (1H, d, J=6 Hz), 1.68 (1H, dd, J=14, 9.5 Hz, H13), 1.87–1.95 (1H, m), 1.91 (1H, dd, J=16, 8 Hz), 2.16 (1H, d, J=19.5 Hz, H15), 2.39 (1H, dd, J=14, 4.5 Hz, H13), 2.51 (1H, br dd, J=9.5, 6.5 Hz, H14), 2.62 (1H, d, J=19.5 Hz, H15), 2.76 (1H, br d, J=16 Hz), 3.11 (1H, d, J=4.5 Hz, H12), 3.21 (1H, br d, J=11 Hz, H19), 3.33 (3H, s), 3.36–3.44 (1H, m), 3.42 (1H, d, J=11 Hz, H19), 3.46–3.55 (1H, m), 3.62–3.67 (2H, m), 4.09 (1H, dd, J=8, 6 Hz, H6), 4.16 (1H, d, J=6.5 Hz), 4.59 (2H, s). In the same manner, **35** (1 mg, quantitative) was obtained from **34** (1 mg, 1.98 μmol) by oxidation with PCC–Al_2O_3 (20 wt %, 11 mg, 10.2 μmol).

4.2.9. Hydroboration–oxidation of 16 to form 36, 37, and 38. As described in the text, the reproducibility of this reaction is low. The following was the best result. $BH_3 \cdot SMe_2$ (64 μl, 0.674 mmol) was added to a cooled (0 °C) solution of **16** (11 mg, 22.4 μmol) in THF (2.5 ml) under an Ar atmosphere and the mixture was stirred at 0–24 °C for 15 h. After the mixture had been cooled again in an ice bath, EtOH (76 μl, 1.35 mmol) was added and the mixture was vigorously stirred for 5 min. NaOH–H_2O (1 N, 0.90 ml, 0.90 mmol) and H_2O_2–H_2O (30%, 203 μl, 1.79 mmol) were successively added, and the whole was further stirred at 0 °C for 30 min and at 25 °C for 5 h. Saturated NH_4Cl–H_2O and saturated $Na_2S_2O_3$–H_2O were added and the whole was extracted with CH_2Cl_2. Usual work-up followed by separation by PTLC (3% MeOH–CH_2Cl_2) afforded **36** (5.5 mg, 48%), **37** (3 mg, 26%), and **38** (2 mg, 18%) in order of decreasing polarity. **36**: Colorless glass. HRMS Calcd for $C_{28}H_{47}NO_7$: 509.3350. Found: 509.3334. MS *m/z*: 509 (M^+, 1), 420 (3), 408 (13), 364 (29), 320 (19), 302 (23), 57 (100), 45 (76), 41 (27). IR ($CHCl_3$) cm^{-1}: 1674. ^1H NMR (at 50 °C) δ: 0.94 (3H, s), 0.98 (1H, ddd, J=13, 10, 4.5 Hz, H1), 1.11–1.16 (1H, m), 1.31 (1H, ddd, J=13.5, 11, 4.5 Hz, H3), 1.40–2.15 (15H, m, including OH×2), 1.46 (9H, s), 1.56 (1H, d, J=7 Hz, H5), 3.14–3.29 (1H, m), 3.30 (1H, d, J=10.5 Hz, H19), 3.36 (3H, s), 3.44–3.52 (1H, m), 3.58–3.79 (5H, m), 4.01–4.10 (1H, m, H6), 4.04 (1H, d, J=6.5 Hz, H20), 4.22 (1H, dddd, J=10, 10, 7.5, 7.5 Hz, H12), 4.63 (2H, s). **37**: Colorless glass. HRMS Calcd for $C_{28}H_{47}NO_7$: 509.3350. Found: 509.3345. MS *m/z*: 509 (M^+, 0.6), 420 (5), 408 (10), 364 (5), 320 (18), 302 (52), 284 (32), 258 (11), 57 (100), 45 (78), 41 (30). IR ($CHCl_3$) cm^{-1}: 1674. ^1H NMR (at 50 °C) δ: 0.91–1.03 (1H, m), 0.96 (3H, s), 1.08 (1H, br s), 1.33 (1H, ddd, J=13.5, 12, 5 Hz, H3), 1.43–1.87 (8H, m, including OH), 1.47 (9H, s), 1.55 (1H, d, J=6.5 Hz, H5), 2.00–2.10 (1H, m), 2.13–2.19 (1H, m), 2.18–2.28 (1H, m), 2.36 (1H, ddd, J=13.5, 4, 4 Hz, H1), 3.21 (1H, br d, J=10 Hz, H19), 3.34 (1H, d, J=10 Hz, H19), 3.36 (3H, s), 3.46–3.53 (1H, m), 3.61–3.83 (6H, m, including H12), 4.05 (1H, dd, J=8.5, 6.5 Hz, H6), 4.18 (1H, d, J=6.5 Hz, H20), 4.63 (2H, s), 4.78 (1H, J=10 Hz, CHO*H*). **38**: Colorless syrup. HRMS Calcd for $C_{28}H_{47}NO_6$: 493.3401. Found: 493.3376. MS *m/z*: 493 (M^+, 1), 404 (4), 392 (18), 348 (34), 304 (22), 287 (29), 256 (25), 57 (100), 45 (75), 41 (30). IR ($CHCl_3$) cm^{-1}: 1672. ^1H NMR (at 50 °C) δ: 0.90–1.01 (1H, m), 0.94 (3H, s), 1.03 (1H, br s, H9), 1.16 (1H, br s, OH), 1.25–1.38 (2H, m), 1.39–1.56 (3H, m), 1.46 (9H, s), 1.58–1.72 (5H, m), 1.60 (1H, d, J=7.5 Hz, H5), 1.72–1.90 (1H, m, H2), 1.93–2.16 (4H, m), 2.10 (1H, dd, J=15.5, 9.5 Hz, H7), 3.15–3.29 (1H, br m), 3.33 (1H, d, J=11 Hz, H19), 3.36 (3H, s), 3.49 (1H, ddd, J=10.5, 5, 4.5 Hz), 3.57–3.78 (5H, m), 4.03 (1H, d, J=6.5 Hz, H20), 4.64 (2H, s).

4.2.10. Respective oxidation of 36 and 37 to form 39 and 40. The procedure for the preparation of **39** from **36** is described as a representative example. To a cooled (0 °C) solution of **36** (16 mg, 31.4 μmol) in CH_2Cl_2 (2.5 ml) were added TEMPO (0.5 mg, 3.21 μmol) and $PhI(OAc)_2$ (11 mg, 34.2 μmol), and the mixture was stirred at the same temperature for 20 min and at 25 °C for 6 h. Saturated $Na_2S_2O_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was successively washed with saturated $NaHCO_3$–H_2O and H_2O, then treated as usual. The resulting residue was separated by PTLC (3% MeOH–CH_2Cl_2) to afford **39** (12 mg, 75%) along with recovered **36** (1 mg, 6%) in order of increasing polarity. **39**: Colorless glass. HRMS Calcd for $C_{28}H_{45}NO_7$: 507.3193. Found: 507.3178. MS *m/z*: 507 (M^+, 0.4), 489 (2), 408 (13), 406 (7), 388 (8), 362 (17), 344 (14), 318 (13), 300 (17), 283 (16), 57 (100), 45 (76), 41 (29). IR ($CHCl_3$) cm^{-1}: 1714, 1674. ^1H NMR (at 50 °C) δ: 0.95 (3H, s), 1.01 (1H, ddd, J=13, 10, 5 Hz, H1), 1.20–2.25 (12H, m, including OH), 1.45 (9H, s), 1.60 (1H, d, J=7 Hz, H5), 2.25–2.34 (1H, m), 2.63 (1H, br d, J=16.5 Hz, CH_2CHO), 2.77 (1H, br d, J=16.5 Hz, CH_2CHO), 3.23 (1H, br d, J=10.5 Hz, H19), 3.31 (1H, d, J=10.5 Hz, H19), 3.36 (3H, s), 3.47–3.55 (1H, m), 3.59–3.71 (3H, m), 4.02–4.11 (1H, m), 4.09 (1H, d, J=6.5 Hz, H20), 4.26 (1H, dddd, J=10, 10, 7.5, 7.5 Hz, H12), 4.64 (2H, s), 9.85 (1H, dd, J=2, 2 Hz, CHO). In the same manner as above, **40** (6 mg, 75%) was obtained from **37** (8 mg, 15.7 μmol) as a colorless glass after PTLC (2% MeOH–CH_2Cl_2). HRMS Calcd for $C_{28}H_{45}NO_7$: 507.3193. Found: 507.3185. MS *m/z*: 507 (M^+, 0.7), 418 (5), 406 (11), 362 (11), 318 (24), 300 (47),

282 (23), 57 (100), 45 (74), 41 (27). IR ($CHCl_3$) cm^{-1}: 1714, 1676. ^1H NMR (at 50 °C) δ: 0.97 (3H, s), 0.99 (1H, ddd, J=13.5, 11, 4 Hz, H1), 1.29–1.33 (1H, m, H9), 1.34 (1H, ddd, J=13.5, 12.5, 4.5 Hz, H3), 1.44–1.83 (4H, m), 1.46 (9H, s), 1.59 (1H, d, J=7 Hz, H5), 1.90–2.05 (2H, m), 2.06–2.22 (2H, m), 2.32–2.46 (3H, m), 2.42 (1H, dd, J=16, 2 Hz, CH_2CHO), 2.55 (1H, dd, J=16, 2 Hz, CH_2CHO), 3.23 (1H, br d, J=11 Hz, H19), 3.35 (1H, d, J=11 Hz, H19), 3.36 (3H, s), 3.48–3.57 (1H, m), 3.64–3.81 (3H, m), 4.07 (1H, dd, J=8, 7 Hz, H6), 4.23 (1H, d, J=7 Hz, H20), 4.63 (2H, s), 4.81 (1H, d, J=10 Hz, OH), 9.85 (1H, dd, J=2, 2 Hz, CHO).

4.2.11. Conversion of 39 and 40 to 41 and 42, respectively. The procedure for the preparation of **41** from **39** was typical. K_2CO_3 (18 mg, 0.130 mmol) was added to a solution of **39** (11 mg, 21.7 μmol) and dimethyl (1-diazo-2-oxopropyl)-phosphonate (33 mg, 0.172 mmol) and the mixture was stirred under an Ar atmosphere at 25 °C for 3.5 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 (3:1)] furnished **41** (10.5 mg, 96%) as a colorless glass. HRMS Calcd for $C_{29}H_{45}NO_6$: 503.3244. Found: 503.3260. MS m/z: 503 (M^+, 1), 414 (2), 402 (13), 358 (38), 314 (19), 297 (26), 278 (7), 57 (100), 45 (76), 41 (26). IR ($CHCl_3$) cm^{-1}: 2116, 1674. ^1H NMR (at 50 °C) δ: 0.95–1.04 (1H, m, H1), 0.96 (3H, s), 1.24–1.28 (1H, m, H9), 1.32 (1H, ddd, J=13.5, 11.5, 4.5 Hz, H3), 1.41–1.70 (5H, m, including OH), 1.47 (9H, s), 1.58 (1H, d, J=7 Hz, H5), 1.72–1.86 (1H, m), 1.86–2.06 (3H, m), 1.93 (1H, dd, J=2.5, 2.5 Hz, C≡CH), 2.13–2.19 (1H, m), 2.20 (1H, br d, J=16.5 Hz, CH_2C≡CH), 2.25–2.54 (3H, m), 3.23 (1H, br d, J=10.5 Hz, H19), 3.32 (1H, d, J=10.5 Hz, H19), 3.36 (3H, s), 3.44–3.55 (1H, m), 3.57–3.70 (3H, m), 4.09 (1H, d, J=6.5 Hz, H20), 4.24 (1H, dddd, J=10, 10, 7.5, 7.5 Hz, H12), 4.63 (2H, s). In the same manner, **42** (4.5 mg, 91%) was obtained from **40** (5 mg, 9.86 μmol) as a colorless glass after separation by PTLC [hexane–EtOAc (3:2)]. HRMS Calcd for $C_{29}H_{45}NO_6$: 503.3244. Found: 503.3254. MS m/z: 503 (M^+, 2), 414 (10), 402 (14), 358 (12), 314 (22), 297 (31), 296 (72), 278 (27), 57 (100), 45 (70), 41 (27). IR ($CHCl_3$) cm^{-1}: 2112, 1675. ^1H NMR (at 50 °C) δ: 0.97 (3H, s), 0.98 (1H, ddd, J=13.5, 11.5, 4 Hz, H1), 1.16–1.22 (1H, m), 1.33 (1H, ddd, J=13.5, 12, 5 Hz, H3), 1.48 (9H, s), 1.48–1.81 (4H, m), 1.57 (1H, d, J=7 Hz, H5), 1.92–1.99 (3H, m, H11×2 and C≡CH), 2.13–2.31 (4H, m, H7, H14, and CH_2C≡CH), 2.16 (1H, ddd, J=16, 7, 3 Hz, H13), 2.36 (1H, ddd, J=13.5, 4, 4 Hz, H1), 2.39 (1H, d, J=16 Hz, H7), 3.23 (1H, br d, J=10.5 Hz, H19), 3.36 (3H, s), 3.36 (1H, d, J=10.5 Hz, H19), 3.47–3.55 (1H, m), 3.65–3.81 (4H, m), 4.09 (1H, dd, J=8, 7 Hz, H6), 4.23 (1H, d, J=6 Hz, H20), 4.63 (2H, s), 4.82 (1H, d, J=10 Hz, OH).

4.2.12. Preparation of xanthate 43 from 41. NaH (60% in mineral oil, 22 mg, 0.550 mmol) and imidazole (2 mg, 29.4 μmol) were added to a solution of **41** (11 mg, 21.9 μmol) in THF (3 ml) and the mixture was refluxed with stirring under an Ar atmosphere for 3 h. CS_2 (0.33 ml, 5.47 mmol) was added to this and the resulting solution was further refluxed for 40 min, during this time it gradually changed into a yellow-white slurry. MeI (0.41 ml, 6.58 mmol) was further added to this and the whole was heated for 40 min. After the mixture had been cooled, saturated NH_4Cl–H_2O was added and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$–H_2O and then treated as usual. Separation by PTLC [hexane–EtOAc (3:1)] gave **43** (11 mg, 85%) and recovery of **41** (1 mg, 9%) in order of increasing polarity. **43**: Colorless glass. HRMS Calcd for $C_{31}H_{47}NO_6S_2$: 593.2842. Found: 593.2861. MS m/z: 593 (M^+, 0.5), 518 (1), 504 (1), 492 (4), 448 (7), 385 (37), 346 (22), 280 (39), 57 (74), 45 (100), 41 (42). IR ($CHCl_3$) cm^{-1}: 2112, 1675. ^1H NMR (at 50 °C) δ: 0.96 (3H, s), 0.99 (1H, ddd, J=13, 10.5, 4.5 Hz, H1), 1.27–1.38 (2H, m), 1.45–1.55 (1H, m, H2), 1.48 (9H, s), 1.58 (1H, d, J=7 Hz, H5), 1.62–1.75 (3H, m), 1.75–1.91 (1H, m, H2), 1.95 (1H, dd, J=2.5, 2.5 Hz, C≡CH), 2.08–2.18 (1H, m), 2.13 (1H, ddd, J=13, 5, 4.5 Hz, H1), 2.19–2.53 (6H, m), 2.54 (3H, s, SCH_3), 3.23 (1H, br d, J=11 Hz, H19), 3.34 (1H, d, J=11 Hz, H19), 3.35 (3H, s), 3.51 (1H, ddd, J=10.5, 6.5, 4 Hz), 3.60 (1H, ddd, J=10.5, 5, 4 Hz), 3.68 (1H, ddd, J=11, 5, 4 Hz), 3.75 (1H, ddd, J=11, 6.5, 4 Hz), 4.05–4.15 (1H, m, H6), 4.63 (2H, s), 6.03 (1H, dddd, J=10, 10, 7.5, 7.5 Hz, H12).

4.2.13. Radical cyclization of 43 to form 44. Bu_3SnH (22 μl, 81.8 μmol) and AIBN (1 mg, 6.10 μmol) were added to a solution of **43** (5 mg, 8.43 μmol) in toluene (5 ml) and Ar gas was bubbled into the mixture for 15 min at an ambient temperature. Then the solution was stirred under reflux for 15 min under an Ar atmosphere. After evaporation of the reaction solvent in vacuo, the residue was separated by PTLC [hexane–EtOAc (4:1)] to provide **44** (3.5 mg, 85%) as a colorless glass. HRMS Calcd for $C_{29}H_{45}NO_5$: 487.3295. Found: 487.3280. MS m/z: 487 (M^+, 3), 398 (2), 386 (18), 342 (24), 298 (15), 281 (46), 69 (15), 57 (100), 45 (66), 41 (34). IR ($CHCl_3$) cm^{-1}: 1674. ^1H NMR (at 50 °C) δ: 0.81–0.93 (1H, m, H1), 0.97 (3H, s, H18), 1.11 (1H, br d, J=10 Hz, H9), 1.25–1.51 (3H, m), 1.46 (9H, s), 1.53 (1H, d, J=6.5 Hz, H5), 1.58–1.82 (5H, m), 1.72 (1H, dd, J=16, 8 Hz, H7), ca. 2.04–2.10 (1H, m, H14), 2.05 (1H, br d, J=16 Hz, H7), 2.11 (1H, br d, J=18 Hz, H15), 2.17 (1H, ddd, J=13, 4.5, 4.5 Hz, H1), 2.26–2.41 (1H, m), 2.38 (1H, ddd, J=18, 2.5, 2 Hz, H15), 3.18 (1H, br d, J=11 Hz, H19), 3.32 (1H, dt, J=10.5, 5 Hz), 3.37 (3H, s), 3.40 (1H, d, J=11 Hz, H19), 3.48 (1H, dt, J=10.5, 5 Hz), 3.68 (2H, dd, J=5, 5 Hz), 3.95 (1H, d, J=6.5 Hz, H20), 3.99 (1H, br dd, J=8, 6.5 Hz, H6), 4.48 (1H, ddd, J=2, 2, 2 Hz, H17), 4.62–4.65 (1H, m, H17), 4.65 (2H, s).

4.3. Preparation of enyne radical cyclization precursors (Scheme 6)

4.3.1. Oxidation of 16 and 18 to form 45 and 46, respectively. The procedure for the preparation of **45** from **16** is described as a representative example. PCC–Al_2O_3 (20 wt %, 348 mg, 0.323 mmol) was added to a solution of **16** (53 mg, 0.108 mmol) in CH_2Cl_2 (8 ml) and the mixture was stirred at 0 °C for 1 h. Saturated $NaHCO_3$–H_2O was added and the whole was filtered through a Celite bed. The filtrate was extracted with CH_2Cl_2. Usual work-up followed by PTLC [hexane–EtOAc (3:1)] afforded **45** (48 mg, 91%) as a colorless glass. HRMS Calcd for $C_{28}H_{43}NO_6$: 489.3088. Found: 489.3091. MS m/z: 489 (M^+, 4), 400 (4), 388 (13), 346 (33), 344 (25), 300 (25), 300 (25), 282 (28), 91 (10), 89 (11), 57 (100), 45 (76), 41 (28). IR

($CHCl_3$) cm^{-1}: 1713, 1675. ^1H NMR (at 50 °C) δ: 0.95 (3H, s), 1.01 (1H, ddd, J=12.5, 10, 5.5 Hz, H1), 1.28 (1H, ddd, J=13.5, 11, 5 Hz, H3), 1.39–1.53 (2H, m), 1.46 (9H, s), 1.66 (1H, d, J=7.5 Hz, H5), 1.66 (1H, ddd, J=13.5, 5, 5 Hz, H3), 1.80–1.96 (1H, m), 2.01 (1H, ddd, J=12.5, 4.5, 4.5 Hz, H1), 2.09 (1H, dddd, J=19.5, 5, 2, 2 Hz, H11), 2.10–2.36 (3H, m), 2.53 (1H, dd, J=6, 5.5 Hz, H14), 2.67 (2H, br s, CH_2CHO), 3.18–3.30 (1H, br m), 3.30 (1H, br d, J=10.5 Hz, H19), 3.35 (3H, s), 3.40 (1H, dt, J=10.5, 5 Hz), 3.53 (1H, dt, J=10.5, 5 Hz), 3.65 (2H, dd, J=5, 5 Hz), 4.07–4.18 (1H, m, H6), 4.08 (1H, d, J=6 Hz, H20), 4.62 (1H, d, J=6.5 Hz), 4.64 (1H, d, J=6.5 Hz), 5.52–5.63 (2H, m), 9.82 (1H, t, J=2 Hz, CHO). In the same manner, **46** (62 mg, 84%) was obtained from **18** (74 mg, 0.141 mmol) as a colorless glass after purification by PTLC [hexane–EtOAc (2:1)]. HRMS Calcd for $C_{31}H_{41}NO_6$: 523.2932. Found: 523.2918. MS m/z: 523 (M^+, 2), 480 (1), 478 (1), 434 (6), 390 (15), 388 (10), 351 (9), 298 (4), 91 (100), 89 (6), 45 (38). IR ($CHCl_3$) cm^{-1}: 1712, 1684. ^1H NMR (at 50 °C) δ: 0.95 (3H, s), 1.01 (1H, ddd, J=12.5, 10, 5.5 Hz, H1), 1.29 (1H, ddd, J=13.5, 11.5, 5 Hz, H3), 1.40–1.56 (2H, m), 1.62–1.72 (1H, m), 1.68 (1H, d, J=7 Hz, H5), 1.88 (1H, ddddd, J=12.5, 11, 9.5, 6.5, 4.5 Hz, H2), 2.01 (1H, ddd, J=12.5, 4.5, 4.5 Hz, H1), ca. 2.01–2.39 (4H, m), 2.51 (1H, dd, J=6, 5 Hz, H14), 2.65 (2H, br s, CH_2CHO), 3.18–3.42 (3H, m), 3.33 (3H, s), 3.51 (1H, ddd, J=10.5, 5, 4.5 Hz), 3.60–3.66 (2H, m), 4.06 (1H, d, J=6 Hz, H20), 4.17–4.26 (1H, m), 4.61 (2H, s), 5.10 (1H, d, J=12.5 Hz), 5.18 (1H, d, J=12.5 Hz), 5.52–5.62 (2H, m), 7.26–7.37 (5H, m), 9.79 (1H, br s, CHO).

4.3.2. Preparation of enyne derivatives 47 and 48 from 45 and 46, respectively. In the same manner as described for the preparation of **41** from **39** (Section 4.2.11), **45** (44 mg, 0.090 mmol) was stirred with dimethyl (1-diazo-2-oxopropyl)phosphonate (86 mg, 0.448 mmol) and K_2CO_3 (49 mg, 0.355 mmol) in MeOH (5 ml) at 0 °C for 5 min and at 25 °C for 4 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by PTLC [hexane–EtOAc (4:1)] furnished **47** (42 mg, 96%) as a colorless glass. HRMS Calcd for $C_{29}H_{43}NO_5$: 485.3139. Found: 485.3149. MS m/z: 485 (M^+, 1), 446 (1), 384 (9), 346 (22), 340 (17), 324 (9), 296 (17), 279 (36), 57 (100), 45 (76), 41 (31). IR ($CHCl_3$) cm^{-1}: 2116, 1673. ^1H NMR (at 50 °C) δ: 0.95 (3H, s), 0.99 (1H, ddd, J=12.5, 10, 5.5 Hz, H1), 1.27 (1H, ddd, J=13.5, 11.5, 5 Hz, H3), 1.32–1.38 (1H, m, H9), 1.38–1.51 (1H, m, H2), 1.48 (9H, s), 1.61–1.71 (1H, m, H3), 1.64 (1H, d, J=7 Hz, H5), 1.79–1.95 (1H, m, H2), 1.91 (1H, dd, J=2.5, 2.5 Hz, C≡CH), 2.00 (1H, ddd, J=12.5, 4.5, 4.5 Hz, H1), 2.08–2.34 (4H, m, H11×2 and CH_2C≡CH), 2.35–2.42 (1H, m, H14), 2.41–2.64 (2H, m, H7×2), 3.16–3.33 (1H, br m), 3.30 (1H, br d, J=10.5 Hz, H19), 3.35 (3H, s), 3.39 (1H, dt, J=10, 5 Hz), 3.52 (1H, dt, J=10, 5 Hz), 3.65 (2H, dd, J=5, 5 Hz), 4.09 (1H, d, J=6 Hz, H20), 4.16 (1H, br dd, J=8, 7 Hz, H6), 4.62 (1H, d, J=6.5 Hz), 4.64 (1H, d, J=6.5 Hz), 5.50–5.59 (2H, m). In the same manner, **48** (36 mg, 98%) was obtained from **46** (37 mg, 0.071 mmol) as a colorless glass after PTLC [hexane–EtOAc (3:1)]. HRMS Calcd for $C_{32}H_{41}NO_5$: 519.2982. Found: 519.2984. MS m/z: 519 (M^+, 1), 480 (2), 430 (5), 386 (11), 294 (4), 280 (4), 91 (100), 45 (38). IR ($CHCl_3$) cm^{-1}: 2105, 1683. ^1H NMR (at 50 °C) δ: 0.96 (3H, s), 0.99 (1H, ddd, J=13, 10, 5.5 Hz, H1), 1.28 (1H, ddd, J=13.5, 11, 5 Hz, H3), 1.31–1.40 (1H, m, H9), 1.45 (1H, ddddd, J=14.5, 5, 5, 5, 5 Hz, H2), 1.61–1.72 (1H, m), 1.67 (1H, d, J=7 Hz, H5), 1.80–1.96 (1H, m), 1.91 (1H, dd, J=2.5, 2.5 Hz, C≡CH), 2.00 (1H, ddd, J=13, 4.5, 4.5 Hz, H1), 2.09–2.30 (4H, m, including CH_2C≡CH), 2.34–2.41 (1H, m), 2.45–2.67 (2H, m), 3.23–3.42 (3H, m), 3.33 (3H, s), 3.50 (1H, ddd, J=10.5, 4.5, 4.5 Hz), 3.60–3.65 (2H, m), 4.08 (1H, d, J=6 Hz, H20), 4.25 (1H, ddd, J=9, 7, 1 Hz, H6), 4.59 (1H, d, J=6.5 Hz), 4.62 (1H, d, J=6.5 Hz), 5.12 (1H, d, J=12.5 Hz), 5.20 (1H, d, J=12.5 Hz), 5.49–5.59 (2H, m), 7.26–7.41 (5H, m).

4.3.3. Cleavage of MOM group of 48 to form 9. HCl–H_2O (20%, 1 ml) was added to a cooled (0 °C) solution of **48** (33 mg, 63.6 μmol) in DME (3 ml) and the mixture was stirred for 10 min and at 22 °C for 9 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by PTLC [hexane–EtOAc (7:4)] provided **9** (29 mg, 96%) as a colorless glass. HRMS Calcd for $C_{30}H_{37}NO_4$: 475.2721. Found: 475.2719. MS m/z: 475 (M^+, 3), 430 (3), 386 (8), 370 (4), 340 (9), 91 (100), 65 (5), 45 (8), 41 (4). IR ($CHCl_3$) cm^{-1}: 2120, 1684. ^1H NMR (at 50 °C) δ: 0.97 (3H, s), 1.02 (1H, ddd, J=13, 10, 5 Hz, H1), 1.31 (1H, ddd, J=13.5, 11.5, 5 Hz, H3), 1.34–1.41 (1H, m, H9), 1.44–1.56 (2H, m, including OH), 1.60–1.71 (1H, m, H3), 1.68 (1H, d, J=7 Hz, H5), 1.71–1.85 (1H, m, H2), 1.91 (1H, dd, J=2.5, 2.5 Hz, C≡CH), 2.02 (1H, ddd, J=13, 4.5, 4.5 Hz, H1), 2.14–2.32 (4H, m), 2.41 (1H, dd, J=6, 5.5 Hz, H14), 2.46–2.64 (2H, m), 3.27–3.38 (3H, m), 3.43 (1H, ddd, J=9.5, 6.5, 3.5 Hz), 3.58–3.76 (2H, m, CH_2OH), 4.10 (1H, d, J=6 Hz, H20), 4.26 (1H, dd, J=8, 7 Hz, H6), 5.13 (1H, d, J=12.5 Hz), 5.20 (1H, d, J=12.5 Hz), 5.51–5.62 (2H, m), 7.28–7.40 (5H, m).

4.4. C-ring formation from 47 and 9 (Scheme 7, Table 2)

4.4.1. Radical cyclization of 47 to form 44 and 49 (Table 2, runs a–d). The procedure for run c of Table 2 is described as a representative example among runs a–d. A benzene (3 ml) solution of **47** (9 mg, 18.6 μmol), tributyltin hydride (25 μl, 93 μmol), and azobisisobutyronitrile (0.5 mg, 3.05 μmol) was degassed by bubbling of Ar gas for 10 min at 25 °C. The solution was then refluxed with stirring for 2 h under an Ar atmosphere. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (3 ml). SiO_2 (1.0 g, well-dried prior to use) was added to this and the mixture was stirred at 25 °C for 14 h. The whole was filtered under reduced pressure and the filtered SiO_2 was rinsed with 10% MeOH–CH_2Cl_2. The solvent was evaporated off and the residue was separated by PTLC [hexane–EtOAc (11:1)] to give **44** (3 mg, 33%) and **49** (7.5 mg, 52%). The former was identical with the authentic specimen (see Section 4.2.13) by ^1H NMR and IR. **49**: Colorless glass. HRMS Calcd for $C_{41}H_{71}NO_5Sn$: 777.4349. Found: 777.4383. MS m/z: 778, 777, 776, 775, 774, 773 (M^+, 0.02, 0.11, 0.15, 0.13, 0.10, 0.10), 721, 720, 719, 718, 717, 716 (11, 27, 14, 21, 11, 11), 677, 676, 675, 674, 673, 672 (1, 2, 1, 2, 1, 1), 621, 620, 619, 618, 617, 616 (0.5, 0.9, 0.5, 1, 0.7, 1), 619, 618, 617, 616, 615, 614 (0.5, 1, 0.7, 1, 0.7, 1), 515, 514, 513, 512, 511, 510 (1, 4, 2, 3, 1, 2), 486 (8), 430 (5), 386 (21), 280 (83), 180, 179, 178, 177, 176,

175 (1, 21, 6, 19, 7, 13), 57 (100), 45 (44), 41 (27). IR ($CHCl_3$) cm^{-1}: 1675. ^1H NMR (at 50 °C) δ: 0.56 (1H, dd, J=7.5, 4 Hz, H12), 0.77 (1H, ddd, J=13, 10, 6 Hz, H1), 0.79–1.00 (10H, m), 0.89 (9H, t, J=7.5 Hz), 0.96 (3H, s, H18), 1.08 (1H, d, J=13 Hz, H17), 1.24–1.68 (16H, m), 1.38 (1H, d, J=6 Hz, H5), 1.47 (9H, s), 1.63 (1H, d, J=12 Hz, H15), 1.71 (1H, dd, J=15, 7 Hz, H7), 1.75 (1H, dd, J=14, 9.5 Hz, H11), 2.01 (1H, dd, J=14, 4 Hz, H11), 2.26 (1H, ddd, J=13, 5, 5 Hz, H1), 2.42 (1H, dd, J=6.5, 4 Hz, H14), 2.50 (1H, br d, J=15 Hz, H7), 3.12 (1H, d, J=10.5 Hz, H19), 3.37 (3H, s), 3.40 (1H, d, J=10.5 Hz, H19), 3.41–3.50 (1H, m), 3.67–3.76 (3H, m), 3.83 (1H, d, J=6.5 Hz, H20), 3.87 (1H, dd, J=7, 6 Hz, H6), 4.65 (1H, d, J=6.5 Hz), 4.68 (1H, d, J=6.5 Hz).

4.4.2. Reductive Pd-catalyzed cyclization of 47 to form 44, 50, and 51 (Table 2, run e). A benzene (2 ml) solution containing **47** (8 mg, 16.5 μmol), poly(methylhydrosiloxane) (21 μl, 0.333 mmol), tris(benzylideneacetone)dipalladium(0)-chloroform adduct (2 mg, 1.93 μmol), *N*,*N*′-bis(benzylidene)-1,2-ethylenediamine (1 mg, 4.24 μmol), and HOAc (2 μl, 35.0 μmol) was refluxed with stirring under an Ar atmosphere for 30 min. 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 followed by PTLC [hexane–EtOAc (12:1)] afforded crude **50** (2.5 mg), **44** (1.5 mg, 19%), and **51** (2 mg, 25%) in order of increasing polarity. As attempted purification of the crude **50** was unsuccessful, the crude product was treated with OsO_4 (0.5 mg, 1.97 μmol) and $NaIO_4$ (11 mg, 51.4 μmol) in THF–H_2O (5:1, 1.8 ml) at 0 °C for 10 min and at 25 °C for 14 h in order to isolate **50** without change; this was why the concomitant had vinyl group signals in its ^1H NMR spectrum. Saturated $Na_2S_2O_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [hexane–EtOAc (10:1)] gave pure **50** (1.5 mg, 19%). **50**: Colorless glass. HRMS Calcd for $C_{29}H_{45}NO_5$: 487.3295. Found: 487.3275. MS *m*/*z*: 487 (M^+, 4), 431 (6), 386 (7), 342 (5), 326 (10), 298 (10), 281 (100), 57 (99), 45 (61), 41 (29). IR ($CHCl_3$) cm^{-1}: 1674. ^1H NMR (at 50 °C) δ: 0.57 (1H, dd, J=7.5, 4 Hz, H12), 0.77 (1H, ddd, J=13, 9, 5 Hz, H1), 0.81–1.01 (3H, m), 0.96 (3H, s, H18), 1.12 (3H, s, H17), 1.24–1.70 (4H, m), 1.38 (1H, d, J=6 Hz, H5), 1.46 (9H, s), 1.67 (1H, d, J=12 Hz), 1.71 (1H, dd, J=15, 7 Hz, H7), 1.74 (1H, dd, J=14, 9.5 Hz, H11), 2.00 (1H, dd, J=14, 4 Hz, H11), 2.26 (1H, ddd, J=13, 5, 5 Hz), 2.41 (1H, dd, J=6.5, 4 Hz, H14), 2.51 (1H, br d, J=15 Hz, H7), 3.12 (1H, br d, J=11 Hz), 3.37 (3H, s), 3.41 (1H, d, J=11 Hz), 3.42–3.49 (1H, m), 3.67–3.79 (3H, m), 3.84 (1H, d, J=6.5 Hz), 3.87 (1H, dd, J=7, 6 Hz, H6), 4.65 (1H, d, J=6.5 Hz), 4.68 (1H, d, J=6.5 Hz). **51**: Colorless glass. HRMS Calcd for $C_{29}H_{45}NO_5$: 487.3295. Found: 487.3282. MS *m*/*z*: 487 (M^+, 2), 446 (2), 398 (2), 386 (9), 346 (31), 342 (18), 326 (11), 298 (13), 281 (27), 240 (7), 91 (12), 57 (100), 45 (71), 41 (38). IR ($CHCl_3$) cm^{-1}: 1673. ^1H NMR (at 50 °C) δ: 0.93 (3H, s), 0.98 (1H, ddd, J=13.5, 10, 5.5 Hz), 1.17–1.70 (4H, m), 1.47 (9H, s), 1.60 (1H, d, J=7.5 Hz), 1.79–2.04 (3H, m), 2.10–2.35 (5H, m), 2.31 (1H, br dd, J=7, 6 Hz), 3.15–3.30 (1H, br m), 3.28 (1H, br d, J=10 Hz), 3.35 (3H, s), 3.38 (1H, dt, J=10, 5 Hz), 3.52 (1H, dt, J=10, 5 Hz), 3.65 (2H, dd, J=5, 5 Hz), 4.02 (1H, d, J=6 Hz), 4.05–4.16 (1H, m), 4.62 (1H, d, J=6.5 Hz), 4.64 (1H, d, J=6.5 Hz), 4.98–5.06 (2H, m, CH=CH_2), 5.50–5.60 (2H, m, H12, H13), 5.72–5.88 (1H, m, CH=CH_2).

4.4.3. Radical cyclization of 9 to form 10, 52, and 53. A toluene (4 ml) solution of tributyltin hydride (74 μl, 0.275 mmol) was added dropwise to a refluxing solution of **9** (13 mg, 27.4 μmol) and azobisisobutyronitrile (1 mg, 6.10 μmol) in toluene (5 ml) during 1.5 h under an Ar atmosphere and then the resulting mixture was further stirred under reflux for 1.5 h. The solvent was removed in vacuo and the residue (95 mg) was dissolved in CH_2Cl_2 (5 ml). SiO_2 (1.5 g, dried in an oven prior to use) was added, and the mixture was stirred at 20 °C for 18 h. The mixture was filtered through a Celite bed and the bed was rinsed with 10% MeOH–CH_2Cl_2. The filtrate was evaporated off and the residue was purified by PTLC [hexane–EtOAc (11:2)] to provide **52** (6.5 mg, 31%), **53** (1 mg, 8%), and **10** (7.5 mg, 57%) in order of increasing polarity. **10**: Colorless glass. HRMS Calcd for $C_{30}H_{39}NO_4$: 477.2877. Found: 477.2885. MS *m*/*z*: 477 (M^+, 1), 432 (3), 388 (5), 342 (9), 298 (9), 91 (100), 65 (10), 45 (15). IR ($CHCl_3$) cm^{-1}: 1684. ^1H NMR (at 50 °C) δ: 0.90 (1H, ddd, J=13, 10, 5 Hz, H1), 0.99 (3H, s), 1.14 (1H, br d, J=10 Hz, H9), 1.29–1.85 (8H, m, including OH), 1.57 (1H, d, J=6.5 Hz, H5), 1.75 (1H, dd, J=16, 8 Hz, H7), 1.89 (1H, dd, J=13, 4.5 Hz, H13), 1.96–2.11 (2H, m, H12 and H14), 2.11 (1H, d, J=18 Hz, H15), 2.17 (1H, ddd, J=13, 5, 5 Hz, H1), ca. 2.35–2.55 (1H, m, H7), 2.36 (1H, br d, J=18 Hz, H15), 3.23 (1H, ddd, J=9.5, 6, 3.5 Hz, CH_2CH$_2$OH), 3.28 (1H, br d, J=11 Hz, H19), 3.41 (1H, ddd, J=9.5, 5, 3.5 Hz, CH_2CH$_2$OH), 3.46 (1H, d, J=11 Hz, H19), 3.67–3.80 (2H, m, CH_2OH), 3.95 (1H, d, J=6.5 Hz, H20), 4.08 (1H, dd, J=8, 6.5 Hz, H6), 4.49 (1H, ddd, J=2.5, 2, 2 Hz, H17), 4.64 (1H, ddd, J=2.5, 2, 2 Hz, H17), 5.11 (1H, d, J=13 Hz, OCH_2Ph), 5.16 (1H, br d, J=13 Hz, OCH_2Ph), 7.25–7.40 (5H, m). **52**: Colorless glass. MS *m*/*z*: 712, 711, 710, 709, 708, 707 (M^+−Bu, 2, 4, 9, 5, 7, 4), 576, 575, 574, 573, 572, 571 (1, 1, 2, 1, 2, 1), 532, 531, 530, 529, 528, 527 (1, 1, 4, 2, 3, 1), 476 (6), 432 (6), 342 (8), 280 (11), 180, 179, 178, 177, 176, 175 (1, 11, 4, 12, 4, 8), 91 (100), 65 (9), 41 (15). IR ($CHCl_3$) cm^{-1}: 1686. ^1H NMR (at 50 °C) δ: 0.56 (1H, dd, J=7.5, 4 Hz, H12), 0.71–1.03 (10H, m), 0.88 (1H, d, J=13 Hz, H17), 0.89 (9H, t, J=7.5 Hz), 0.98 (3H, s, H18), 1.10 (1H, d, J=13 Hz, H17), 1.24–1.69 (16H, m), 1.42 (1H, d, J=6 Hz, H5), 1.64 (1H, d, J=12 Hz, H15), 1.74 (1H, dd, J=15, 7 Hz, H7), 1.78 (1H, dd, J=14, 10 Hz, H11), 2.01 (1H, dd, J=14, 4 Hz, H11), 2.08 (1H, dd, J=6, 6 Hz, OH), 2.26 (1H, ddd, J=12.5, 5, 5 Hz, H1), 2.42 (1H, dd, J=6.5, 3.5 Hz, H14), 2.58 (1H, br d, J=15 Hz, H7), 3.22 (1H, d, J=11.5 Hz, H19), 3.31–3.38 (1H, m), 3.62–3.76 (3H, m), 3.68 (1H, d, J=11.5 Hz, H19), 3.83 (1H, d, J=6.5 Hz, H20), 3.96 (1H, dd, J=7, 6 Hz, H6), 5.11 (1H, d, J=13 Hz, OCH_2Ph), 5.15 (1H, d, J=13 Hz, OCH_2Ph), 7.25–7.44 (5H, m). **53**: Colorless glass. HRMS Calcd for $C_{30}H_{39}NO_4$: 477.2877. Found: 477.2868. MS *m*/*z*: 477 (M^+, 4), 432 (6), 388 (11), 342 (13), 296 (6), 280 (3), 91 (100), 65 (6), 45 (6). IR ($CHCl_3$) cm^{-1}: 1681. ^1H NMR (at 50 °C) δ: 0.92–1.05 (1H, m), 1.00 (3H, s, H18), 1.10–1.14 (1H, m, H9), 1.14–1.75 (7H, m), 1.60 (1H, d, J=7 Hz, H5), 1.79 (1H, br dd, J=6.5, 6.5 Hz, OH), 2.00–2.16 (2H, m), 2.01 (1H, dd, J=16, 8 Hz, H7), 2.11 (1H, br dd, J=7, 5 Hz, H14),

ca. 2.23–2.44 (2H, m), 2.45 (1H, br d, J=17 Hz, H15), 2.61–2.68 (1H, m, H13), 3.33 (1H, br d, J=11 Hz, H19), 3.43 (1H, ddd, J=9.5, 5, 4.5 Hz), 3.46 (1H, d, J=11 Hz, H19), 3.63 (1H, ddd, J=9.5, 4.5, 4 Hz), 3.70–3.76 (2H, m), 4.10 (1H, dd, J=8, 7 Hz, H6), 4.14 (1H, d, J=7 Hz, H20), 4.66–4.70 (1H, m, C=CH_2), 4.74–4.78 (1H, m, C=CH_2), 5.11 (1H, d, J=12.5 Hz), 5.16 (1H, d, J=12.5 Hz), 7.26–7.40 (5H, m).

4.4.4. Lemieux oxidation of 53 to form 54. $NaIO_4$ (9 mg, 42.1 μmol) and OsO_4 (0.5 mg, 1.97 μmol) were successively added to a solution of **53** (1 mg, 2.10 μmol) in THF (1.5 ml) and H_2O (0.3 ml) at 0 °C and the mixture was stirred for 10 min and then at 21 °C for 14 h. Saturated $Na_3S_2O_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (3:2)] provided **54** (1 mg, quant.) as a colorless syrup. HRMS Calcd for $C_{29}H_{37}NO_5$: 479.2670. Found: 479.2672. MS m/z: 479 (M^+, 0.5), 434 (4), 390 (11), 344 (13), 298 (4), 282 (2), 91 (100), 65 (5), 45 (6). IR ($CHCl_3$) cm^{-1}: 1730, 1682. ^1H NMR (at 50 °C) δ: 0.99–1.08 (1H, m), 1.03 (3H, s), 1.19–1.80 (10H, m, including OH), 1.65 (1H, d, J=7 Hz, H5), 1.96 (1H, br d, J=19 Hz, CH_2CO), 2.08–2.18 (1H, m), 2.11 (1H, dd, J=16, 8 Hz, H7), 2.31 (1H, d, J=19 Hz, CH_2CO), 2.35–2.62 (3H, m), 3.35 (1H, d, J=11 Hz, H19), 3.45 (1H, ddd, J=10, 5, 5 Hz), 3.48 (1H, d, J=11 Hz, H19), 3.56 (1H, ddd, J=10, 4, 4 Hz), 3.67–3.79 (2H, m), 4.15 (1H, dd, J=8, 7 Hz, H6), 4.25 (1H, d, J=6 Hz, H20), 5.11 (1H, d, J=12.5 Hz), 5.18 (1H, br d, J=12.5 Hz), 7.28–7.39 (5H, m).

4.4.5. Preparation of 55 from 9. $(TMS)_2NLi$ (1 M in THF, 0.22 ml, 0.22 mmol) was added to a cooled (−78 °C) solution of **9** (7 mg, 14.7 μmol) in THF (2 ml) and the mixture was stirred under an Ar atmosphere for 1.5 h. A THF (0.5 ml) solution of TMSCl (19 μl, 0.150 mmol) was added dropwise to it, and the resulting mixture was stirred at −78 to 12 °C for 15.5 h. Saturated NH_4Cl–H_2O and saturated $NaHCO_3$–H_2O were successively added and the whole was extracted with CH_2Cl_2. Usual work-up gave a residue (12 mg) and this was dissolved in THF (3 ml). Aqueous HCl (2.5%, 0.25 ml) was added to this at 0 °C and the mixture was stirred for 10 min. Quenching with saturated $NaHCO_3$–H_2O, extraction with CH_2Cl_2, and usual work-up followed by PTLC [hexane–EtOAc (5:2)] furnished **55** (6.5 mg, 81%) along with recovered **9** (1 mg, 14%). **55**: Colorless glass. HRMS Calcd for $C_{33}H_{45}NO_4Si$: 547.3115. Found: 547.3118. MS m/z: 547 (M^+, 8), 502 (1), 486 (2), 458 (5), 442 (5), 412 (7), 368 (3), 352 (4), 294 (4), 91 (100), 73 (19). IR ($CHCl_3$) cm^{-1}: 2170, 1683. ^1H NMR (at 50 °C) δ: 0.13 (9H, s, $SiMe_3$), 0.97 (3H, s), 1.04 (1H, ddd, J=13, 10, 5.5 Hz, H1), 1.31 (1H, ddd, J=13.5, 11, 4.5 Hz, H3), ca. 1.33–1.40 (1H, m), 1.43–1.56 (3H, m, H3 and CH_2C≡CSiMe_3), 1.64 (1H, ddd, J=13.5, 5, 5 Hz, H3), 1.66 (1H, d, J=7 Hz, H5), 1.70–1.85 (1H, m), 1.04 (1H, br s, OH), 2.02 (1H, ddd, J=13, 4.5, 4.5 Hz, H1), 2.10–2.31 (2H, m), 2.36 (1H, dd, J=6, 6 Hz, H14), ca. 2.55–2.74 (1H, m), 2.59 (1H, dd, J=16, 9 Hz, H7), 3.26–3.38 (3H, m), 3.42 (1H, ddd, J=9.5, 6.5, 3.5 Hz), 3.58–3.76 (2H, m), 4.09 (1H, d, J=6 Hz, H20), 4.25 (1H, dd, J=9, 7 Hz, H6), 5.13 (1H, d, J=12 Hz), 5.19 (1H, br d, J=12 Hz), 5.49–5.58 (1H, m, H13), 5.58 (1H, br dd, J=12, 2.5 Hz, H12), 7.27–7.40 (5H, m).

4.5. Completion of the total synthesis of (±)-nominine (Scheme 9)

4.5.1. Mesylation of 10 to form 56. MsCl (10 μl, 129 μmol) was added to a solution of **10** (7.5 mg, 15.8 μmol) and Et_3N (88 μl, 0.633 mmol) in CH_2Cl_2 (2 ml) at −20 °C under an Ar atmosphere and the mixture was stirred for 30 min. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. The organic layer was successively washed with saturated $CuSO_4$–H_2O, saturated $NaHCO_3$–H_2O, and water and then treated as usual. Purification was carried out by PTLC [hexane–EtOAc (2:1)] to provide **56** (8.5 mg, 97%) as a colorless glass. HRMS Calcd for $C_{31}H_{41}NO_6S$: 555.2652. Found: 555.2668. MS m/z: 555 (M^+, 0.3), 432 (11), 420 (6), 388 (14), 296 (7), 123 (7), 91 (100), 79 (8). IR ($CHCl_3$) cm^{-1}: 1684. ^1H NMR (at 50 δ) δ: 0.89 (1H, ddd, J=13, 10, 5.5 Hz, H1), 0.99 (3H, s), 1.14 (1H, d, J=10.5 Hz, H9), 1.30–1.78 (7H, m), 1.57 (1H, d, J=6.5 Hz, H5), 1.75 (1H, dd, J=16, 8 Hz, H7), 1.87 (1H, dd, J=13, 4.5 Hz, H13), 1.96–2.06 (1H, m), 2.05–2.20 (2H, m), 2.11 (1H, d, J=18 Hz, H15), ca. 2.35–2.55 (1H, m, H7), 2.36 (1H, br d, J=18 Hz, H15), 3.00 (3H, s, SO_2CH_3), 3.28 (1H, br d, J=11 Hz, H19), 3.28 (1H, ddd, J=11.5, 5.5, 4.5 Hz), 3.43 (1H, d, J=11 Hz, H19), 3.55 (1H, ddd, J=11.5, 5, 4 Hz), 3.95 (1H, d, J=7 Hz, H20), 4.08 (1H, dd, J=8, 6.5 Hz, H6), 4.30–4.36 (2H, m, CH_2OMs), 4.49 (1H, ddd, J=2, 2, 2 Hz, H17), 4.65 (1H, ddd, J=2, 2, 2 Hz, H17), 5.11 (1H, d, J=12.5 Hz), 5.17 (1H, d, J=12.5 Hz), 7.25–7.41 (5H, m).

4.5.2. Preparation of bromide 57 from mesylate 56. Anhydrous LiBr (19 mg, 0.218 mmol) was added to a solution of **56** (8 mg, 14.4 μmol) in acetone (3 ml) and the mixture was stirred under reflux 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 subsequent separation by PTLC [hexane–EtOAc (5:1)] provided **57** (7 mg, 90%) as a colorless glass. HRMS Calcd for $C_{30}H_{38}BrNO_3$: 541.2014 and 539.2034. Found: 541.2002 and 539.2039. MS m/z: 541, 539 (M^+, 0.7, 0.7), 432 (14), 406, 404 (5, 5), 388 (15), 296 (8), 109, 107 (4, 4), 91 (100), 65 (6). IR ($CHCl_3$) cm^{-1}: 1683. ^1H NMR (at 50 °C) δ: 0.87 (1H, ddd, J=13, 9.5, 5 Hz, H1), 0.99 (3H, s), 1.13 (1H, br d, J=10.5 Hz, H9), 1.28–1.61 (4H, m), 1.57 (1H, d, J=6.5 Hz, H5), 1.63–1.82 (3H, m), 1.75 (1H, dd, J=16, 8.5 Hz, H7), 1.91 (1H, dd, J=13, 4.5 Hz, H13), 1.94–2.04 (1H, m, H14), 2.05–2.11 (1H, m, H12), 2.10 (1H, d, J=18 Hz, H15), 2.21 (1H, ddd, J=13.5, 4.5, 4.5 Hz, H1), ca. 2.35–2.54 (1H, m, H7), 2.36 (1H, br d, J=18 Hz, H15), 3.28 (1H, br d, J=10.5 Hz, H19), 3.38–3.50 (4H, m, H19 and CH_2CH_2Br), 3.56–3.68 (1H, m, CH_2CH_2Br), 3.94 (1H, d, J=7 Hz, H20), 4.08 (1H, dd, J=8.5, 6.5 Hz, H6), 4.49 (1H, ddd, J=2, 2, 2 Hz, H17), 4.64 (1H, ddd, J=2, 2, 2 Hz, H17), 5.11 (1H, d, J=12.5 Hz), 5.17 (1H, br d, J=12.5 Hz), 7.27–7.41 (5H, m).

4.5.3. Oxidation of 57 to form 58, 59, and 60. To a slurry of SeO_2 (6 mg, 54.1 μmol) in CH_2Cl_2 (1.5 ml) was added 70% t-BuOOH/H_2O (28 μl, 0.203 mmol) and the mixture was stirred at 0 °C for 10 min and at 22 °C for 20 min. The mixture was allowed to cool in an ice bath and a CH_2Cl_2 (2.5 ml) solution of **57** (7 mg, 13.0 μmol) was added to this. After the mixture had been stirred at 0–21 °C for 16 h, saturated

$Na_2S_2O_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by PTLC [hexane–EtOAc (5:2)] afforded **58** (5.5 mg, 77%), **60** (<1 mg, trace), and crude **59** (1.5 mg) in order of increasing polarity. The crude **59** was further purified by PTLC (0.5% MeOH–CH_2Cl_2) to give **59** (1 mg, 14%). **58**: Colorless glass. MS *m/z*: 446 ($M^+-CH_2CH_2Br$, 7), 420, 418 (3, 3), 402 (14), 310 (8), 109, 107 (6, 5), 91 (100), 65 (7). IR ($CHCl_3$) cm^{-1}: 1690, 1628. ^1H NMR (at 50 °C) δ: 0.95 (1H, ddd, *J*=13, 10, 5 Hz, H1), 1.00 (3H, s), 1.20–1.61 (5H, m), 1.57 (1H, d, *J*=7 Hz, H5), 1.65–1.86 (2H, m), 1.98 (1H, ddd, *J*=13.5, 2.5, 2.5 Hz, H11), 2.15 (1H, dd, *J*=13, 4.5 Hz, H13), 2.20–2.44 (2H, m), 2.25 (1H, ddd, *J*=13, 4.5, 4.5 Hz, H1), 2.55–2.60 (1H, m, H12), 2.68 (1H, dd, *J*=17, 8.5 Hz, H7), 3.32 (1H, br d, *J*=10.5 Hz, H19), 3.42 (1H, d, *J*=10.5 Hz, H19), 3.43–3.53 (3H, m), 3.57–3.67 (1H, m), 4.05 (1H, d, *J*=7 Hz, H20), 4.17 (1H, dd, *J*=8.5, 7 Hz, H6), 5.04 (1H, d, *J*=2 Hz, H17), 5.13 (1H, d, *J*=13 Hz), 5.17 (1H, d, *J*=13 Hz), 5.85 (1H, d, *J*=2 Hz, H17), 7.26–7.40 (5H, m). **59**: Colorless glass. HRMS Calcd for $C_{30}H_{38}BrNO_4$: 557.1963 and 555.1983. Found: 557.1988 and 555.2004. MS *m/z*: 557, 555 (M^+, 0.4, 0.7), 448 (11), 422, 420 (4, 4), 404 (13), 312 (6), 296 (4), 109, 107 (5, 5), 91 (100), 65 (7). IR ($CHCl_3$) cm^{-1}: 1681. ^1H NMR (at 50 °C) δ: 0.86–0.95 (1H, m), 0.99 (3H, s), 1.10 (1H, br d, *J*=10.5 Hz, H9), 1.28–1.82 (7H, m, including OH), 1.60 (1H, d, *J*=6.5 Hz, H5), 1.78 (1H, ddd, *J*=13.5, 3, 3 Hz, H11), 1.91 (1H, dd, *J*=16, 9 Hz, H7), 1.94 (1H, dd, *J*=13, 4.5 Hz, H13), 2.15–2.34 (3H, m), 2.78 (1H, br d, *J*=16 Hz, H7), 3.31 (1H, br d, *J*=11 Hz, H19), 3.42–3.50 (2H, m), 3.43 (1H, d, *J*=11 Hz, H19), 3.52–3.74 (2H, m), 3.95 (1H, d, *J*=7 Hz, H20), 3.98 (1H, br s, H15), 4.14 (1H, dd, *J*=9, 6.5 Hz, H6), 4.91 (1H, dd, *J*=1.5, 1 Hz, H17), 4.93 (1H, dd, *J*=1.5, 1 Hz, H17), 5.12 (1H, d, *J*=12.5 Hz), 5.18 (1H, d, *J*=12.5 Hz), 7.26–7.40 (5H, m). **60**: Colorless glass. HRMS Calcd for $C_{30}H_{36}BrNO_4$: 555.1807 and 553.1827. Found: 555.1780 and 553.1823. MS *m/z*: 555, 553 (M^+ 0.4, 0.4), 446 (12), 420, 418 (3, 3), 402 (14), 310 (5), 109, 107 (4, 4), 91 (100), 65 (5). ^1H NMR (at 50 °C) only selected signals were given δ: 1.02 (3H, s), 1.65 (1H, d, *J*=6.5 Hz, H5), 2.36 (1H, dd, *J*=16, 8.5 Hz, H7), 3.04–3.09 (1H, m), 3.33 (1H, d, *J*=10.5 Hz, H19), 3.37–3.50 (4H, m), 3.60–3.72 (1H, m), 4.04 (1H, d, *J*=6.5 Hz, H20), 4.20 (1H, dd, *J*=8.5, 6.5 Hz, H6), 5.15 (2H, s), 6.77 (1H, s, H15), 7.24–7.40 (5H, m), 9.41 (1H, s, H17).

4.5.4. Oxidation of 59 to form the enone 58. MnO_2 (12 mg, 0.138 mmol) was added to a solution of **59** (2 mg, 3.60 μmol) in CH_2Cl_2 (2 ml) and the mixture was stirred at 20 °C for 15 h. The whole was filtered through a Celite bed and the Celite was washed with CH_2Cl_2. The solvent was evaporated off and the residue was purified by PTLC [hexane–EtOAc (3:1)] to give a colorless glass (2 mg, quant.), whose ^1H NMR spectrum was identical with that of the enone **58**.

4.5.5. Reduction of 58 to form β-allyl alcohol 61. $NaBH_4$ (3 mg, 78.9 μmol) was added to a solution of **58** (5.5 mg, 9.93 μmol) and $CeCl_3\cdot 7H_2O$ (31 mg, 83.2 μmol) in MeOH (2.5 ml) at 0 °C, and the mixture was stirred for 20 min. The reaction was quenched by successive addition of saturated NH_4Cl–H_2O and saturated $NaHCO_3$–H_2O, and the mixture was extracted with CH_2Cl_2. Usual work-up followed by separation by PTLC [hexane–EtOAc (2:1)] afforded **61** (5.5 mg, quant.) as a colorless glass. HRMS Calcd for $C_{30}H_{38}BrNO_4$: 557.1963 and 555.1983. Found: 557.1971 and 555.1969. MS *m/z*: 557, 555 (M^+, 0.5, 0.6), 448 (20), 422, 420 (5, 5), 404 (16), 312 (9), 296 (4), 109, 107 (3, 4), 91 (100), 65 (2). IR ($CHCl_3$) cm^{-1}: 1682. ^1H NMR (at 50 °C) δ: 0.88 (1H, ddd, *J*=13, 10, 5 Hz, H1), 0.99 (3H, s), 1.20–1.55 (5H, m, including OH), 1.58 (1H, d, *J*=6.5 Hz, H5), 1.64–1.83 (4H, m), 1.92 (1H, dd, *J*=13.5, 4.5 Hz, H13), 1.93–2.10 (2H, m), 2.14–2.20 (1H, m, H12), 2.19 (1H, ddd, *J*=13, 4.5, 4.5 Hz, H1), 2.66 (1H, dd, *J*=16, 8.5 Hz, H7), 3.30 (1H, br d, *J*=10.5 Hz, H19), 3.40–3.49 (3H, m), 3.44 (1H, d, *J*=10.5 Hz, H19), 3.53–3.65 (1H, m), 3.97–4.04 (1H, m, H15), 4.01 (1H, d, *J*=6.5 Hz, H20), 4.20 (1H, dd, *J*=8.5, 6.5 Hz, H6), 4.91 (1H, br s, H17), 4.99 (1H, br s, H17), 5.15 (2H, s), 7.28–7.38 (5H, m).

4.5.6. Acetylation of 59 and 61 to form 62 and 63, respectively. The procedure for the preparation of **63** from **61** is described as a representative example. A solution of **61** (5 mg, 8.99 μmol), Ac_2O (0.2 ml), and pyridine (0.3 ml) in CH_2Cl_2 (1.5 ml) was stirred at 21 °C for 24 h. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [hexane–EtOAc (3:1)] gave **63** (5 mg, 93%) as a colorless glass. HRMS Calcd for $C_{32}H_{40}BrNO_5$: 599.2068 and 597.2088. Found: 599.2075 and 597.2061. MS (*m/z*): 599, 597 (M^+, 0.5, 0.5), 490 (10), 464, 462 (4, 3), 446 (10), 404 (2), 354 (4), 296 (9), 91 (100), 65 (7), 43 (26). IR ($CHCl_3$) cm^{-1}: 1726, 1683. ^1H NMR of two rotamers (ca. 4:1) at 50 °C δ: (major rotamer) 0.84–0.96 (1H, m), 0.99 (3H, s), 1.16–1.60 (6H, m), 1.59 (1H, d, *J*=6.5 Hz, H5), 1.63–1.83 (3H, m), 1.94 (1H, dd, *J*=13, 4 Hz, H13), 1.96–2.34 (4H, m), 2.09 (3H, s, $OCOCH_3$), 3.31 (1H, br d, *J*=11 Hz, H19), 3.42–3.50 (3H, m), 3.43 (1H, d, *J*=11 Hz, H19), 3.55–3.65 (1H, m), 3.99 (1H, d, *J*=7 Hz, H20), 4.06–4.17 (1H, m), 4.80 (1H, br s, H17), 4.87 (1H, br s, H17), 5.10 (1H, d, *J*=12.5 Hz), 5.16 (1H, d, *J*=12.5 Hz), 5.49 (1H, dd, *J*=2, 2 Hz, H15), 7.25–7.40 (5H, m); (minor rotamer) 3.94–3.98 (1H, m), 4.88 (1H, br s, H17), 4.90 (1H, br s, H17), 5.08 (1H, d, *J*=12.5 Hz), 5.19 (1H, d, *J*=12.5 Hz), 5.45 (1H, br s, H15). In the same manner, **59** (1 mg, 1.80 μmol) was acetylated to yield **62** (1 mg, 93%) as a colorless glass after separation by PTLC [hexane–EtOAc (3:1)]. HRMS Calcd for $C_{32}H_{40}BrNO_5$: 599.2068 and 597.2088. Found: 599.2065 and 597.2113. MS (*m/z*): 599, 597 (M^+, 0.6, 0.6), 540, 538 (0.2, 0.2), 490 (15), 464, 462 (5, 4), 446 (13), 354 (6), 296 (11), 91 (100), 43 (17). IR ($CHCl_3$) cm^{-1}: 1716, 1682. ^1H NMR of two rotamers (ca. 7:1) at 50 °C δ: (major rotamer) 0.83–0.95 (1H, m), 0.99 (3H, s), 1.16–2.06 (6H, m), 1.19 (1H, br d, *J*=10.5 Hz, H9), 1.48 (3H, s, $OCOCH_3$), 1.60 (1H, d, *J*=6.5 Hz, H5), 1.77 (1H, ddd, *J*=13.5, 3, 3 Hz, H11), 1.83 (1H, dd, *J*=16, 8.5 Hz, H7), 1.95 (1H, dd, *J*=13, 4.5 Hz, H13), 2.14–2.20 (1H, m, H12), 2.21 (1H, ddd, *J*=13, 4.5, 4.5 Hz, H1), 2.30 (1H, br dd, *J*=9, 7 Hz, H14), ca. 2.38–2.58 (1H, m), 3.31 (1H, br d, *J*=11 Hz, H19), 3.42–3.50 (3H, m), 3.43 (1H, d, *J*=11 Hz, H19), 3.58–3.70 (1H, m), 3.97 (1H, d, *J*=7 Hz, H20), 4.10 (1H, dd, *J*=8.5, 6.5 Hz, H6), 4.88 (1H, br s, H17), 4.91 (1H, br s, H17), 5.08 (1H, d, *J*=12.5 Hz), 5.19 (1H, d, *J*=12.5 Hz), 5.44 (1H, br s, H15), 7.24–7.39 (5H, m); (minor rotamer) 4.13–4.19 (1H, m, H6), 4.99 (1H, br s, H17), 5.02

(1H, br s, H17), 5.09 (1H, d, J=12.5 Hz), 5.17 (1H, d, J=12.5 Hz), 5.64 (1H, br s, H15). NOE (ca. 2.1%) was observed at δ=7.24–7.39 on irradiation at δ=1.48 (3H, s).

4.5.7. Reductive deprotection of 63 to form 64. A slurry of **63** (5 mg, 8.36 μmol), Zn powder (110 mg, 1.68 mmol), and NH_4Cl (5 mg, 93.5 μmol) in *i*-PrOH–H_2O (14:1, 3.5 ml) was refluxed with stirring for 5 h. After the mixture had been cooled, saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [hexane–EtOAc (5:2)] provided **64** (4 mg, 97%) as a colorless glass. HRMS Calcd for $C_{30}H_{37}NO_5$: 491.2670. Found: 491.2657. MS (*m*/*z*): 491 (M^+, 6), 356 (37), 312 (5), 239 (5), 91 (100), 65 (8), 43 (26). IR ($CHCl_3$) cm^{-1}: 1725, 1682. ^1H NMR of two rotamers (ca. 4:1) at 50 °C δ: (major rotamer) 0.90–1.05 (1H, m), 1.00 (3H, s), 1.17–1.63 (8H, m, including OH), 1.59 (1H, d, J=6.5 Hz, H5), 1.67–1.85 (3H, m), 191–2.29 (4H, m), 2.10 (3H, s), 3.28 (1H, br d, J=11 Hz, H19), 3.46 (1H, d, J=11 Hz, H19), 4.13 (1H, dd, J=8.5, 6.5 Hz, H6), 4.49 (1H, d, J=7.5 Hz, H20), 4.77 (1H, br s, H17), 4.86 (1H, br s, H17), 5.08 (1H, d, J=12.5 Hz), 5.16 (1H, d, J=12.5 Hz), 5.51 (1H, br s, H15), 7.26–7.40 (5H, m); (minor rotamer) 4.06–4.13 (1H, m, H6), 4.44–4.50 (1H, m, H20), 4.87 (1H, br s, H17), 4.91 (1H, br s, H17), 5.05 (1H, d, J=12.5 Hz), 5.20 (1H, d, J=12.5 Hz), 5.44 (1H, br s, H15).

4.5.8. Cyclization of 64 to form *O*-acetylnominine (65). $Pd(OAc)_2$ (1 mg, 4.45 μmol) and Et_3N/CH_2Cl_2 (5% v/v, 13 μl, 4.67 μmol) were successively added to a solution of **64** (4.5 mg, 9.16 μmol) and Et_3SiH (0.22 ml, 1.38 mmol) in CH_2Cl_2 (0.2 ml) under an Ar atmosphere and the mixture was stirred at 23 °C for 3 h. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up gave a residue (37 mg, containing Et_3SiH polymer). The residue was dissolved in CH_2Cl_2 (2.5 ml) and to this were added pyridine (56 μl, 0.693 mmol) and $SOCl_2$ (20 μl, 0.274 mmol) in this order at 0 °C under an Ar atmosphere. After the mixture had been stirred at the temperature for 30 min and at 22 °C for 48 h, saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by Al_2O_3 column chromatography [20 g, benzene–DME (2:1)] afforded **65** (2.5 mg, 80%) as colorless prisms, mp: 153–155 °C (CH_2Cl_2–hexane). HRMS Calcd for $C_{22}H_{29}NO_2$: 339.2197. Found: 339.2183. MS (*m*/*z*): 339 (M^+, 100), 324 (5), 311 (4), 296 (14), 280 (17), 160 (12), 146 (32), 91 (13), 79 (14), 55 (15), 43 (62), 41 (24). IR ($CHCl_3$) cm^{-1}: 1728, 1714. ^1H NMR δ: 0.97 (3H, s, H18), 1.12 (1H, ddd, J=13, 2.5, 2.5 Hz, H13), 1.19–1.33 (2H, m), 1.42–1.50 (1H, m), 1.44 (1H, s, H5), 1.54–1.99 (7H, m), 1.66 (1H, dd, J=13, 3 Hz, H7), 1.71 (1H, dd, J=13, 3 Hz, H7), 1.94 (1H, dd, J=14, 4.5 Hz, H11), 2.07 (3H, s), 2.16–2.21 (1H, m, H12), 2.40 (1H, d, J=12 Hz, H19), 2.54 (1H, d, J=12 Hz, H19), 2.54 (1H, br s, H20), 3.20–3.24 (1H, m, H6), 4.93 (1H, s, H17), 4.97 (1H, s, H17), 5.44 (1H, s, H15). ^{13}C NMR δ: 19.6 (CH_2, C2), 21.3 (CH_3, CO*C*H3), 26.4 (CH_2, C11), 26.9 (CH_2, C1), 28.7 (CH_3, C18), 32.6 (CH_2, C7), 33.2 (CH_2, C13), 33.7 (CH, C12), 34.0 (CH_2, C3), 37.8 (C, C4), 43.4 (CH, C9 or C14), 44.1 (CH, C14 or C9), 44.8 (C, C10), 49.5 (C, C8), 60.9 (CH, C5), 62.4 (CH_2, C19), 65.0 (CH, C6), 72.8 (CH, C15), 74.6 (CH, C20), 110.6 (CH_2, C17), 144.6 (C, 16), 170.1 (C, *C*OCH_3).

4.5.9. (±)-Nominine (1). A solution of **65** (3 mg, 8.85 μmol) in 2% w/v K_2CO_3/MeOH (2 ml) was refluxed with stirring for 30 min under an Ar atmosphere. After the mixture had been cooled, water was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by Al_2O_3 column chromatography (20 g, 2% MeOH–CH_2Cl_2) provided (±)-nominine (**1**, 2.5 mg, 95%), colorless prisms, mp: 233–236 °C (MeOH–acetone) [cf. natural nominine,[4] mp: 255–258 °C (MeOH–acetone)]. HRMS Calcd for $C_{20}H_{27}NO$: 297.2091. Found: 297.2087. MS (*m*/*z*): 297 (M^+, 100), 282 (6), 280 (5), 269 (6), 160 (9), 148 (11), 146 (30), 105 (10), 91 (18), 79 (10), 77 (12), 55 (12), 53 (10), 41 (22). IR ($CHCl_3$) cm^{-1}: 2925 (s), 2870 (w), 1648 (w), 1632 (w), 1616 (w), 1578 (w), 1558 (w), 1538 (w), 1520 (w), 1487 (w), 1455 (m), 1437 (w), 1373 (w), 1317 (w), 1130 (w), 1112 (m), 1028 (w), 1002 (m), 980 (w), 938 (w), 902 (w), 882 (w), 846 (w). ^1H NMR δ: 0.98 (3H, s, H18), 1.11 (1H, ddd, J=13, 2.5, 2.5 Hz, H13), 1.19–1.34 (2H, m, H1 and H3), 1.38–1.50 (1H, m, H3), 1.44 (1H, s, H5), 1.56 (1H, dddd, J=14, 10, 3, 1.5 Hz, H11), 1.62–1.90 (7H, m, including OH, H1, H2×2, H9, H13, and H14), 1.68 (1H, dd, J=13, 3 Hz, H7), 1.94 (1H, dd, J=14, 4.5 Hz, H11), 2.05 (1H, dd, J=13, 2.5 Hz, H7), 2.17–2.22 (1H, m, H12), 2.39 (1H, d, J=12 Hz, H19), 2.52 (1H, br s, H20), 2.54 (1H, d, J=12 Hz, H19), 3.24–3.28 (1H, m, H6), 4.01 (1H, br s, H15), 4.94 (1H, dd, J=1.5, 1 Hz, H17), 4.97 (1H, dd, J=1.5, 1 Hz, H17). ^{13}C NMR δ: 19.7 (CH_2, C2), 26.7 (CH_2, C11), 27.0 (CH_2, C1), 28.8 (CH_3, C18), 32.7 (CH_2, C7), 33.1 (CH_2, C13), 33.7 (CH, C12), 34.0 (CH_2, C3), 37.8 (C, C4), 43.5 (CH, C9 or C14), 43.9 (CH, C14 or C9), 45.5 (C, C10), 49.6 (C, C8), 60.9 (CH, C5), 62.5 (CH_2, C19), 65.3 (CH, C6), 71.7 (CH, C15), 74.7 (CH, C20), 108.3 (CH_2, C17), 156.5 (C, 16).

4.5.10. Single-crystal X-ray analysis of (±)-nominine (1). Crystal data: $C_{20}H_{27}NO$, M=297.44, monoclinic, $P2_1/n$, a=7.059(1) Å, b=11.614(1) Å, c=18.959(1) Å, β=94.44(1)°, V=1549.7(2) $Å^3$, Z=4, ρ_c=1.275 g/cm^3, $F(000)$=648, λ=1.54178 Å, T=296(1) K, μ(Cu Kα)=5.92 cm^{-1}, crystal size=0.20×0.25×0.30 mm^3, 3336 reflections (2922 independent, R_{int}=0.012) were collected on a Rigaku AFC7R diffractometer. The structure was solved by direct methods (SHELXS-97)[27] and 203 variable parameters were refined using the least-squares method on F^2. The maximum electron density residue: 0.36e^-/$Å^3$, R_1[for $I>2\sigma(I)$]=0.048 and wR=0.206 (all data) with $R_1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$ and $wR=[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{0.5}$. Crystallographic data for (±)-nominine (**1**) reported in this paper have been deposited at the Cambridge Crystallographic Data Centre, under publication number CCDC 244252. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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