18
Daphniphyllum alkaloids: Structures, Biogenesis, and Activities

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18.1
Introduction

Daphniphyllum alkaloids are a structurally diverse group of natural products, which are elaborated by the oriental tree ''Yuzuriha'' (*Daphniphyllum macropodum*; Daphniphyllaceae), dioecious evergreen trees, and shrubs native to central and southern Japan. *Daphniphyllum* comes from the Greek and refers to ''Daphne'' and ''leaf.'' ''Yuzurisha'' means that the old leaf is replaced by a new leaf in the succeeding season. That is, to take over or take turns, with the old leaf dropping after the new leaf emerges, thus there is no interruption of the foliage. ''Yuzurisha'' in Japan is used as an ornamental plant for the New Year to celebrate the good relationships of the old and new generations. There are three *Daphniphyllum* species in Japan, *D. macropodum*, *D. teijsmanni*, and *D. humile*. Several other species, such as *D. calycinum*, *D. gracile*, *D. longeracemosum*, *D. yunnanense*, *D. longistylum*, *D. paxianum*, *D. oldhami*, and *D. glaucescens* are widely distributed in New Guinea, China, and Taiwan.

Since Hirata *et al*. began research into daphniphyllum alkaloids in 1966, a number of new alkaloids have been discovered. As a result, the number of known daphniphyllum alkaloids has grown markedly in recent years to a present count of 118 (compounds **1**–**118**). These alkaloids, isolated chiefly by Yamamura and Hirata *et al*. are classified into six different types of backbone skeletons [1–3]. These unusual ring systems have attracted great interest as challenging targets for total synthesis or biosynthetic studies. This chapter covers the reports on daphniphyllum alkaloids that have been published between 1966 and 2006. Since the structures and stereochemistry of these alkaloids are quite complex and the representation of the structure formula has not been unified, all the natural daphniphyllum alkaloids (**1**–**118**) are listed. Classification of the alkaloids basically follows that of the previous reviews [1,2], but sections on the newly found skeletons have been added.

It was of substantial interest when Heathcock and coworkers proposed a biogenetic pathway for daphniphyllum alkaloids [4,5] and demonstrated a biomimetic total synthesis of several of them. This review describes the recent studies on alkaloids isolated from the genus *Daphniphyllum*, the proposed biogenetic pathway, syntheses of daphniphyllum alkaloids based on these biogenetic proposals, and their activities.

Modern Alkaloids: Structure, Isolation, Synthesis and Biology. Edited by E. Fattorusso and O. Taglialatela-Scafati

ISBN: 978-3-527-31521-5

Section 18.2 surveys all the daphniphyllum alkaloids isolated so far, including our recent work, while Sections 18.3–18.5 mainly deal with biogenetic pathways, total syntheses, the biomimetic synthesis, and the activities of these compounds.

18.2
Structures of Daphniphyllum alkaloids

18.2.1
Daphnane-type Alkaloids

In 1909, Yagi isolated daphnimacrine, the parent compound of the C_{30}-type Daphniphyllum alklalaoids [6]. The structure elucidation of daphniphylline (**1**), one of the major C_{30}-type daphniphyllum alkaloids, was carried out by X-ray crystallographic analysis of the hydrobromide [7–10]. Yamamura and Hirata also reported the structures of codaphniphylline (**2**) [10–12] and daphniphyllidine (**3**) [13], both of which are closely related to daphniphylline. Furthermore, they isolated methyl homodaphniphyllate (**7**), and the structure lacking the C_8 unit of daphniphylline was elucidated by chemical correlations from daphniphylline [19,20,37]. On the other hand, Nakano isolated daphnimacropine (**4**) [14], daphmacrine (**5**) [15–17], and daphmacropodine (**6**) [15,18], the structures of which were elucidated by X-ray crystallographic analysis of their methiodides. The structures of these alkaloids are listed in Figure 18.1.

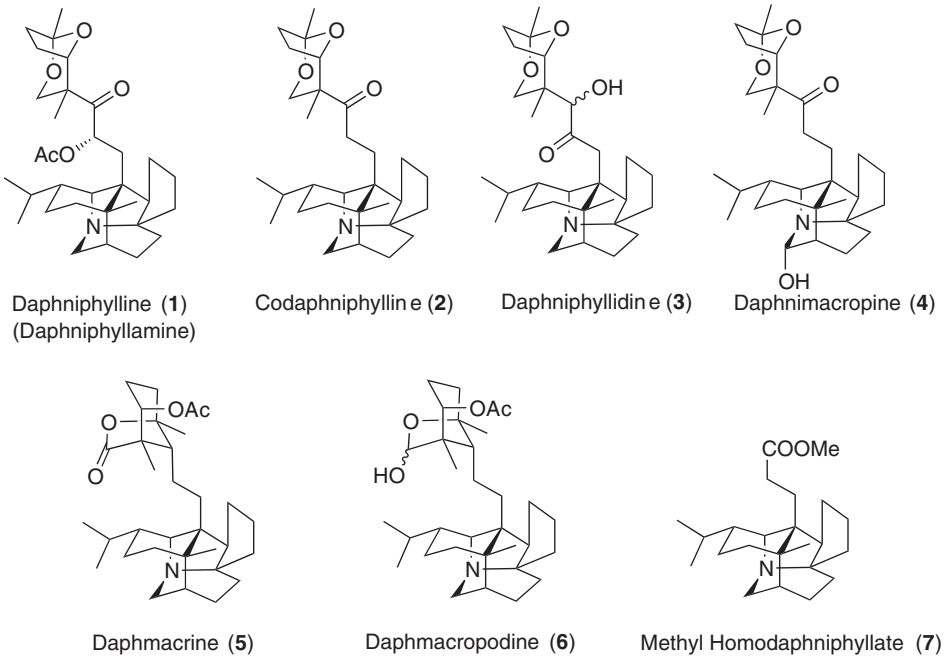


Fig. 18.1 Daphnane-type alkaloids.

18.2.2
Secodaphnane-type Alkaloids

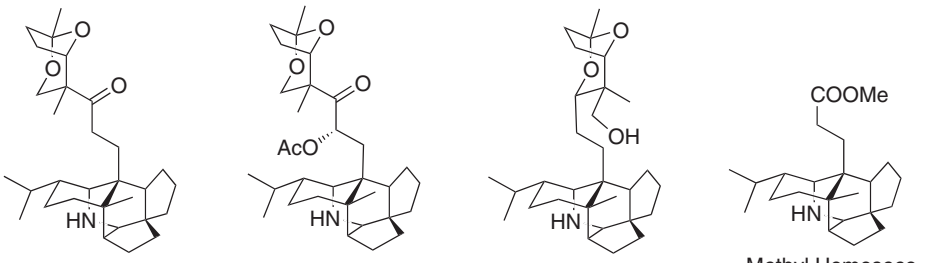
Two secodaphnane-type alkaloids (Figure 18.2), secodaphniphylline (**8**) [19,21,22] and methyl homosecodaphniphyllate (**11**) [19,21,22], were isolated by Yamamura and Hirata, and their structures were elucidated by X-ray analysis of methyl *N*-bromoacetyl homosecodaphniphyllate and chemical correlations between **8** and **11**. The structures of the two related alkaloids, daphniteijsmine (**9**) [23] and daphniteijsmanine (**10**) [24], were elucidated by spectroscopic analysis coupled with an exhaustive comparison of the NMR data of secodaphniphylline and methyl homosecodaphniphyllate (**11**).

18.2.3
Yuzurimine-type Alkaloids

In 1966, Hirata *et al.* isolated yuzurimine (**12**) as one of the major alkaloids from *D. macropodum* and reported the crystal structure of yuzurimine hydrobromide [25]. They also isolated the two related alkaloids yuzurimines A (**13**) and B (**14**), whose structures were elucidated through spectroscopic data and chemical evidence in 1972. At almost the same time, Nakano *et al.* isolated macrodaphniphyllamine (**16**), macrodaphniphyllidine (**17**), and macrodaphnine (**18**) [15,29], whose structures were identical with deacetyl yuzurimine A, acetyl yuzurimine B, and dihydroyuzurimine, respectively. Yamamura *et al.* isolated deoxyyuzurimine (**19**) from *D. humile* [30], and daphnijsmine (**20**) and deacetyl daphnijsmine (**21**) from the seeds of *D. teijsmanni* [23]. Calycinine A (**22**) was isolated from *D. calycinum* distributed in China, together with deacetyl daphnijsmine, deacetyl yuzurimine, and the zwitterionic alkaloid **26** [31] (Figure 18.3).

18.2.4
Daphnilactone A-type Alkaloids

Hirata and Sasaki isolated daphnilactone A (**23**) as one of the minor alkaloids from *D. macropodum*, and the structure was determined by X-ray analysis [32,33]. The skeleton of daphnilactone A is considered to be constructed by the insertion of a C_1



Secodaphniphylline (**8**) Daphniteijsmine (**9**) Daphniteijsmanine (**10**) Methyl Homoseco-daphniphyllate (**11**)

Fig. 18.2 Secodaphnane-type alkaloids.

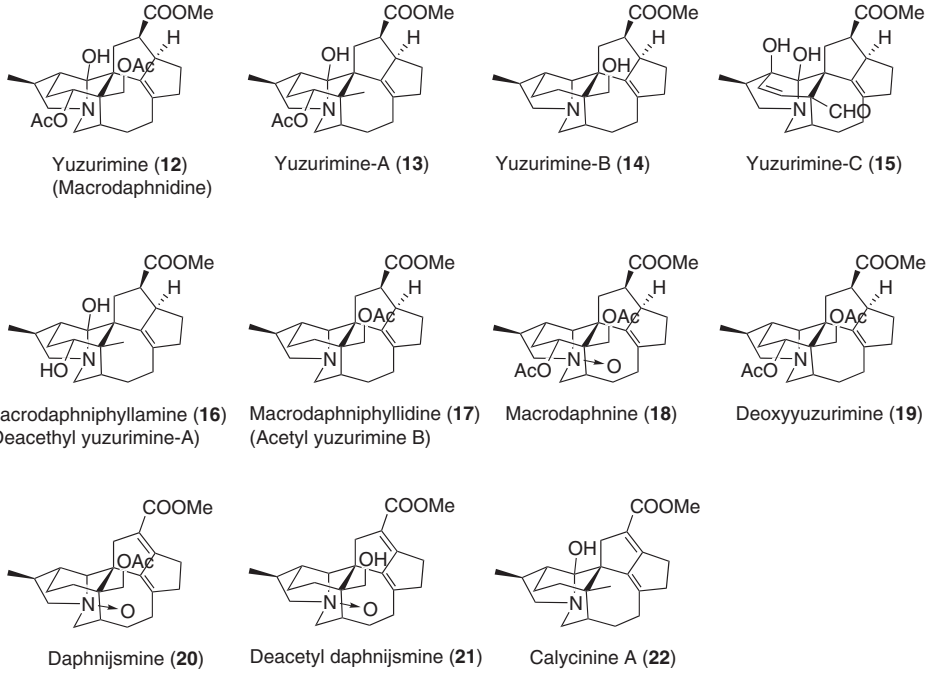


Fig. 18.3 Yuzurimine-type alkaloids.

unit into a nitrogen–carbon bond in the daphnane type skeleton, such as methyl homodaphniphyllate, followed by lactonization (Figure 18.4).

18.2.5
Daphnilactone B-type Alkaloids

Daphnilactone B (**24**) was isolated as one of the major alkaloids from the fruits of three *Daphniphyllum* species in Japan, *D. macropodum*, *D. teijsmanni*, and *D. humile*, and the structure was deduced by extensive spectral analysis, as well as by chemical evidence, and finally assigned by X-ray crystallographic analysis [34,35,37]. Isodaphnilactone B (**25**) was isolated from the leaves of *D. humile* and the structure was analyzed by spectroscopic methods [30]. A zwitterionic alkaloid **26**, the hydration product of daphnilactone B, was isolated from the fruits of *D. teijsmanni*, and the structure determined on the basis of its spectral and chemical properties [38].

18.2.6
Yuzurine-type Alkaloids

Nine alkaloids belonging to the yuzurine group were isolated from *D. macropodum* and *D. gracile* distributed in New Guinea. The structure of yuzurine (**27**) was

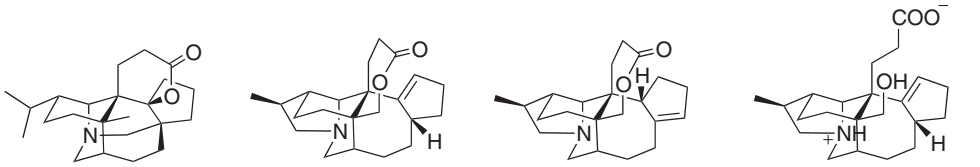


Fig. 18.4 Daphnilactones A- and B-type alkaloids.

established by X-ray crystallographic analysis of yuzurine methiodide [39]. The other alkaloids belonging to this group, daphnigracine (**28**), daphnigraciline (**29**), oxodaphnigracine (**30**), oxodaphnigraciline (**31**), epioxodaphnigraciline (**32**), daphgracine (**33**), daphgraciline (**34**), and hydroxydaphgraciline (**35**), were isolated from *D. gracile* and their structures were assigned by spectroscopic methods.

A new skeletal alkaloid, bukittinggine (**36**), was isolated from *Sapium baccatum* (Euphorbiaceae). The structure, which is closely related to both methyl homosecodaphniphyllate (**11**) and daphnilactone B, was determined by X-ray analysis of its hydrobromide [43]. The presence of bukittinggine indicates that *Sapium baccatum* may be closely related to the genus *Daphniphyllum* (Figure 18.5).

18.2.7
Daphnezomines

During the course of our studies for biogenetic intermediates of the daphniphyllum alkaloids, a project was initiated on the alkaloids of *D. humile*. A series of new daphniphyllum alkaloids, daphnezomines A–S (**37**–**55**), which were isolated from the leaves, stems, and fruits of *D. humile*, are of considerable interest from a biogenetic point of view. All these structures are listed in Figure 18.6.

The leaves, stems, and fruits of *D. humile* collected in Sapporo afforded daphnezomines A (**37**, 0.01 % yield), B (**38**, 0.008 %), C (**39**, 0.0001 %), D (**40**, 0.00007 %), E (**41**, 0.001 %), F (**42**, 0.0002 %), G (**43**, 0.0001 %), H (**44**, 0.0002 %), I (**45**, 0.005 %), J (**46**, 0.002 %), and K (**47**, 0.002 %), as unspecified salts [44–47]. The structures of daphnezomines A–G (**37**–**43**) were elucidated mainly on the basis of extensive spectroscopic studies, including several types of 2D NMR experiments.

From the IR absorptions, daphnezomine A (**37**), $C_{22}H_{35}NO_3$, was suggested to possess OH (3600 cm^{-1}), NH (3430 cm^{-1}), and carboxylate (1570 and 1390 cm^{-1}) functionalities. Detailed analysis of the ^1H–^1H COSY, HOHAHA, HMQC-HOHAHA and HMBC correlations defined the gross structure of **37**, consisting of an aza-adamantane core (N-1, C-1, and C-5–C-12) fused to a cyclohexane ring (C-1–C-5 and C-8) and another cyclohexane ring (C-9–C-11 and C-15–C-17), and three substituents at C-2, C-5, and C-8 [44].

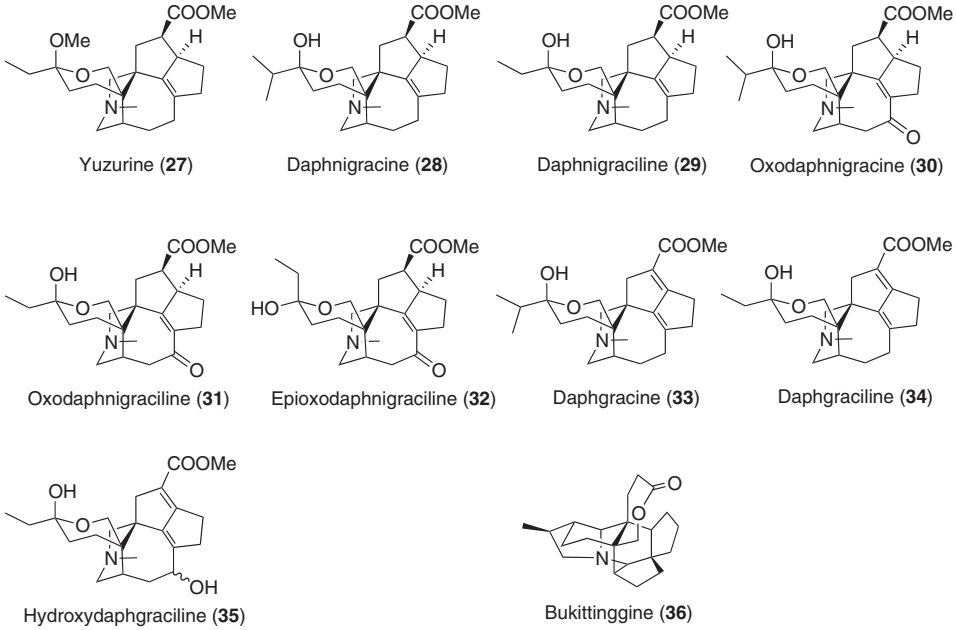
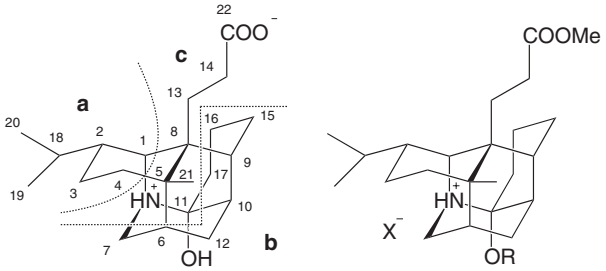
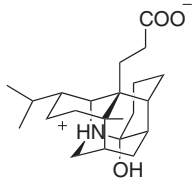


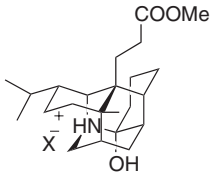
Fig. 18.5 Yuzurine-type alkaloids.



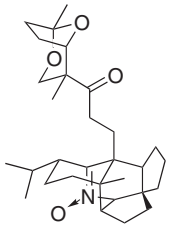
Daphnezomine B (**38**), $C_{23}H_{37}NO_3$, differs by a methoxy signal absent in **37**. Acetylation of **38** afforded the monoacetate **119**, in which the axially oriented tertiary hydroxyl group was acetylated. When daphnezomine B was treated with aqueous Na_2CO_3, it was converted into its free base **120**, showing spectroscopic anomalies as follows (Scheme 18.1). The ^{13}C signals (C-9, C-12, C-16, C-17, and C-18) of the free base showed extreme broadening, while the quaternary carbon (C-11) was not



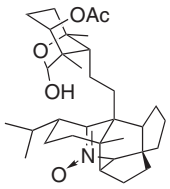
Daphnezomine A (**37**)



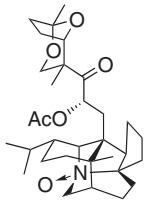
Daphnezomine B (**38**)



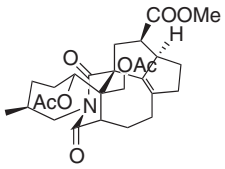
Daphnezomine C (**39**)



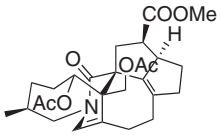
Daphnezomine D (**40**)



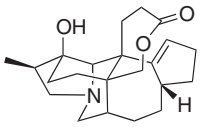
Daphnezomine E (**41**)



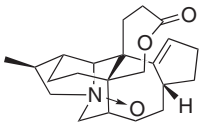
Daphnezomine F (**42**)



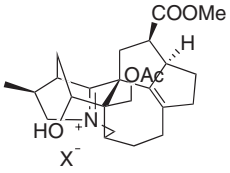
Daphnezomine G (**43**)



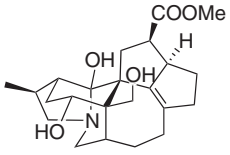
Daphnezomine H (**44**)



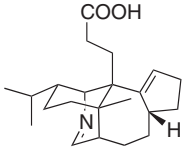
Daphnezomine I (**45**)



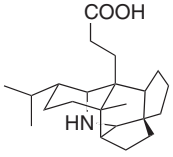
Daphnezomine J (**46**)



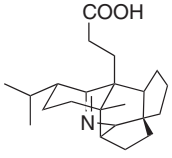
Daphnezomine K (**47**)



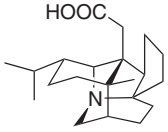
Daphnezomine L (**48**)



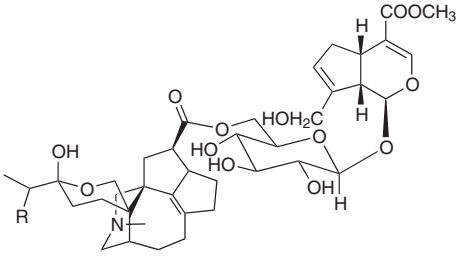
Daphnezomine M (**49**)



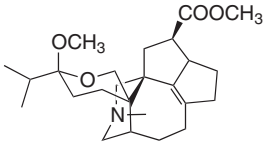
Daphnezomine N (**50**)



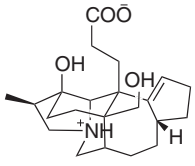
Daphnezomine O (**51**)



Daphnezomine P (**52**): R=Me
Daphnezomine Q (**53**): R=H



Daphnezomine R (**54**)



Daphnezomine S (**55**)

Fig. 18.6 Structures of daphnezomines A–S (**37**–**55**).

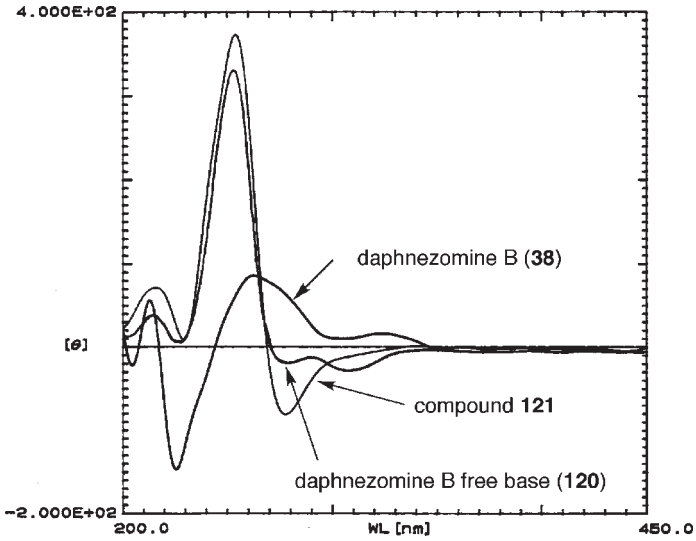
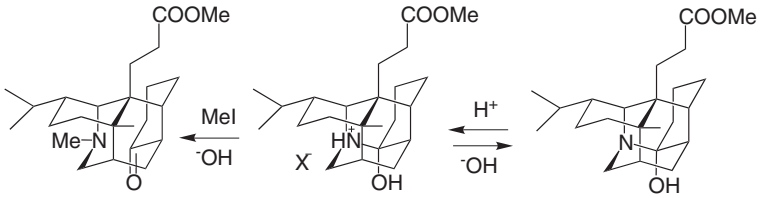


Fig. 18.7 CD spectra of daphnezomine B (**38**), daphnezomine B free base (**120**) and compound **121**[44].

observed. NMR evidence indicating a differently directed nitrogen lone pair was obtained by the ^{15}N NMR spectra (**38**: δ_N 93.7; free base of **38**: δ_N 63.0). On the other hand, in the IR spectrum, the close proximity of the carbonyl and the nitrogen permits pronounced interaction of these two functions to result in a lower shift of the carbonyl peak for **121**, whereas it was not observed for the free base of **38**. In order to examine these spectroscopic anomalies, yuzurimine free base with the similar amino ketal functionality was prepared under the same conditions, but the spectroscopic anomalies were not observed. When the free base was treated with acetic acid, it was easily converted into **38** again. Compound **121** was obtained by treatment of **38** with CH_3I/K_2CO_3 (Scheme 18.1) [40]. Production of **121** could have resulted from N-methylation of the free base followed by the alkaline-induced N–C-11 bond cleavage to generate a ketone at C-11. In the CD spectra (Figure 18.7), the structural similarity between the free bases of **38** showing spectroscopic anomalies and **121** were obtained by the CD spectra (MeOH) [free base of **38**: λ_{max} 255 (θ + 400) and 280 (−80) nm; **121**: λ_{max} 260 (θ + 350), 280 (−20), and 305 (−30) nm], showing a different CD curve from that of **38** [λ_{max} 225 (θ – 150) and 265 (+100) nm]. These data indicated that the balance of the amino ketal in the free base of **38** declined in the keto form in solution. Thus, the structure of daphnezomine B was elucidated to be **38**. The spectral data and the $[\alpha]_D$ value of the methyl ester of **37**, which was obtained by treatment of **37** with trimethylsilyldiazomethane, were in complete agreement with those of natural daphnezomine B [44].

In order to determine the absolute configurations of **37** and **38**, a crystal of the hydrobromide of **38** generated from MeOH/acetone (1 : 9) was submitted to X-ray crystallographic analysis [44]. The crystal structure containing the absolute



Scheme 18.1

configuration, which was determined through the Flack parameter [52], $\chi = -0.02(2)$, is shown in Figure 18.8. Daphnezomines A and B consisting of all six-membered rings are the first natural products containing an aza-adamantane core [53–56] with an amino ketal bridge, although there are reports on a number of daphniphyllum alkaloids containing five-membered rings, which may be generated from a nitrogen-involved squalene intermediate via the secodaphnane skeleton [1,2].

Daphnezomines C (**39**) and D (**40**), possess the secodaphniphylline-type skeleton with a nitrone functionality, while daphnezomine E (**41**) is the first *N*-oxide of a daphniphylline-type alkaloid, though the *N*-oxides of several yuzurimine-type alkaloids have been reported [45].

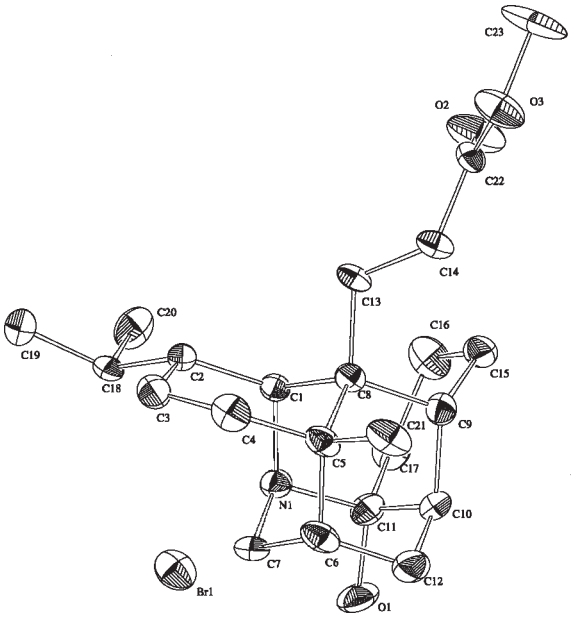
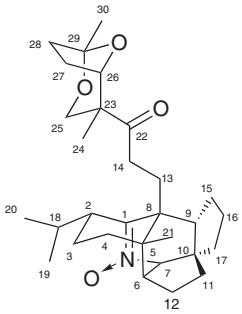


Fig. 18.8 Molecular structure of daphnezomine B (**38**) hydrobromide obtained by X-ray analysis (ORTEP drawing; ellipsoids are drawn at the 30 % probability level). Hydrogen atoms are omitted for clarity [44].



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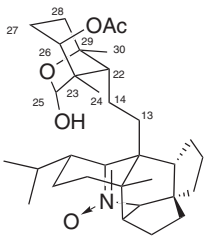

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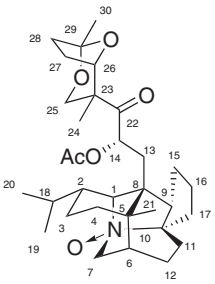
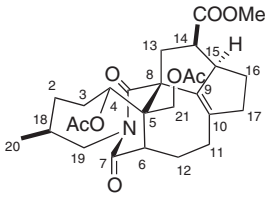


41

Spectral investigations of daphnezomines F (**42**) and G (**43**), whose molecular formulas are $C_{27}H_{35}NO_8$ and $C_{27}H_{35}NO_7$, respectively, revealed that they are structurally related and possess a 1-azabicyclo[5.2.2]undecane moiety. The conformation of the 1-azabicyclo[5.2.2]undecane ring in **43** was elucidated by a low-temperature NMR study and computational analysis [46].



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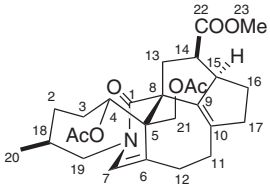
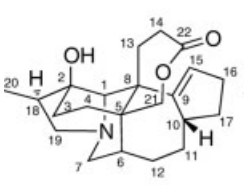


43

The structures, including relative stereochemistry, of daphnezomines H (**44**), I (**45**), J (**46**), and K (**47**), four new alkaloids possessing a daphnilactone-type (**44** and **45**) or a yuzurimine-type skeleton (**46** and **47**) were elucidated on the basis of spectroscopic data [47]. Daphnezomine I is the first *N*-oxide alkaloid having a daphnilactone-type skeleton, while daphnezomine J is the first alkaloid possessing a yuzurimine-type skeleton with an anti-Bredt-rule imine [57,58].



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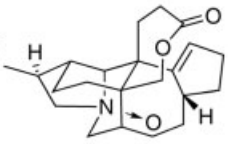

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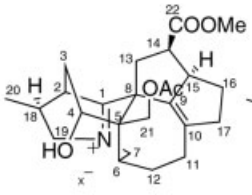
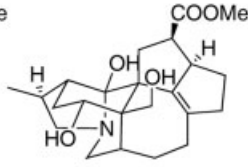


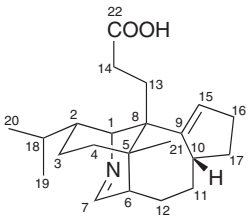
46



47

Relatively polar fractions prepared from the stems of *D. humile* afforded daphnezomines L (**48**, 0.0001 %), M (**49**, 0.00007 %), N (**50**, 0.00007 %), and O (**51**, 0.001 %) as colorless solids, together with the known zwitterionic alkaloid (**26**) (0.0005 %) [48].

Daphnezomine L (**48**) was close structurally to a biogenetic intermediate between the secodaphnane and daphnane skeletons.



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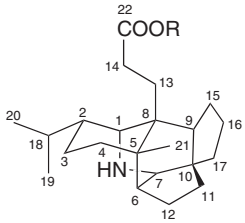
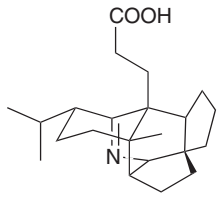


49: R=H
11: R=Me



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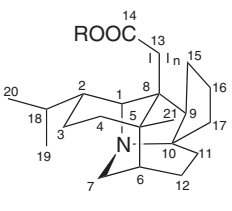
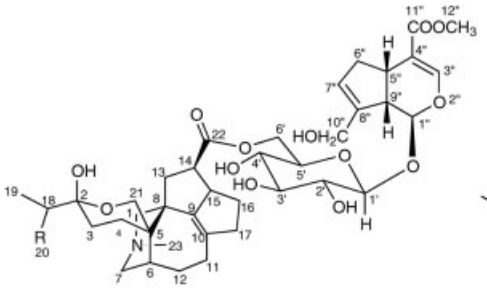
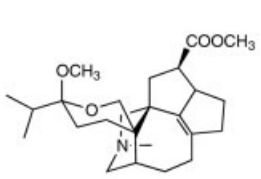


51: R=H, n=1
7: R=Me, n=2

Four new alkaloids, daphnezomines P–S (**52**–**55**) have been isolated from the fruits of *D. humile* and daphnezomines P (**52**) and Q (**53**) were the first daphniphyllum alkaloids with an iridoid glycoside moiety [78].



52: R=Me
53: R=H



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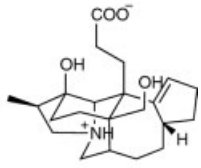
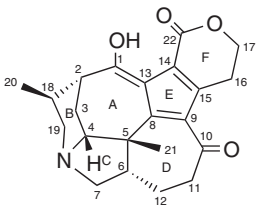


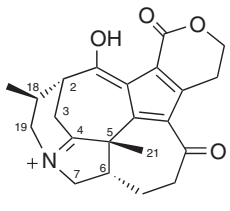
55

18.2.8
Daphnicyclidins

Eight highly modified daphniphyllum alkaloids with unprecedented fused hexa- or pentacyclic skeletons, daphnicyclidins A (**56**, 0.003 % yield), B (**57**, 0.0003 %), C (**58**, 0.001 %), D (**59**, 0.002 %), E (**60**, 0.001 %), F (**61**, 0.001 %), G (**62**, 0.001 %), and H (**63**, 0.004 %) were isolated from the stems of *D. teijsmanni* and *D. humile* [49] (Figure 18.9).



56



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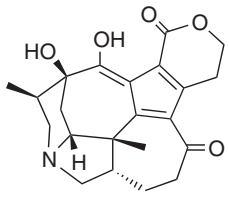


58

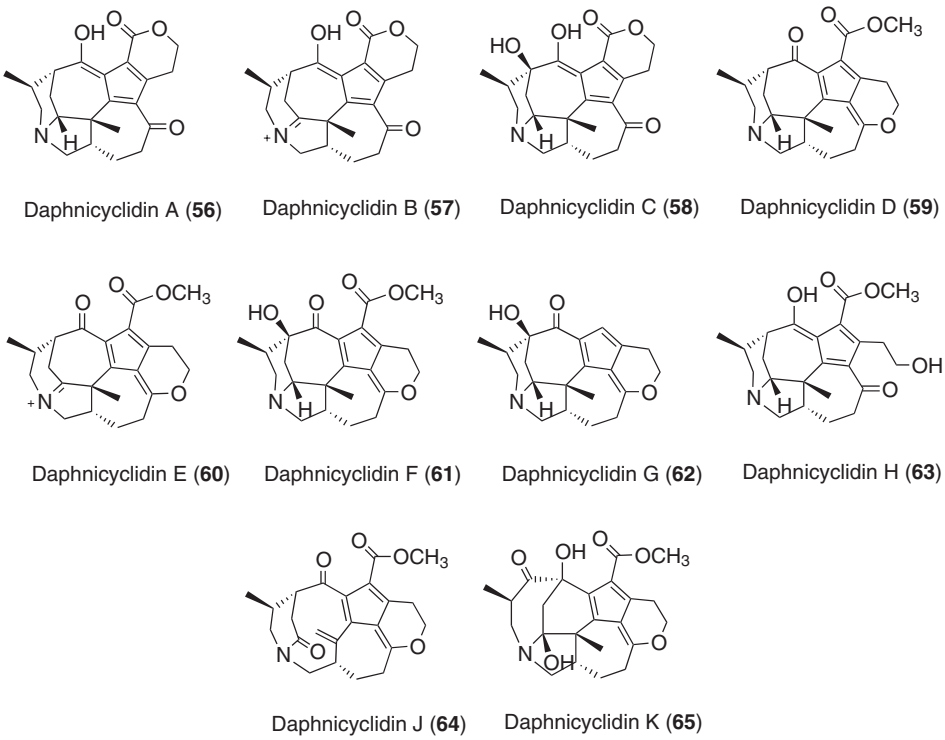


Fig. 18.9 Structures of daphnicyclidins A–K (**56**–**65**).

Daphnicyclidin A, $C_{22}H_{25}NO_4$, showed IR absorptions that implied the presence of OH and/or NH (3440 cm^{-1}) and conjugated carbonyl (1680 cm^{-1}) functionalities. Three partial structures, **a** (from C-2 to C-4 and from C-18 to C-19 and C-20), **b** (from C-6 to C-7 and C-12 and from C-11 to C-12), and **c** (from C-16 to C-17) were deduced from extensive analyses of 2D NMR data, including the ^1H–^1H COSY, HOHAHA, HMQC, and HMBC spectra in $CDCl_3$–CD_3OD (9 : 1). The connections of the three partial structures through a nitrogen atom (N-1) and also through a quaternary carbon (C-5) was established by the ^1H–^{13}C long-range (two- and three-bond) couplings detected in the HMBC spectrum to afford a proposed structure. The X-ray crystal structure (Figure 18.10) of daphnicyclidin A TFA salt revealed a unique fused-hexacyclic ring system consisting of two each of five-, six-, and seven-membered rings containing a nitrogen atom and two methyls at C-5 and C-18, in which an intramolecular hydrogen bond was observed between the C-1 hydroxyl proton and the C-22 carbonyl oxygen. The relative configurations at C-4, C-5, C-6, and C-18 were deduced from NOESY correlations, together with a stable chair conformation of ring B as depicted in the computer-generated 3D drawing (Figure 18.11).

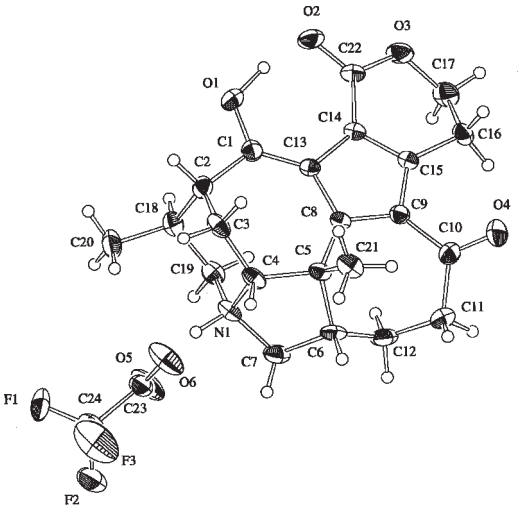


Fig. 18.10 Molecular structure of daphnicyclidin A (**56**) TFA salt obtained by X-ray analysis (ORTEP drawing; ellipsoids are drawn at the 30 % probability level) [49].

The FABMS spectrum of daphnicyclidin B showed the molecular formula $C_{22}H_{24}NO_4$. The 2D NMR data of **57** were similar to those of the imine (C-4 and N-1) form of daphnicyclidin A. Spectral investigation of daphnicyclidin C, whose molecular formula is $C_{22}H_{25}NO_5$, revealed that it was the 2-hydroxy form of daphnicyclidin A [49].

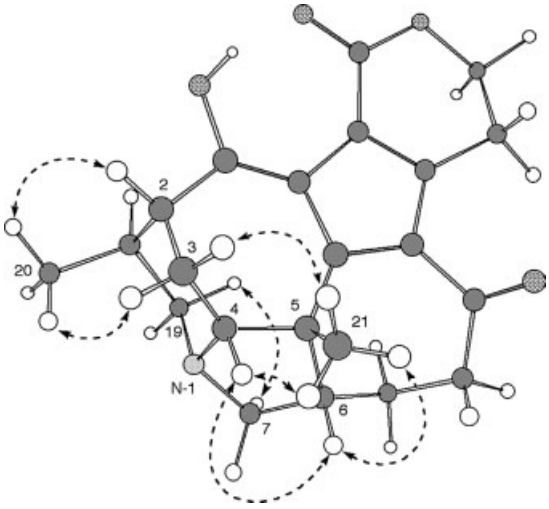
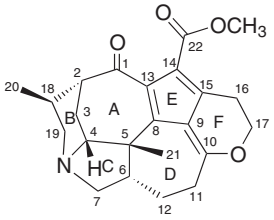


Fig. 18.11 Selected NOESY correlations (dotted arrows) and relative configurations for daphnicyclidin A (**56**)[49].



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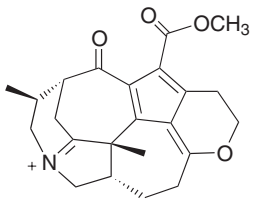

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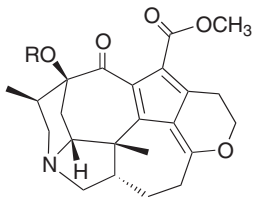
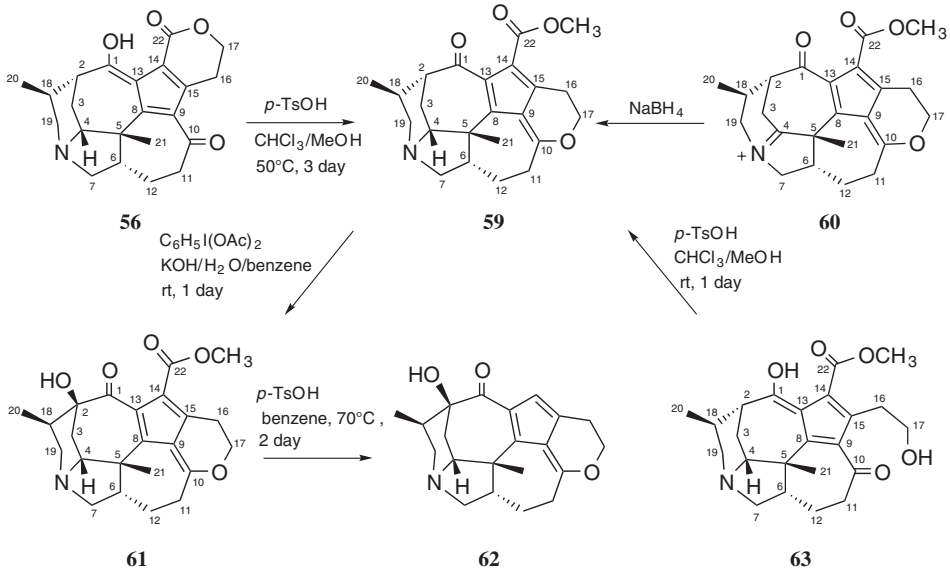


61: R=H
122: R=*p*-Br-Bz

The molecular formula, $C_{23}H_{27}NO_4$ of daphnicyclidin D (**59**), was larger than that of daphnicyclidin A by a CH_2 unit. ^1H and ^{13}C NMR data of **59** were similar to those of **56** in the left-hand part consisting of rings A to C with a nitrogen atom, except that a methoxy signal absent for **56** was observed for **59**. The structure of **59** was elucidated by 2D NMR data. HMBC cross-peaks indicated that C-10 and C-17 were connected through an oxygen atom to form a dihydropyran ring. In addition, the presence of a conjugated cyclopentadiene moiety (C-8–C-9 and C-13–C-15) as in **56** was suggested by HMBC correlations. Treatment of **56** with methanolic *p*-TsOH gave daphnicyclidin D (Scheme 18.2). Thus, the structure of daphnicyclidin D was assigned as **59** [49].

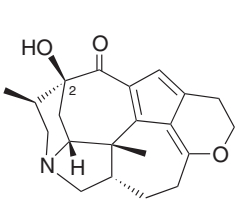
The IR spectrum of daphnicyclidin E (**60**), $C_{23}H_{25}NO_4$ was indicative of the presence of conjugated carbonyl and/or imine (1680 cm^{-1}) functionalities. The presence of an iminium carbon (C-4) was indicated by HMBC correlations for H_3-21 and H_b-3 to C-4, and H_2-7 and H_a-19 to C-4 through a nitrogen atom. Treatment of



Scheme 18.2 Chemical correlations for daphnicyclidins A (**56**) and D–H **(59–63)** [49].

60 with $NaBH_4$ afforded daphnicyclidin D (Scheme 18.2). Thus, daphnicyclidin E was concluded to be the imine form at C-4 of daphnicyclidin D [49].

2D NMR analysis of daphnicyclidin F (**61**), $C_{23}H_{27}NO_5$, and chemical correlation of daphnicyclidin D with **61**, indicated that **61** is the 2-hydroxy form of daphnicyclidin D [49].



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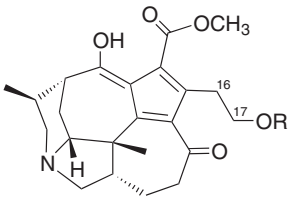


63 : R=H
123 : R=Ac

Daphnicyclidin F possesses a methoxy carbonyl moiety at C-14, while the ^1H and ^{13}C NMR data of **62** showed signals due to an sp^2 methine. Treatment of **61** with *p*-TsOH at 70 °C for two days gave daphnicyclidin G (**62**) (Scheme 18.2). Therefore, daphnicyclidin G was elucidated to be the 14-demethoxycarbonyl form of daphnicyclidin F [49].

Daphnicyclidin H (**63**), $C_{23}H_{29}NO_5$, showed IR absorptions at 3435 and 1680 cm^{-1} indicating the presence of hydroxyl and conjugated carbonyl groups, respectively. ^1H NMR signals assignable to H_2-17 were observed to be equivalent. Treatment of **63** with acetic anhydride afforded the monoacetate **123**, in which the hydroxyl group at C-17 was acetylated. On the other hand, the presence of a methoxy carbonyl group at C-14 and rings A–E with a ketone at C-10 was deduced from the 2D NMR analysis. The 2D NMR data indicated that the conjugated keto-enol moiety of **63** was the same as that of daphnicyclidin A. Treatment of daphnicyclidin H with *p*-TsOH gave daphnicyclidin D (Scheme 18.2) [49].

The absolute configuration of daphnicyclidin F was analyzed by applying the exciton chirality method [61] after introduction of a *p*-bromobenzoyl chromophore into the hydroxyl group at C-2. As the sign of the first Cotton effect [λ_{max} 280 (θ + 20 000) and 225 (−16 000) nm] was positive, the chirality between the cyclopentene moiety and the benzoate group of the *p*-bromobenzoyl derivative **122** of **61** was assigned as shown in Figure 18.12 (right-handed screw), indicating that the absolute stereochemistry at C-2 was (*S*) [49].

Daphnicyclidins J (**64**) and K (**65**), two alkaloids with unprecedented fused penta- or hexacyclic skeletons, respectively, were isolated from the stems of *D. humile* [50]. Daphnicyclidin J, $C_{23}H_{25}NO_5$, showed IR absorptions at 1690 and 1660 cm^{-1}, corresponding to ketone and amide carbonyl functionalities, respectively. The ^1H–^1H COSY and HOHAHA spectra proved information on the proton-connectivities for three partial structures **a** (C-2 to C-3 and C-18, and C-18 to C-19 and C-20), **b** (C-6 to C-7 and C-12, and C-11 to C-12), and **c** (C-16 to C-17). Long range ^1H–^{13}C

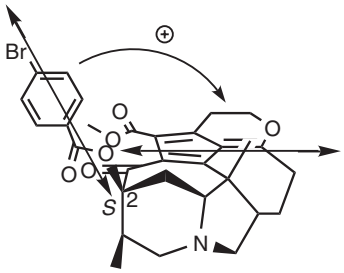
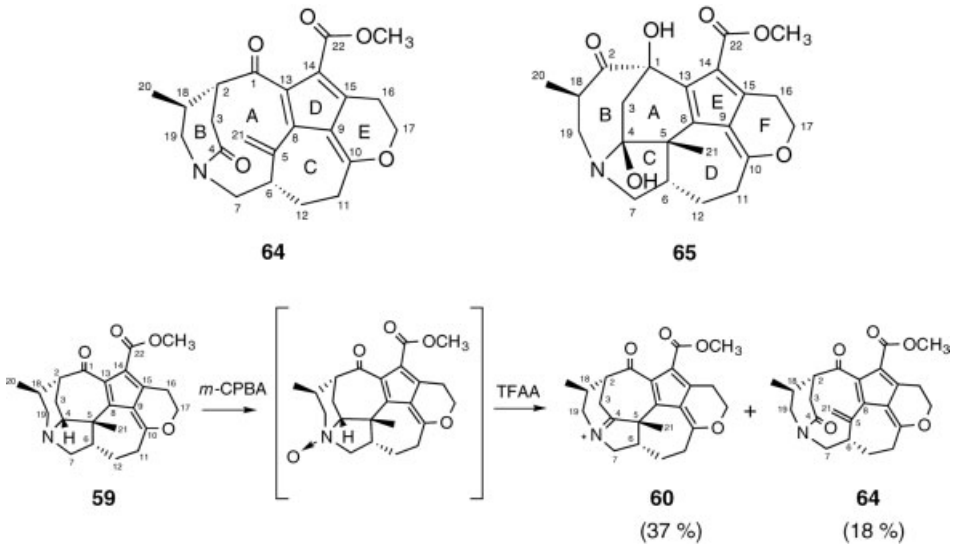


Fig. 18.12 Stereostructure of the *p*-bromobenzoate (**122**) of daphnicyclidin F (**61**). Arrows denote the electric transition dipole of the chromophore [49].

correlations showed that the partial structures are linked. The presence of a fulvene functionality (C-8–C-10 and C-13–C-15), which was conjugated with two carbonyl groups (C-1 and C-22) and an exo-methylene group (C-5 and C-21), was deduced by comparison of the carbon chemical shifts with those of daphnicyclidin D. UV absorptions (245, 320, and 330 nm) also supported the existence of the conjugated fulvene functionality. Thus, the structure of daphnicyclidin J was assigned as **64**, which has a uniquely fused-pentacyclic ring system (one five-, two six-, one seven-, and one ten-membered rings) containing a δ-lactam and a pyran ring. The absolute configuration was established by chemical correlation with a known related alkaloid, daphnicyclidin D, through a modified Polonovski reaction (Scheme 18.3) [50].



Scheme 18.3 Chemical transformation of daphnicyclidin D to daphnicyclidins E and J by a modified Polonovski reaction.

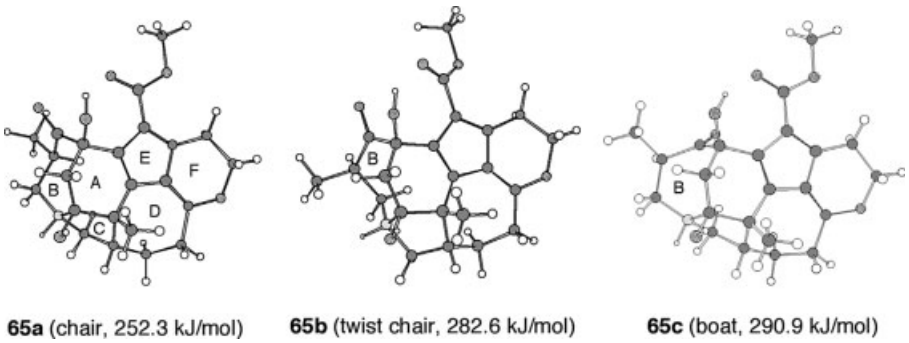


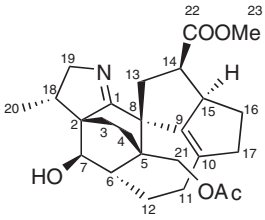
Fig. 18.13 Three representative stable conformers (**65a**–**65c**) for daphnicyclidin K (**65**) analyzed by Monte Carlo simulation followed by minimization and clustering analysis [50].

Daphnicyclidin K was shown to have the molecular formula $C_{23}H_{27}NO_6$. IR absorptions implied the presence of hydroxyl (3600 cm^{-1}), ester carbonyl (1700 cm^{-1}), and conjugated carbonyl (1650 cm^{-1}) functionalities. Analysis of 2D NMR data showed that the structure of **65** has an unusual skeleton consisting of a 6/7/5/7/5/6 hexacyclic ring system [50].

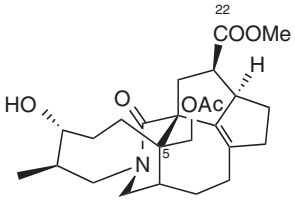
The relative configuration was assigned from NOESY correlations and conformational calculations by Monte Carlo simulation [59], which suggested that the seven-membered ring (ring B) with a chair conformation (**65a**) was the most stable, whereas those with twist chair (**65b**) and boat (**65c**) conformations had considerably higher energy (Figure 18.13). In addition, the NOESY correlations indicated that another seven-membered ring (ring D) assumed a twist-boat conformation similar to the crystal structure of daphnicyclidin A.

18.2.9
Daphmanidins

Further investigation of extracts of the leaves of *D. teijsmanii* resulted in the isolation of daphmanidin A (**66**, 0.0001 % yield), an alkaloid with an unprecedented fused-hexacyclic ring system, and daphmanidin B (**67**, 0.00003 %) with a pentacyclic ring system [51] (Figure 18.14).



66



67

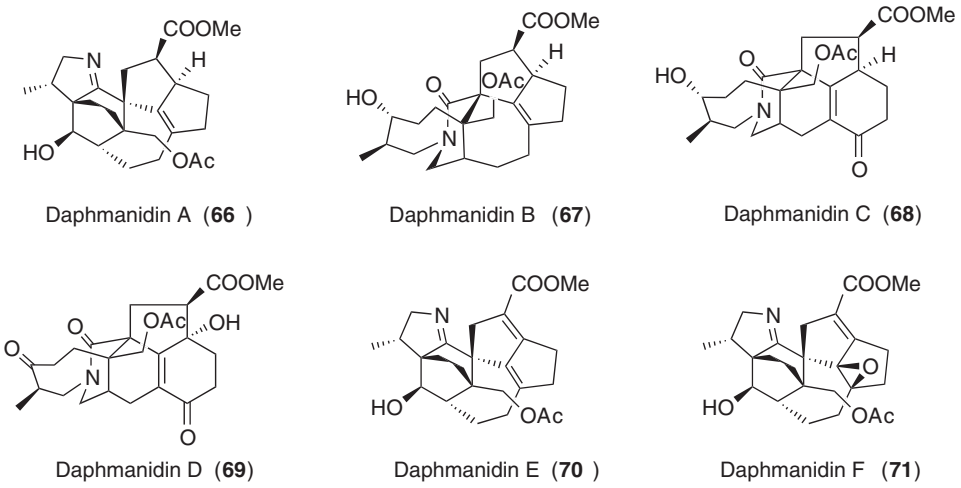


Fig. 18.14 Structures of daphmanidins A–F (**66**–**71**).

The IR absorptions of daphmanidin A (**66**), $C_{25}H_{33}NO_5$, implied the presence of hydroxyl (3616 cm^{-1}), ester carbonyl (1730 cm^{-1}), and imine (1675 cm^{-1}) functionalities. Detailed spectroscopic analysis revealed that the gross structure of daphmanidin A possesses a fused-hexacyclic ring system consisting of a dihydropyrrole ring (N-1, C-1, C-2, C-18, and C-19) with a methyl group at C-18, a bicyclo[2.2.2]octane ring (C-1–C-8) with a hydroxyl at C-7, and a decahydrocyclopenta [*cd*] azulene ring (C-5, C-6, C-8–C-17) with a methoxy carbonyl group at C-14 and an acetoxy methyl group at C-5. The relative and absolute stereochemistry of **66** was determined by a combination of NOESY correlations (Figure 18.15) and the modified Mosher method.

The structure of daphmanidin B (**67**), $C_{25}H_{36}NO_6$, was elucidated by 2D NMR data to possess a 1-azabicyclo[5.2.2]undecane moiety, like daphnezomines F and G [46]. The relative stereochemistry was deduced from NOESY correlations. The conformation of the unit (C-2–C-5, C-18 to C-2, C-19, and N) in the 1-azabicyclo[5.2.2]undecane moiety, with a twist-chair form as shown in Figure 18.16, was consistent with the results of a conformational search using MMFF force field [60] implemented in the Macromodel program [59].

Two novel alkaloids with an unprecedented fused-pentacyclic skeleton, daphmanidins C (**68**) and D (**69**), consisting of 1-azabicyclo[5.2.2]undecane, hexahydronaphthalen-1-one, and cyclopentane rings, have been isolated from the leaves of *D. teijsmanii* [79]. Daphmanidin C elevated the activity of NGF biosynthesis. New daphniphyllum alkaloids, daphmanidins E (**70**) and F (**71**), have also been isolated from the leaves of *D. teijsmannii*, and Daphmanidins E and F showed a moderate vasorelaxant effect on rat aorta [80].

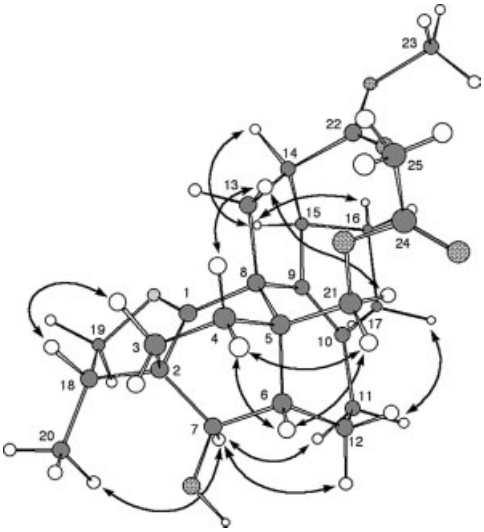


Fig. 18.15 Key NOESY correlations (arrows) and relative stereochemistry for daphmanidin A (**66**) [51].

18.2.10
Daphniglaucins

Two cytotoxic quaternary daphniphyllum alkaloids with an unprecedented fused-polycyclic skeleton containing a 1-azoniatetracyclo[5.2.2.0.^{1,6}0.^{4,9}]undecane ring

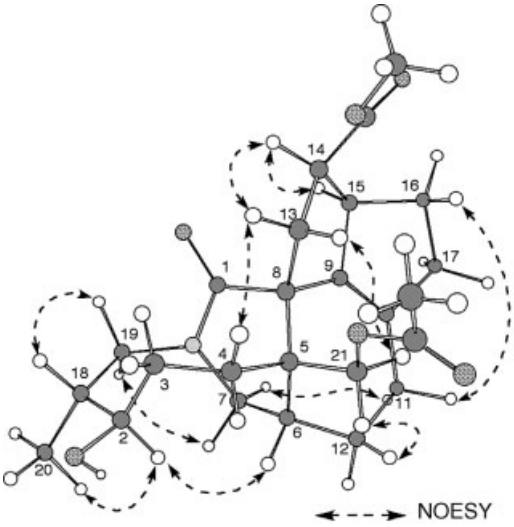


Fig. 18.16 Selected 2D NMR correlations and relative stereochemistry for daphmanidin B (**67**) [51].

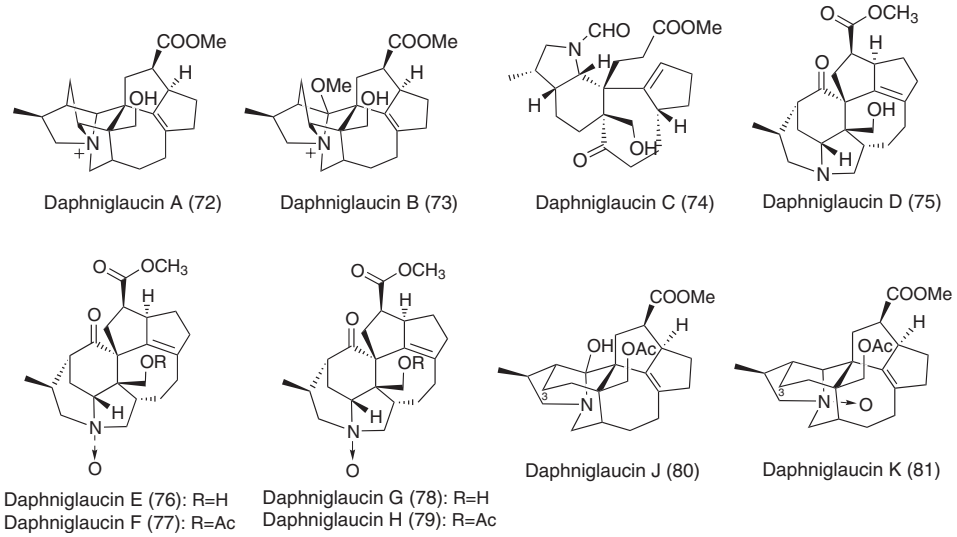


Fig. 18.17 Structures of daphniglaucins A–K (**72**–**81**).

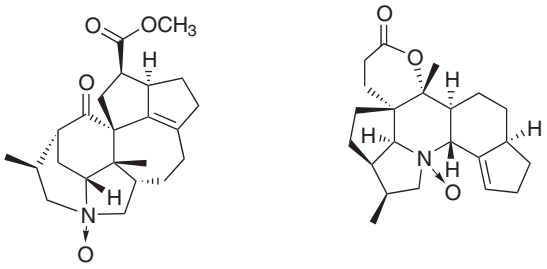
system, daphniglaucins A (**72**) and B (**73**), have been isolated from the leaves of *Daphniphyllum glaucescens* [81]. A novel daphniphyllum alkaloid with an unprecedented tetracyclic ring system consisting of octahydroindole and hexahydroazulene rings, daphniglaucin C (**74**), has been isolated from the leaves of *Daphniphyllum glaucescens* as a tubulin polymerization inhibitor [82]. Five new fused-hexacyclic alkaloids, daphniglaucins D (**75**), E (**76**), F (**77**), G (**78**), and H (**79**), and two new yuzurimine-type alkaloids, daphniglaucins J (**80**) and K (**81**), have also been isolated from the leaves of *D. glaucescens* [83] (Figure 18.17).

18.2.11
Calyciphyllines

Two types of daphniphyllum alkaloids with unprecedented fused-hexacyclic ring systems, calyciphyllines A (**82**) and B (**83**), have been isolated from the leaves of *Daphniphyllum calycinum* (Daphniphyllaceae) [84]. The structure of calyciphylline A was assigned as **82**, with a fused-hexacyclic ring system (three five-, two six-, and one seven-membered rings) containing an *N*-oxide group, and that of calyciphylline B was assigned as **83**, with a hexacyclic ring system consisting of a hexahydroindene ring and an octahydroindolizine ring fused to a cyclopentane ring with a δ-lactone ring at C-5 and C-8 as shown in Figure 18.18.

18.2.12
Daphtenidines

Daphtenidines A (**84**)–D (**87**) were isolated from the leaves of *D. teijsmannii* [85]. Daphtenidines A (**84**) and B (**85**) possess the daphnilactone A-type skeleton. This is



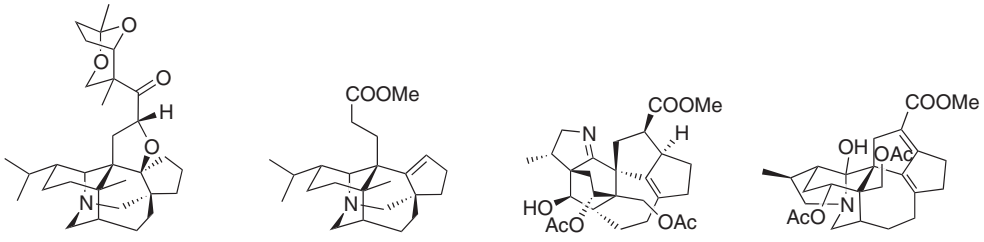
Calyciphylline A (**82**) Calyciphylline B (**83**)

Fig. 18.18 Structures of calyciphyllines A (**82**) and B (**83**).

the second isolation of daphnilactone A-type alkaloids from natural sources. Daphtenidine C (**86**) is the 4-acetoxy form of daphmanidin A, while daphtenidine D (**87**) is the 14-dehydro form of yuzurimine (Figure 18.19).

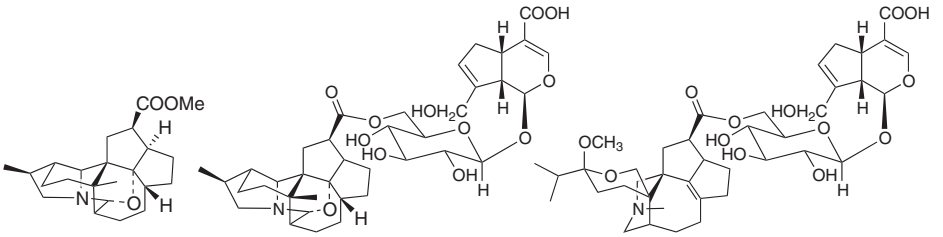
18.2.13
Other Related Alkaloids

Jossang *et al*. and Bodo *et al*. investigated the various parts of *D. calycinum* collected in Vietnam and isolated daphcalycine (**88**) [86], daphcalycinosidines A (**89**), B (**90**), and C (**92**), and the related alkaloids shown in Figure 18.20 [87,88]. Daphcalycinosidine A (**89**), B (**90**), and C (**92**) are characterized by an iridoid glucoside moiety linked to daphniphyllum alkaloid moieties such as daphnezomines P and Q [78]. Yue *et al*. also isolated the related alkaloids caldaphnidines A (**95**)–F (**100**) from *D. calycinum* [89] (Figure 18.20). Yue *et al*. also isolated various related daphniphyllum alkaloids (**101**–**118**) from various species distributed in China, such as *D. subverticillatum* [90], *D. paxianum* [91,92], *D. oldhami* [93], *D. longistylum* [94], *D. longeracemosum* [95], and *D. yunnanense* [96] as shown in Figure 18.21. Most of them belong to the categories that have already been isolated [3].

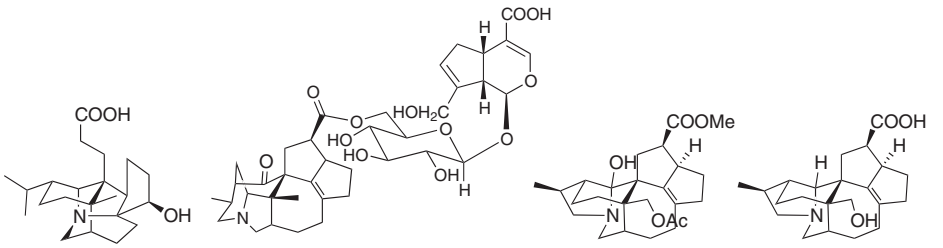


Daphtenidine A (**84**) Daphtenidine B (**85**) Daphtenidine C (**86**) Daphtenidine D (**87**)

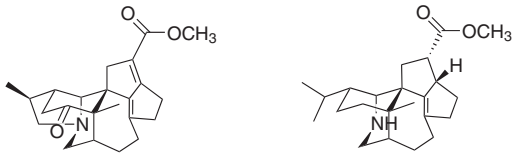
Fig. 18.19 Structures of daphtenidines A–D (**84**–**87**).



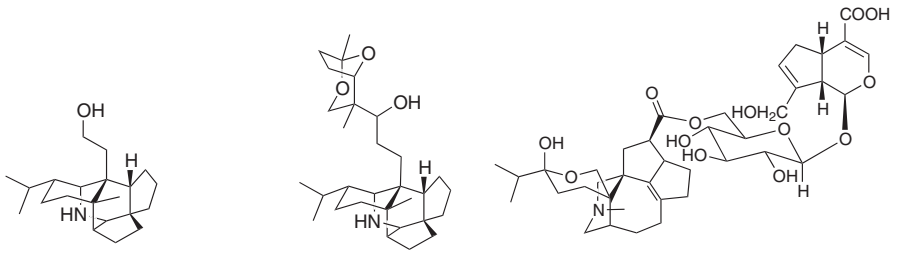
Daphcalycine (**88**) Daphcalycinosidine A (**89**) Daphcalycinosidine B (**90**)



17-Hydroxyhomo daphniphyllic acid (**91**) Daphcalycinosidine C (**92**) Yuzurimine E (**93**) Yuzurimic acid B (**94**)



Caldaphnidine A (**95**) Caldaphnidine B (**96**) Caldaphnidine C (**97**)



Caldaphnidine D (**98**) Caldaphnidine E (**99**) Caldaphnidine F (**100**)

Fig. 18.20 Structures of other related alkaloids (**88**–**100**).

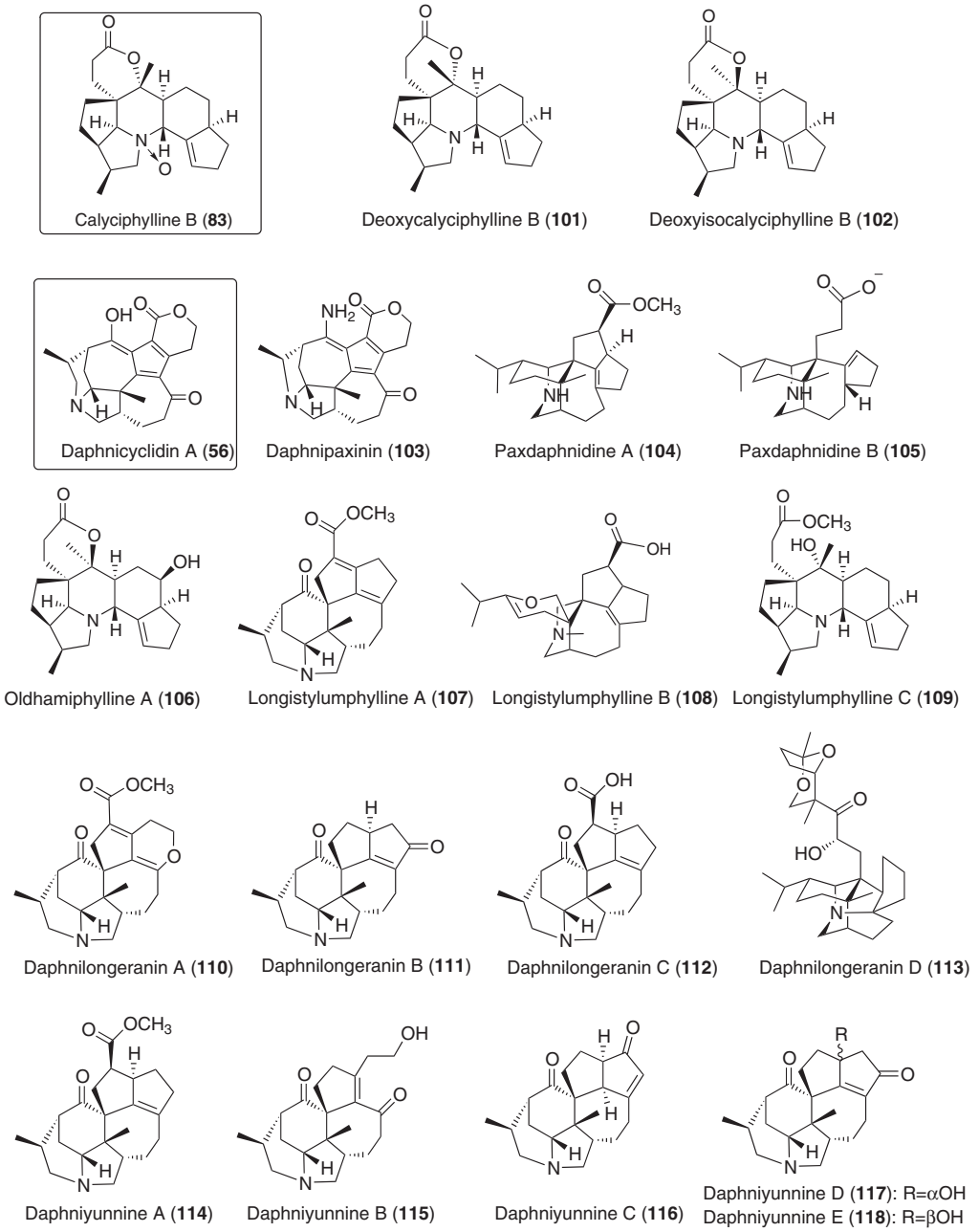


Fig. 18.21 Structures of other related alkaloids (**101**–**118**).

18.3
Biosynthesis and Biogenesis

18.3.1
Biosynthesis of Daphniphyllum Alkaloids

Suzuki and Yamamura conducted feeding experiments on the daphniphyllum alkaloids, using the leaves of *D. macropodum* [62]. The alkaloids present, as well as their amounts, varied with season, and the highest incorporation of DL-mevalonic acid (**124**, MVA) and squalene (**125**) into daphniphylline was recorded in June and July. From the feeding experiments, followed by degradation studies, daphniphylline and codaphniphylline were biosynthesized from six moles of MVA (**124**) through a squalene-like intermediate (Figure 18.22). In addition, feeding experiments using the fruits of *D. teijsmanni* resulted in the incorporation of four moles of MVA (**124**) into one of the major C_{22}-type daphniphyllum alkaloids, daphnilactone B [36].

18.3.2
Biogenesis of the Daphnane and Secodaphnane Skeletons

Heathcock proposed a biosynthetic pathway to the daphniphyllum alkaloids [4,5]. The linear squalene (**125**) molecule may be traced in the pentacyclic domain of the skeleton of secodaphniphylline. To convert squalene into secodaphniphylline, four C–C bonds must be formed: C-10 to C-14; C-6 to C-15; C-3 to the C-15 methyl group; and C-7 to the C-10 methyl group. In addition, the nitrogen atom is inserted between C-7 and the C-15 methyl group. For daphniphylline, however, the nitrogen seems to have been inserted between C-10 and its methyl group, which is also connected to C-7. Thus, it is likely that secodaphniphylline precedes daphniphylline in the biosynthetic pathway, and that an unsaturated amine such as compound **126** provides a biogenetic link between the two skeletons [5] (Scheme 18.4). The hypothetical

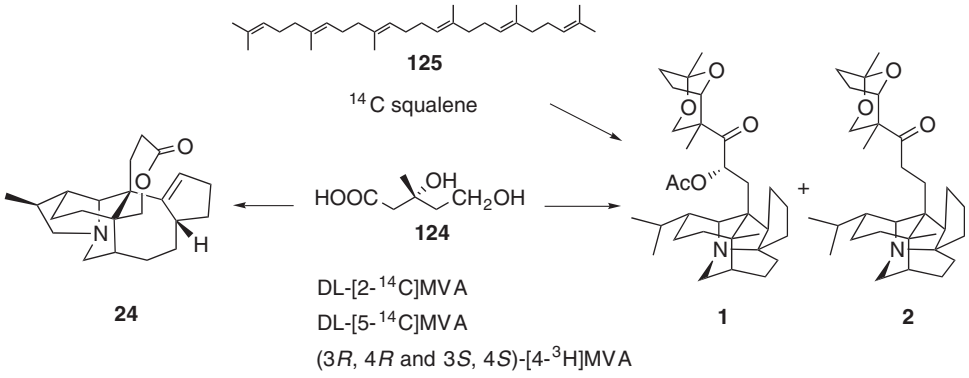
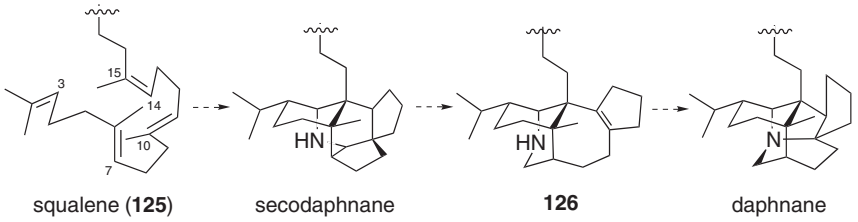


Fig. 18.22 Feeding experiments with labeled mevalonic acid (**124**) and squalene (**125**) into daphniphylline (**1**), codaphniphylline (**2**), and daphnilactone B (**24**) [62].



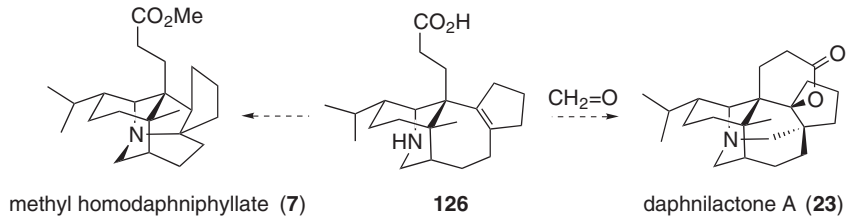
Scheme 18.4

unsaturated amine **126** also contains the bicyclo[4.4.1]undecane feature that is seen in yuzurimine, and could account for the extra carbon that is found in daphnilactone A (**23**) (Scheme 18.5).

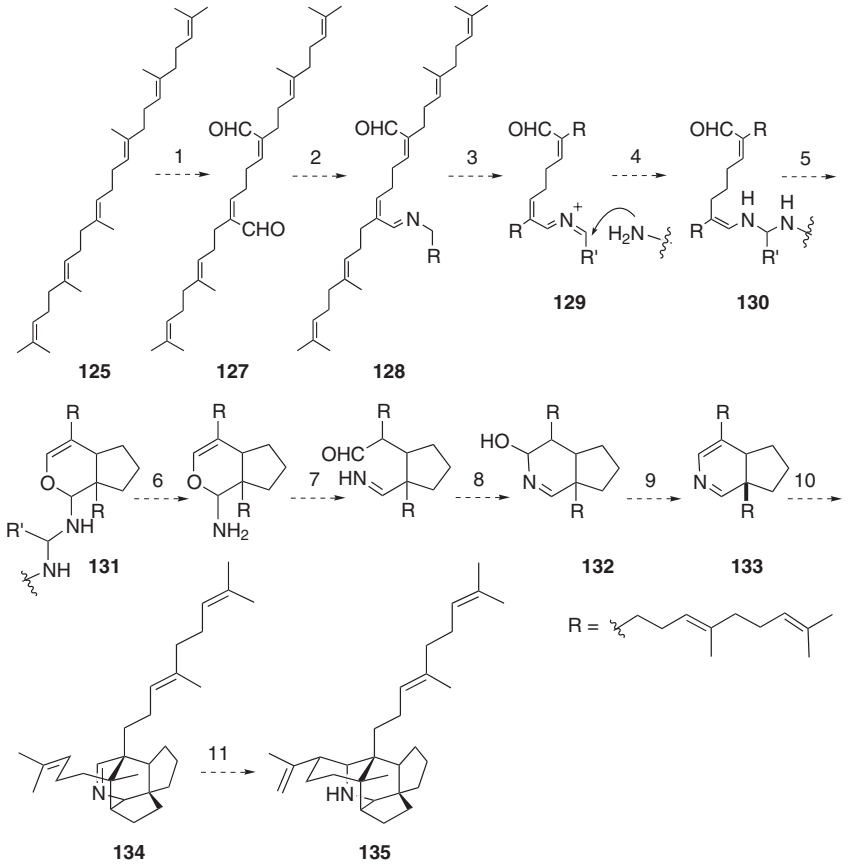
This hypothesis led to the postulation of various scenarios whereby squalene (**125**) might acquire a nitrogen atom and be transformed into the pentacyclic secodaphniphylline skeleton. The outline of this proposal is shown in Scheme 18.6. Step 1 is an oxidative transformation of squalene **125** into a dialdehyde, **127**. In step 2, it is proposed that some primary amine, perhaps pyridoxamine or an amino acid, condenses with one of the carbonyl groups of compound **127**, affording the imine **128**. Step 3 is the prototopic rearrangement of a 1-azadiene **128** to a 2-azadiene **129**. A nucleophilic species adds to the imine bond of **129** in step 4 to give the product **130**, followed by subsequent cyclization to give compound **131**. In steps 6–9, the resulting bicyclic dihydropyran derivative **131** is transformed into a dihydropyridine derivative **133** by a sequence of proton-mediated addition and elimination processes. Alkaloid **133** would then be converted into **134** by a catalyzed Diels–Alder reaction, and the final ring would result from an ene-like cyclization, giving alkaloid **135**. Because **135** is the first pentacyclic alkaloid to occur in the biogenesis of the daphniphyllum alkaloids, it was named proto-daphniphylline (**135**).

18.3.3
Biogenesis of the Daphnezomines

Daphnezomines A and B consisting of all six-membered rings are the first natural products containing an aza-adamantane core with an amino ketal bridge. A biogenetic pathway for daphnezomine B is proposed in Scheme 18.7. Daphnezomines A



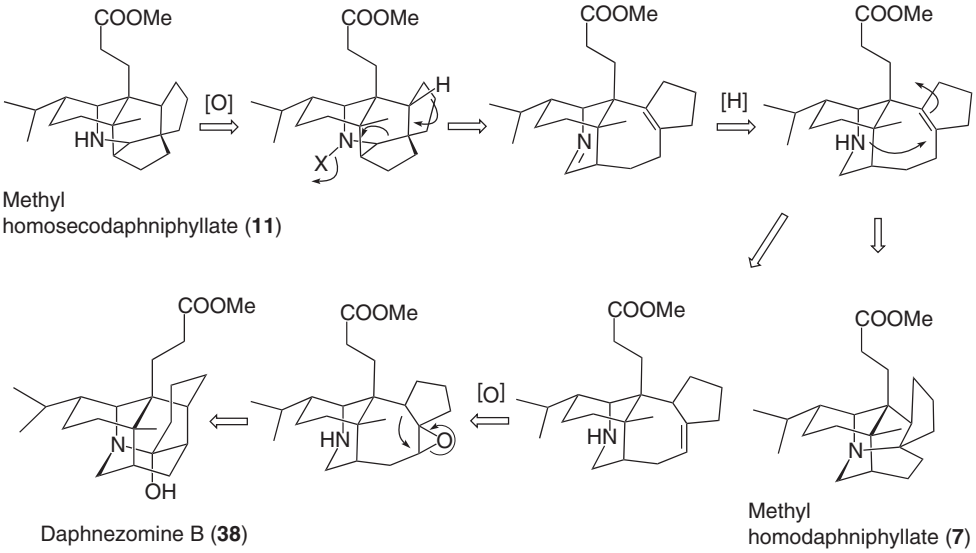
Scheme 18.5



Scheme 18.6 Biogenesis of proto-daphniphylline (**135**).

and B might be generated through ring expansion accompanying backbone rearrangement of a common fragmentation intermediate.

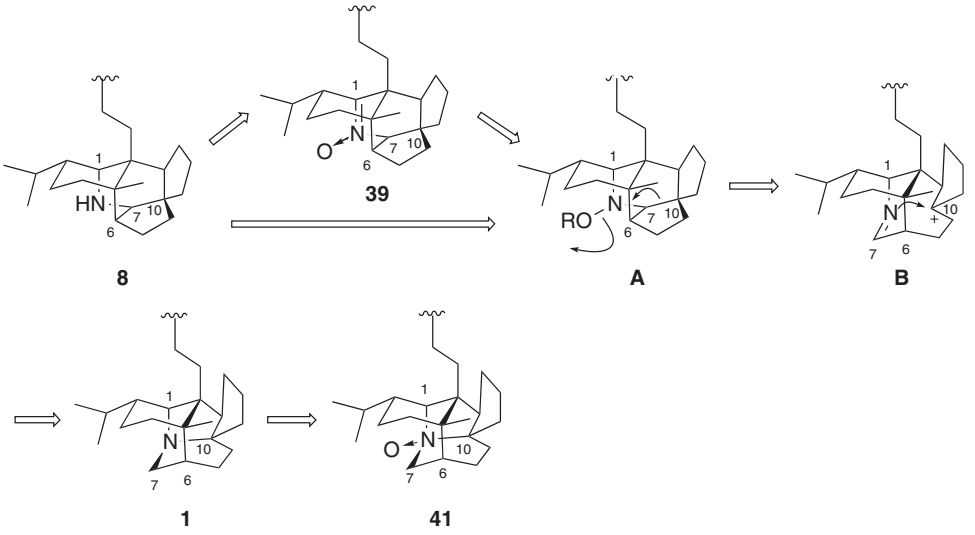
Daphnezomines C and D are the first alkaloids possessing the secodaphniphylline-type skeleton with a nitrone functionality, while daphnezomine E is the first *N*-oxide of a daphniphylline-type alkaloid, although the *N*-oxides of yuzurimine-type alkaloids have been reported [23,29]. Heathcock offered a biogenetic conversion of the secodaphniphylline-type to the daphniphylline-type skeleton, in which an initial oxidation of the secodaphniphylline-type skeleton occurs on the nitrogen atom, followed by transformation into the daphniphylline-type skeleton through a ring-opened intermediate such as **B** (Schemes 18.4 and 18.8) [4,5]. The structures of daphnezomines C and D are very similar to that of a nitrone intermediate synthesized by Heathcock *et al.*[73]. Biogenetically, the daphniphylline-type skeleton (e.g. **1**) may be generated from the secodaphniphylline-type skeleton (e.g. **8**) through N-oxidation to generate an intermediate (**A**) or a nitrone such as **39**. Cleavage of the C-7–C-10



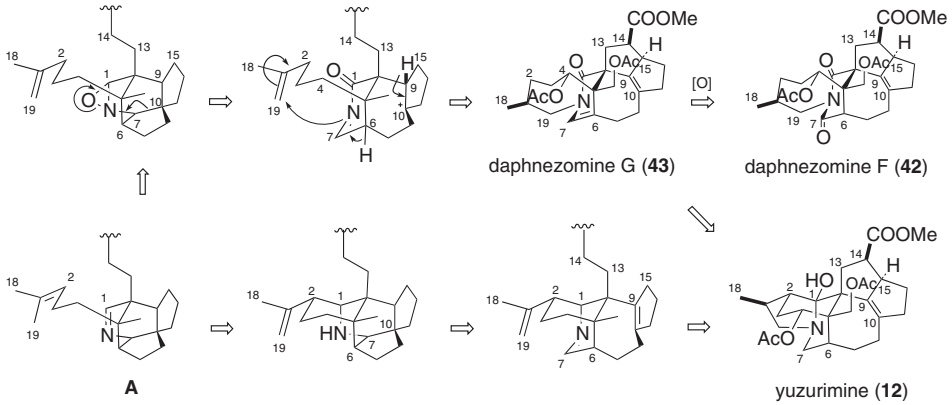
Scheme 18.7 Biogenesis of daphnezomine B (**38**).

bond, generation of a ring-opened imine intermediate (**B**), and formation of another C–N bond between N-1 and C-10, follows Heathcock's proposal (Figures 18.36 and 18.40).

The structures of daphnezomines F and G are similar to that of yuzurimine, but they lack the C-1–C-2 bond. A biogenetic pathway for daphnezomines F and G is proposed in Scheme 18.9. Daphnezomine G might be generated through oxidation



Scheme 18.8 Biogenesis of the daphniphylline skeleton of **1**.



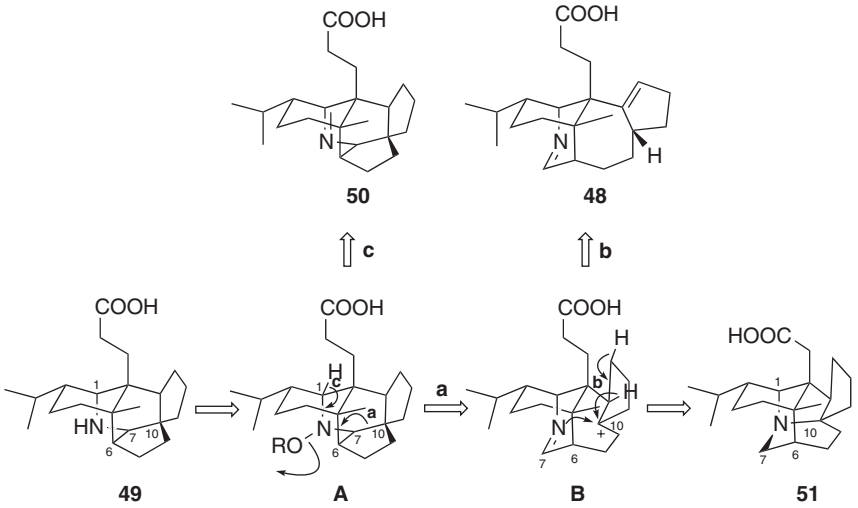
Scheme 18.9 Biogenesis of daphnezomines F (**42**) and G (**43**).

of a common imine intermediate **A** (proposed as a precursor of the secodaphniphylline-type skeleton by Heathcock *et al.*), and subsequent cleavage of the C-7–C-10 bond, followed by formation of the C-19–N-1 and C-14–C-15 bonds to give daphnezomine G. Daphnezomine F may be derived from daphnezomine G through oxidation of the C-7–C-6 bond. On the other hand, yuzurimine might be generated from the intermediate **A** through the secodaphniphylline-type skeleton, although an alternative pathway through **43** is also possible.

Biogenetically, daphnezomine I may be derived from daphnilactone B through oxidation at N-1, while daphnezomine J may be generated from yuzurimine through dehydroxylation at C-1. Daphnezomine L is structurally close to a biogenetic intermediate on the pathway from the secodaphnane to the daphnane skeleton [48]. Yamamura *et al*. suggested that a pentacyclic skeleton such as **48** is a biogenetic intermediate to the daphnane skeleton **51** [77], while Heathcock *et al*. proposed a biogenetic route from the secodaphnane to the daphnane skeletons through intermediates **A** and **B** (Scheme 18.10) [73]. Daphnezomines L and O might be biosynthesized through intermediates **A** and **B**, while daphnezomine N might be generated through intermediate **A** [48].

18.3.4
Biogenesis of the Daphnicyclidins

Daphnicyclidins A–G (**56–62**) and H (**63**) are novel alkaloids consisting of fused hexa- or pentacyclic ring systems, respectively. A biogenetic pathway for daphnicyclidins A–H is proposed in Scheme 18.11. The biogenetic origin of these alkaloids seems to be yuzurimine-type alkaloids, such as yuzurimine A and macrodaphniphyllamine, with an appropriate leaving group at C-4 and a methyl group at C-21. Rings B and C might be constructed by loss of the leaving group at C-4 followed by N-1–C-4 bond formation. Subsequently, cleavage of the C-1–C-8 bond followed by formation of the C-1–C-13 bond would result in enlargement of ring A, and aromatization of ring E to generate an intermediate **A**. Furthermore, oxidative cleavage of the C-10–C-17 bond



Scheme 18.10 Biogenesis of daphnezomines L–O (**48**–**51**).

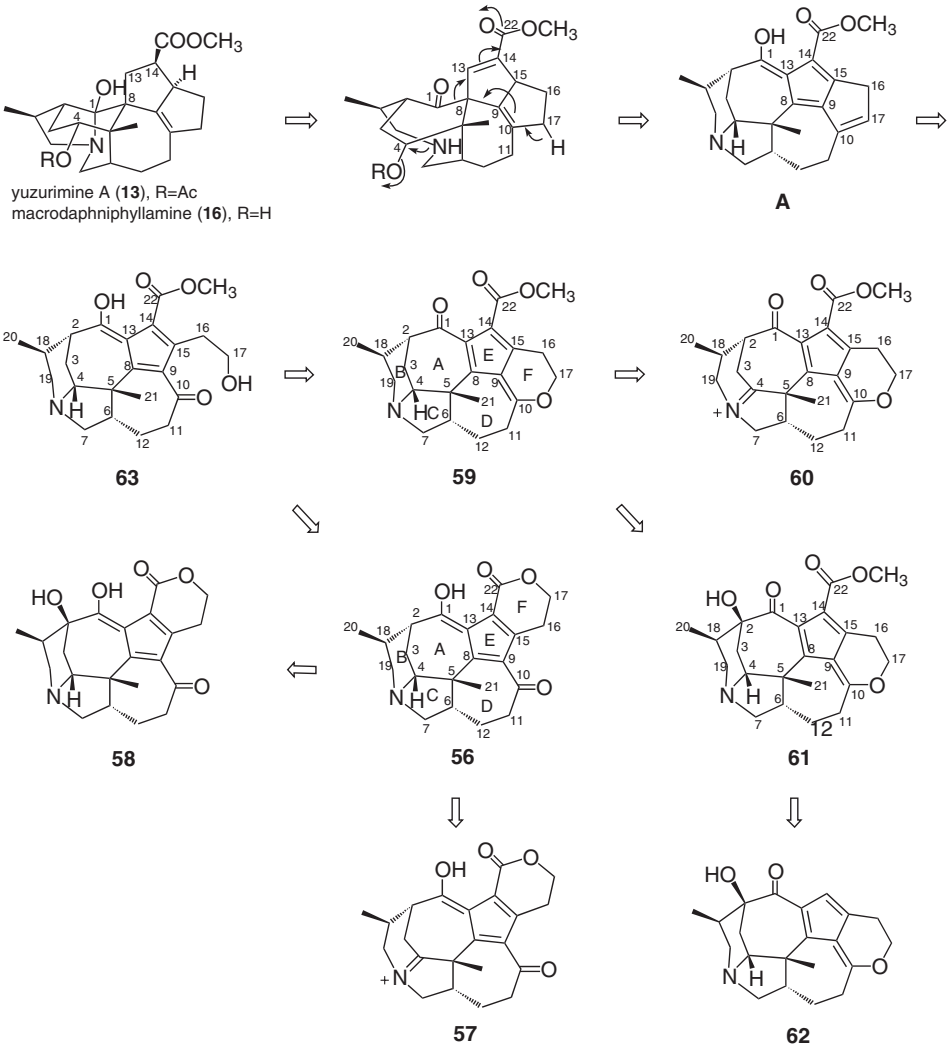
could lead to daphnicyclidin H, followed by cyclization and dehydration to produce daphnicyclidin D, which may be oxidized to give daphnicyclidins E and F. On the other hand, cyclization of the 17-OH to C-22 in **63** to form ring F would generate daphnicyclidins A, B, and C.

A biogenetic pathway for daphnicyclidins J and K is proposed in Scheme 18.12. Daphnicyclidins J and K, as well as daphnicyclidins A–H reported more recently, might be derived from the yuzurimine-type alkaloids such as yuzurimine A and macrodaphniphyllamine. Daphnicyclidin J might be generated through N-oxidation of daphnicyclidin D, while daphnicyclidin K might be derived from an imine form **60** of daphnicyclidin D through introduction of hydroxy groups at C-2 and C-4, followed by acyloin rearrangement (Scheme 18.12).

18.3.5
Biogenesis of the Daphmanidins

A biogenetic pathway for daphmanidins A and B is proposed in Scheme 18.13. Daphmanidin A might be generated from a common imine intermediate **A**, which has been proposed as a precursor of the secodaphniphylline-type skeleton **B** by Heathcock *et al.* [4,5]. Cleavage of the C-7–C-10 bond in **B** will afford an intermediate with the yuzurimine-type skeleton, such as macrodaphniphyllidine, while subsequent cleavage of the N-1–C-7 bond, followed by formation of the C-7–C-2 bond will afford daphmanidin A. On the other hand, daphmanidin B might be derived from the imine intermediate **A** through formation of the N-1–C-19 bond.

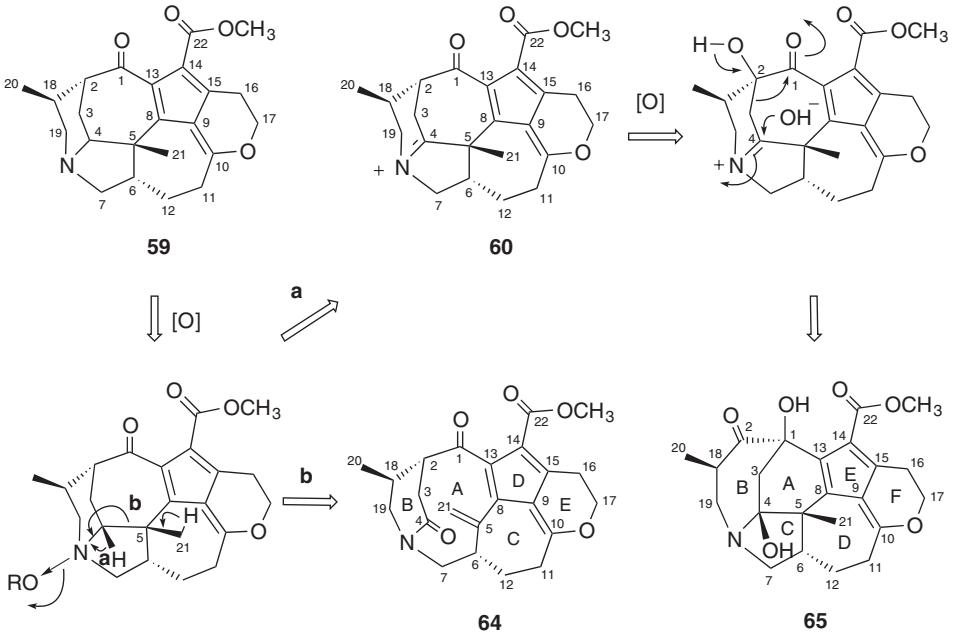
Daphmanidins C and D might be derived through oxidative C–C bond fission followed by aldol-type condensation from daphmanidin B as shown in Scheme 18.14 [79].



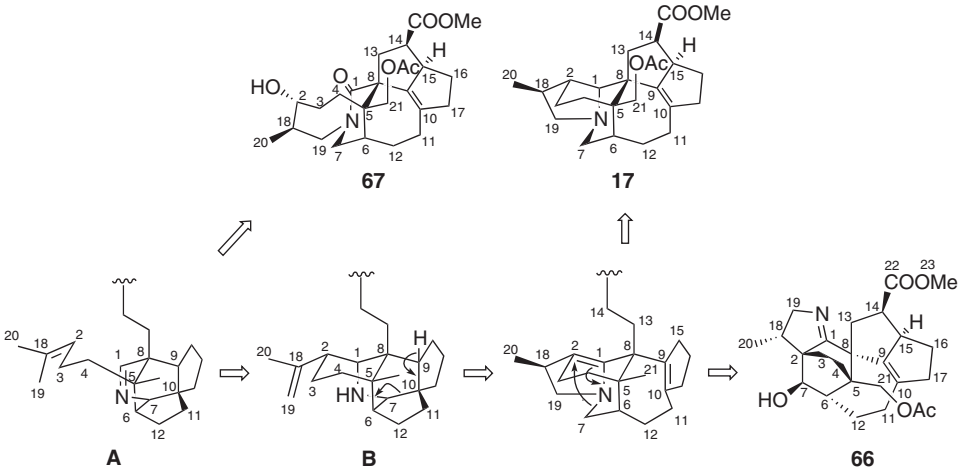
Scheme 18.11 Biogenetic pathway of daphnicyclidins A–H (**56**–**63**).

18.3.6
Biogenesis of the Daphniglaucins

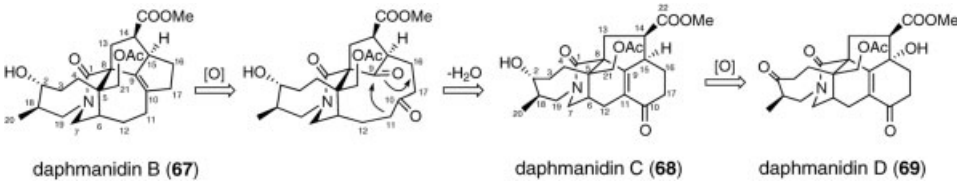
A plausible biogenetic pathway for daphniglaucins A and D is proposed as shown in Scheme 18.15 [81,83]. Daphniglaucin A might be generated from the yuzurimine-type alkaloids such as yuzurimine A and macrodaphniphyllamine through a common imine intermediate **A**, which has been proposed as a precursor of the secodaphniphylline-type skeleton **B** by Heathcock *et al*. Loss of the leaving group at C-4 by attack of the nitrogen to form the N-1–C-4 bond will give daphniglaucin A [81].



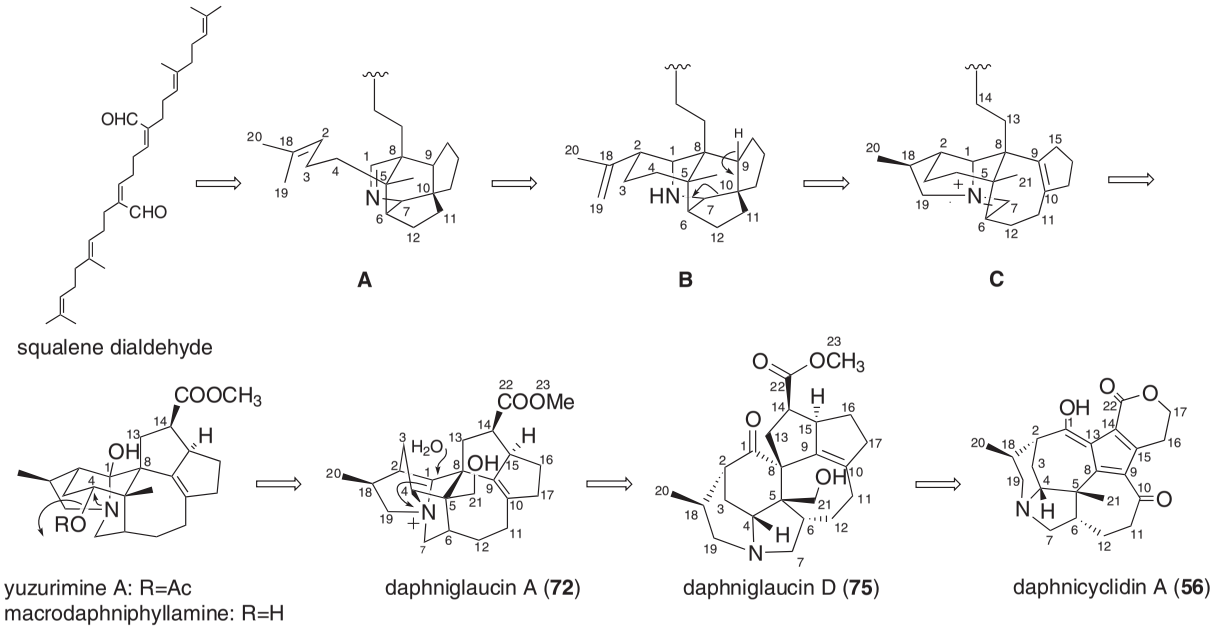
Scheme 18.12 Biogenetic pathway of daphnicyclidins J (**64**) and K (**65**).



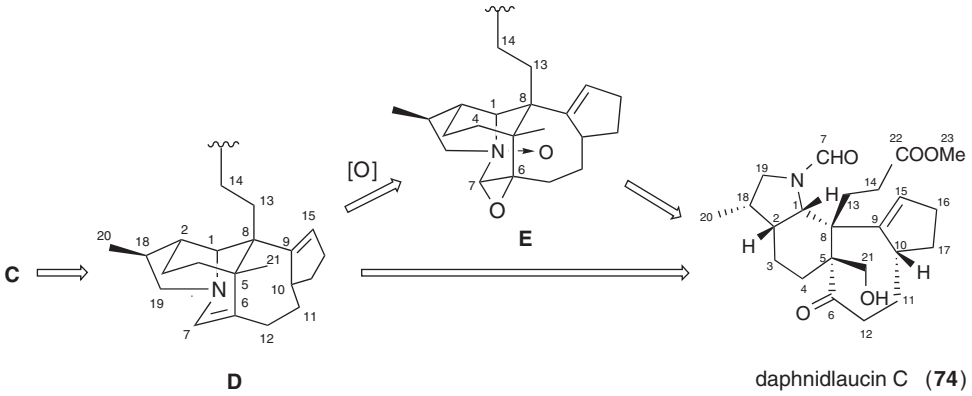
Scheme 18.13 Biogenesis of daphmanidins A (**66**) and B (**67**).



Scheme 18.14 Biogenesis of daphmanidins C (**68**) and D (**69**).



Scheme 18.15 Biogenesis of daphniglaucins A (**72**) and D (**75**).



Scheme 18.16 Biogenesis of daphniglaucin C (**74**).

Cleavage of the C-1–N-1 bond of daphniglaucin A will give the skeleton of daphniglaucin D [83]. Furthermore, daphniglaucins A and D may be biogenetically related to daphnicyclidin A.

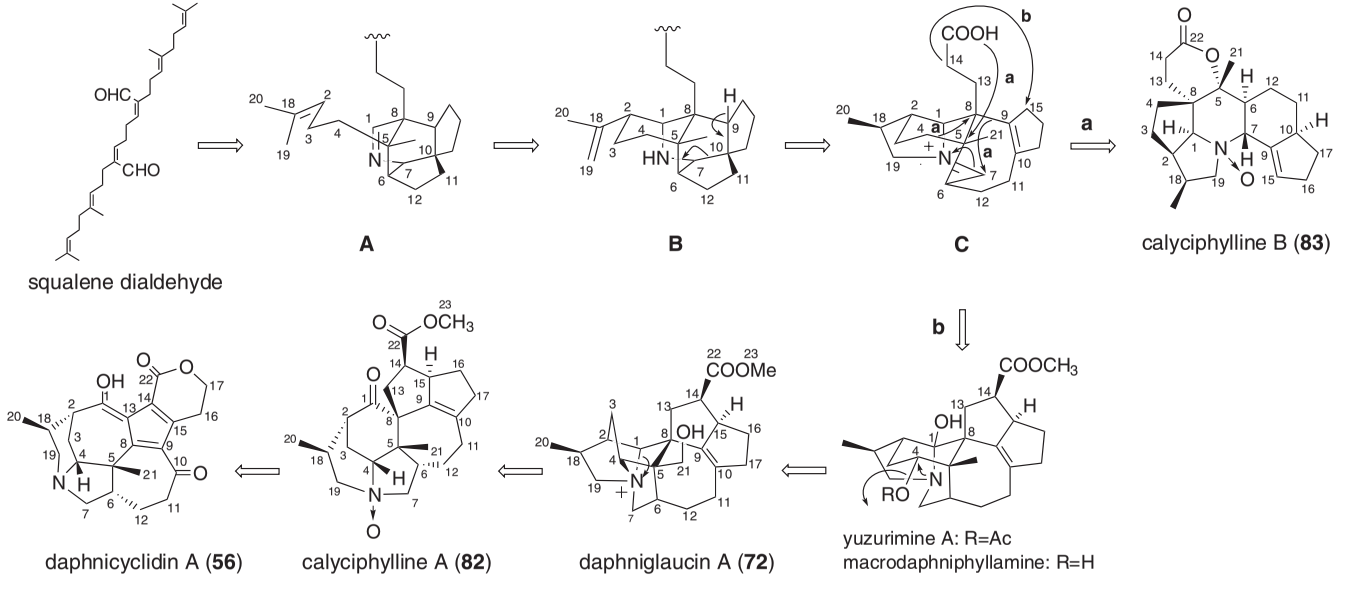
A plausible biogenetic pathway for daphniglaucin C is proposed in Scheme 18.16. The biogenetic origin of daphniglaucin C seems to be an imine intermediate **C** in Scheme 18.15. Oxidation of N-1, C-6, and C-7 of the intermediate **D** and cleavage of the C-6–C-7 bond of an intermediate **E** by Polonovski-type reaction will give the skeleton of daphniglaucin C, although an alternative path through oxidative cleavage of C-6–C-7 bond is also possible [82].

18.3.7
Biogenesis of the Calyciphyllines

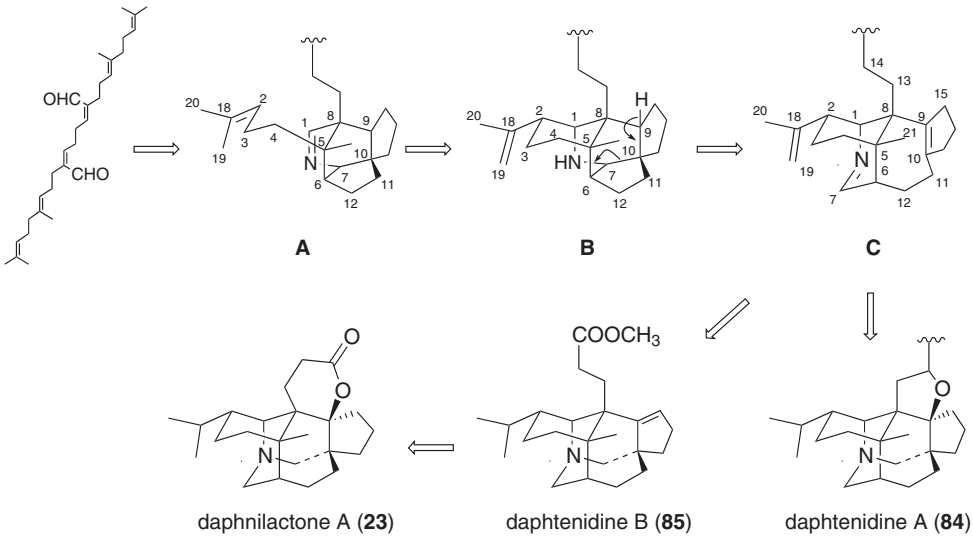
A plausible biogenetic pathway for calyciphyllines A (**82**) and B (**83**) is shown in Scheme 18.17 [84]. Calyciphylline A (**82**) might be generated from the yuzurimine-type alkaloids such as daphniglaucin D. On the other hand, the biogenetic origin of calyciphylline B (**83**) seems to be an imine intermediate **C**, which might be produced through fragmentation reaction of the secodaphniphylline-type skeleton (**B**) derived from an imine intermediate **A**. Calyciphylline B (**83**) might be generated from attack of the carbonyl group to C-5 of the intermediate **C** and cleavage of the C-4–C-5 and C-8–C-9 bonds followed by C-7–C-9 bond formation. The stereochemistry at C-6 was suggested to epimerize through enamine formation during these backbone rearrangements.

18.3.8
Biogenesis of the Daphtenidines

Biogenetically, daphtenidines A (**84**) and B (**85**) might be generated through an intermediate **C** from secodaphnane-type alkaloid **B**, followed by the formation of daphnilactone A (**23**) in Scheme 18.18 [85].



Scheme 18.17 Biogenesis of calyciphyllines A (**82**) and B (**83**).



Scheme 18.18 Biogenesis of daphtenidines A (**84**) and B (**85**).

18.4 Synthesis

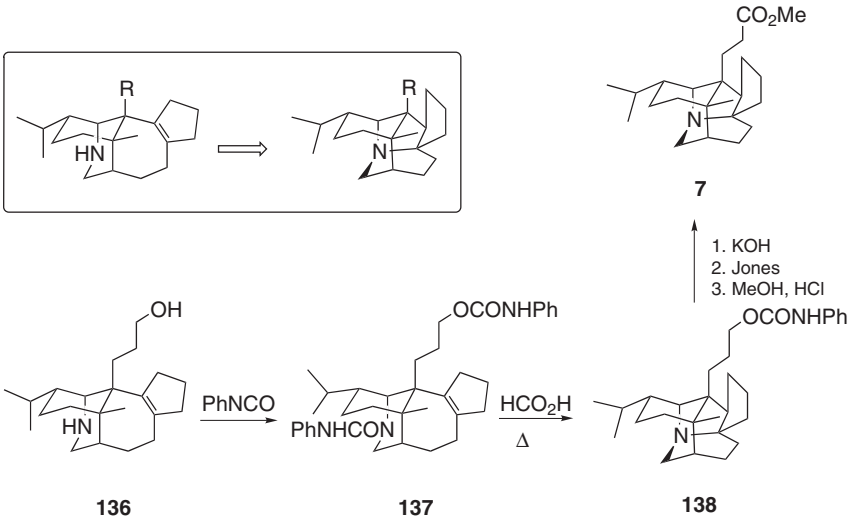
18.4.1 Biomimetic Chemical Transformations

18.4.1.1 Transformation of an Unsaturated Amine to the Daphnane Skeleton

Heathcock *et al.* suggested that the daphnane skeleton, such as methyl homodaphniphyllate, might arise by the cyclization of an unsaturated amine **136** [63]. Failure of this transformation under various acidic conditions presumably results from preferential protonation of the amine. In contrast, the bis-carbamoyl derivative **137**, obtained by treatment of the amino alcohol **136** with phenyl isocyanate, cyclizes smoothly in refluxing formic acid to provide the carbamate **138** (Scheme 18.19) [63]. The ease of cyclization of **137** raises the interesting question of whether a similar process might also be involved in the biosynthetic formation of the daphnane skeleton. The biogenetic carbamoylating agent could be carbamoyl phosphate.

18.4.1.2 Transformation of Daphnicyclidin D to Daphnicyclidins E and J

Daphnicyclidin J was obtained together with daphnicyclidin E from daphnicyclidin D through a modified Polonovski reaction [64] as shown in Scheme 18.20. Treatment of **59** with *m*-chloroperbenzoic acid (*m*-CPBA) followed by reaction with trifluoroacetic anhydride (TFAA) gave two compounds in 37 % and 18 % yields, whose spectral data were identical with those of natural daphnicyclidins E and J, respectively [50]. This result indicated that daphnicyclidin J might be generated through N-oxidation of daphnicyclidin D.



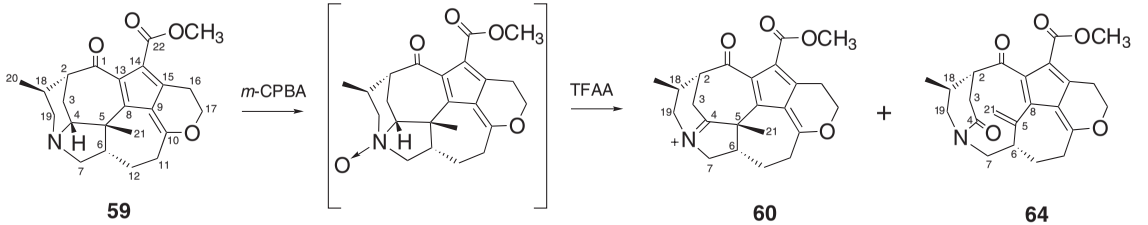
Scheme 18.19 Chemical transformation of **136** methyl homodaphniphyllate (**7**)[63].

18.4.2 Biomimetic Total Synthesis

18.4.2.1 Methyl Homosecodaphniphyllate and Protodaphniphylline

Heathcock *et al*. have embarked on a program to establish experimental methods to accomplish their proposals for the transformations of these alkaloids [4,5]. They initially focused their attention on the final stages of the polycyclization reaction leading to the secodaphniphylline skeleton [65,66]. Three simple building blocks, amide **139**, unsaturated ester **140**, and unsaturated iodide **141**, were combined in a highly convergent conjugate addition/enolate alkylation process to obtain the ester amide **142** in high yield. Straightforward methods were then employed to convert this substance into the dialdehyde **145**. Compound **145** was treated with ammonia, and then buffered acetic acid, to obtain the unsaturated amine **146** in excellent yield (64 % overall from **142** to **146**). The additional functional groups are used to convert **146** into racemic methyl homosecodaphniphyllate (**11**) [65,66].

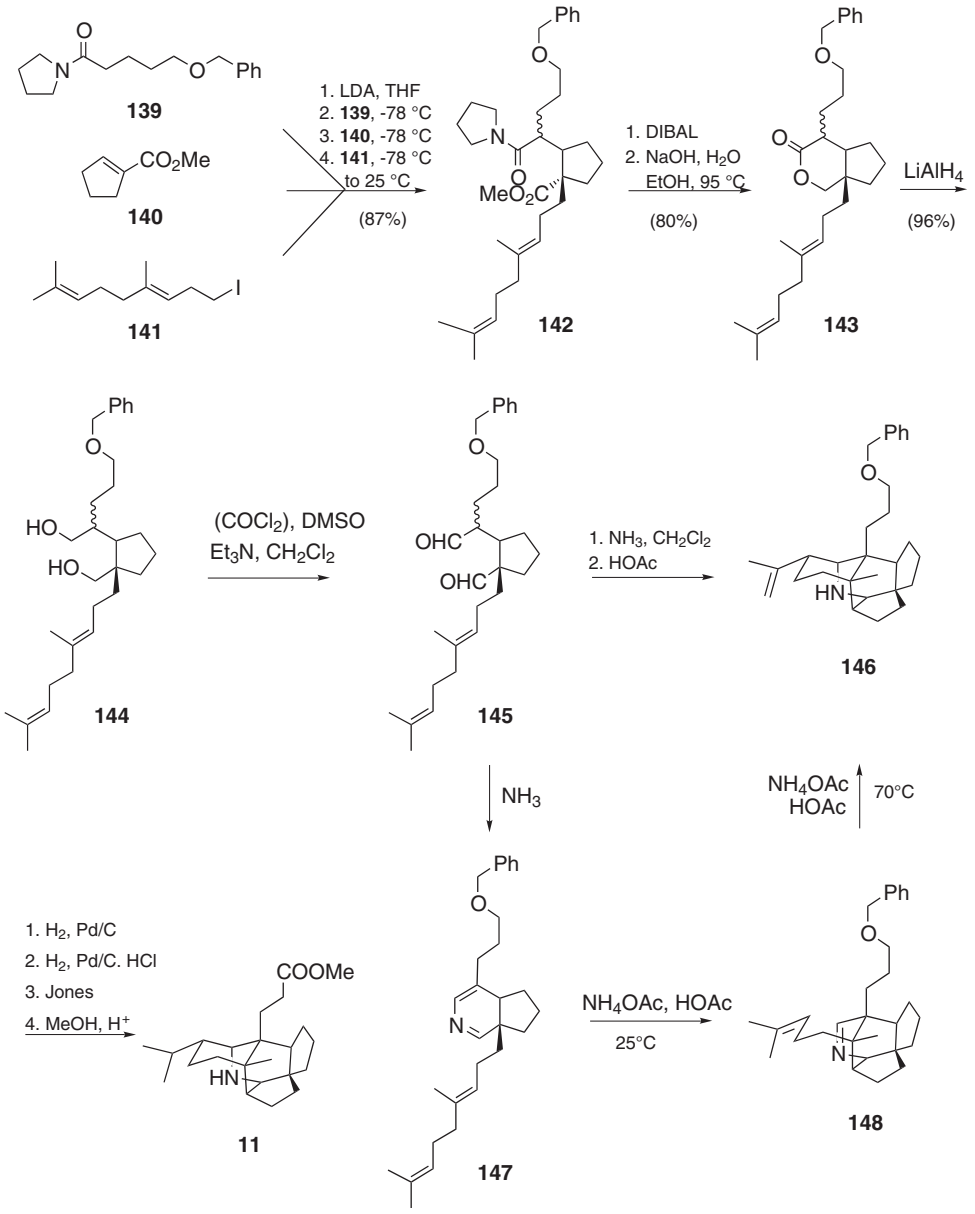
The transformation of compound **145** to **146** involves a cascade of reactions and the two intermediates can be isolated. Thus, treatment of compound **145** with ammonia causes almost instantaneous transformation of the nonpolar dialdehyde to a complex mixture of polar materials, from which the dihydropyridine **147** can be isolated in about 45 % yield. This compound reacts rapidly on being treated with ammonium acetate in acetic acid at room temperature to give compound **148**, as the result of a formal intramolecular Diels–Alder reaction. Continued treatment



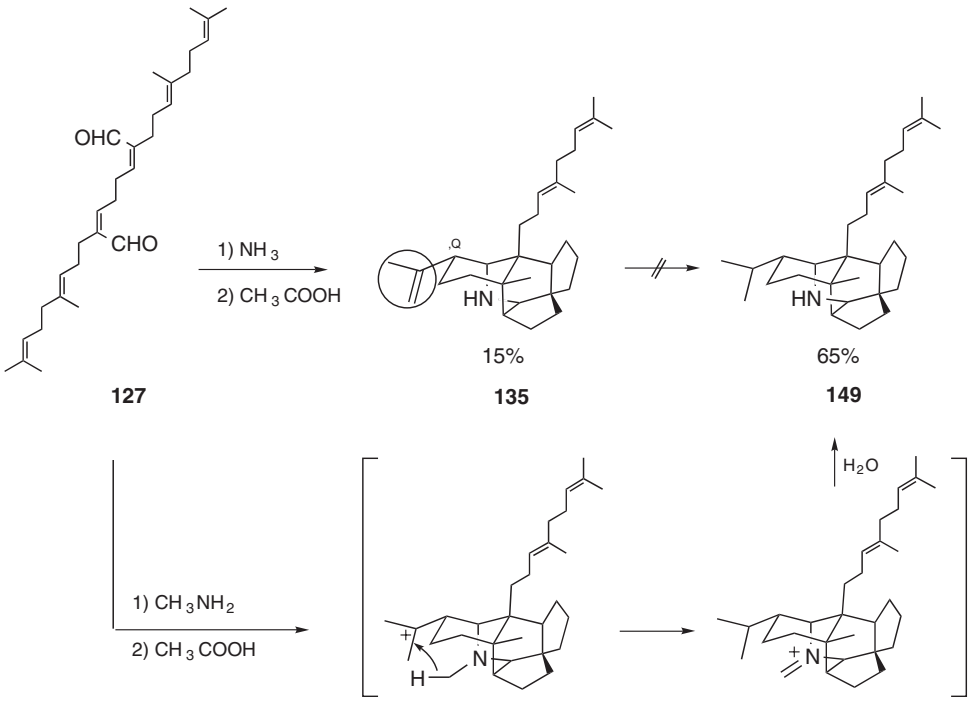
Scheme 18.20 Chemical transformation of daphnicyclidin D (**59**) to daphnicyclidins E (**60**) and J (**64**)[50].

with warm acetic acid converts compound **148** into compound **146** [65,66] (Scheme 18.21).

In addition, Heathcock and coworkers have intervened at an earlier stage in the biogenetic pathway depicted in Scheme 18.6. They prepared the dihydrosqualene



Scheme 18.21



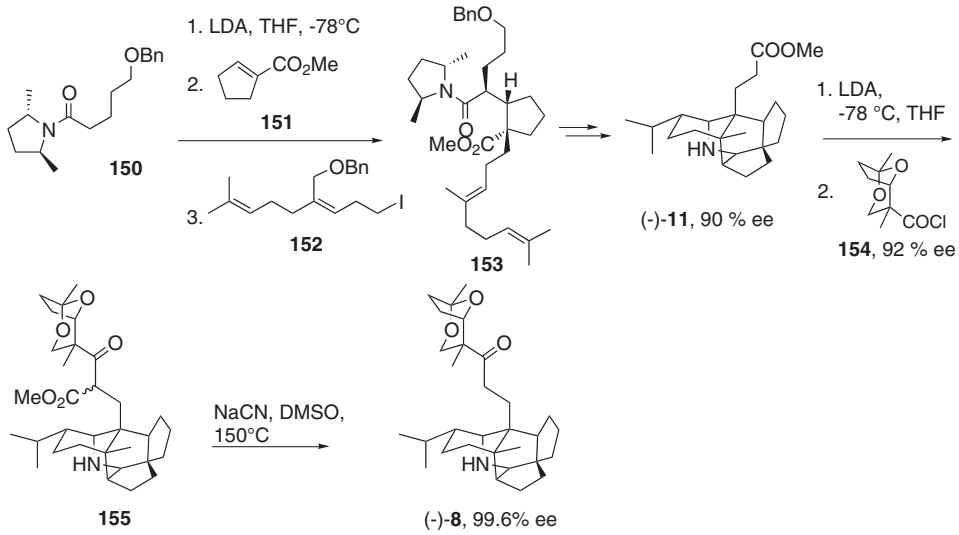
Scheme 18.22 Synthesis of dihydroprotodaphniphylline (**149**) (**79**).

dialdehyde **127** and treated it sequentially with ammonia and warm acetic acid. It was gratifying to find proto-daphniphylline **135** among the products of this reaction [67]. Although the isolation yield of **135** was only modest (15 %), a great deal has been accomplished, theoretically and practically, by the use of the simple reaction conditions. The fortuitous use of methylamine in place of ammonia suggested a possible solution to the problem of a low yield in the pentacyclization process with dihydrosqualene dialdehyde **127**. When compound **127** was treated successively with methylamine and warm acetic acid, dihydroprotodaphniphylline **149** was formed in 65 % yield (Scheme 18.22) [67].

This marvelous transformation results in the simultaneous formation of seven new sigma bonds and five rings. It is fully diastereoselective, and a necessary consequence of the reaction mechanism is that one of three similar carbon–carbon double bonds is regioselectively saturated.

18.4.2.2 **Secodaphniphylline**

An asymmetric total synthesis of (−)-secodaphniphylline was carried out using a mixed Claisen condensation between (−)-methyl homosecodaphniphyllate (**11**) and a carboxylic acid derivative **154** with the characteristic 2,8-dioxabicyclo[3.2.1]octane structure commonly found in the daphniphyllum alkaloids (Scheme 18.23) [68,69]. The necessary chirality was secured by an asymmetric Michael addition reaction of

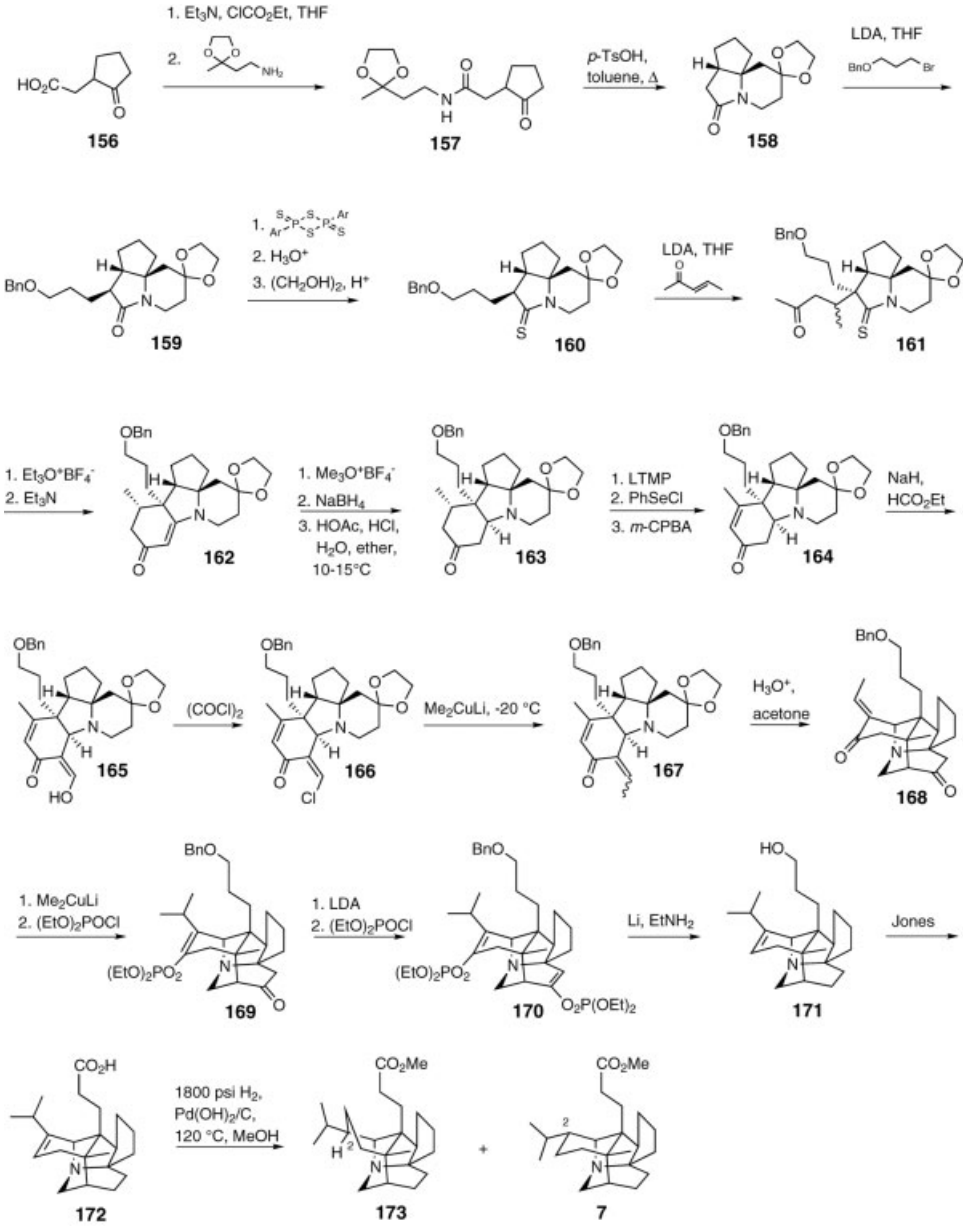


Scheme 18.23 Synthesis of (−)-secodaphniphylline (**8**) [68,69].

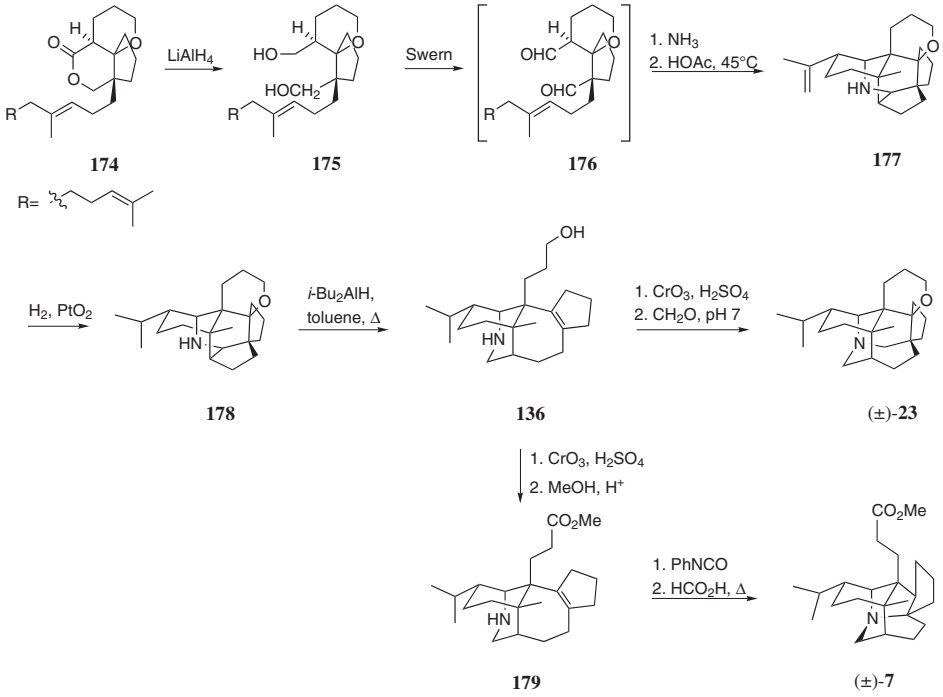
the lithium enolate of the C_2-symmetric amide **150** to the α,β-unsaturated ester **151** to give ester amide **153**. The conversion of **153** to (−)-**11** was performed by the same route as in the racemic series. Ester (−)-**11** and acid chloride **154** were joined by a mixed Claisen condensation and the resulting diastereomeric β-keto ester was demethylated and decarboxylated by treatment with NaCN in hot DMSO to obtain (−)-secodaphniphylline.

18.4.2.3 Methyl Homodaphniphyllate and Daphnilactone A

Synthetic work on the daphniphyllum alkaloids has been dominated by the versatile biomimetic synthesis developed by Heathcock and his collaborators. The first total synthesis of daphniphyllum alkaloids was achieved for methyl homodaphniphyllate (Scheme 18.24) [70,71]. The overall yield was about 1.1 %. They employed network analysis outlined by Corey and chose an intramolecular Michael reaction for the strategic bond formation, since examination of molecular models of the hypothetical intermediate showed that there are conformations in which the indicated carbon in the tetrahydropyridone ring is within easy bonding distance of the β carbon of the cyclohexenone ring. The pentacyclic intermediate **167**, synthesized from the known keto acid **156**, was treated with a mixture of HCl and H_2SO_4 in aqueous acetone for two days to give two isomers in a ratio of 3 : 1. The major isomer was in full agreement with the expected Michael cyclization product **168**. Finally, racemic methyl homodaphniphyllate was obtained by reduction of **172** with hydrogen in the presence of Pearlman's catalyst, $Pd(OH)_2$ in ethanol at 120 °C and 1800 psi hydrogen pressure for 20 h, together with its isomer **173** at C-2 in the ratio of 1 : 1.



Scheme 18.24 Synthesis of methyl homodaphniphyllate (**7**). [71]



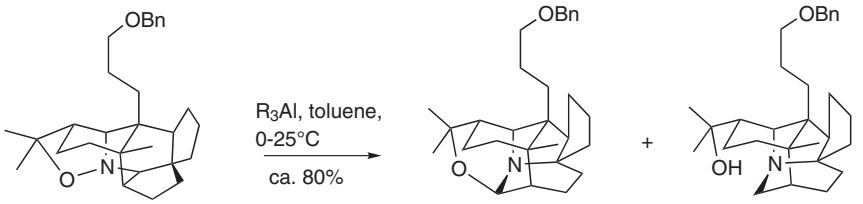
Scheme 18.25 Synthesis of (±)-methyl homodaphniphyllate (**7**) [63,72].

In addition, biomimetic total synthesis of (±)-methyl homodaphniphyllate has been carried out [63,72]. The synthesis began with the preparation of the tricyclic lactone ether **174**, which was reduced to the diol **175** with $LiAlH_4$. Oxidation of **175** gave a sensitive dialdehyde **176**, which was treated sequentially with ammonia and warm acetic acid to obtain the hexacyclic amino ether **177**. The tetracyclization process leading from **175** to **177** proceeded in 47% yield and resulted in the formation of five new sigma bonds and four new rings. Unsaturated amino alcohol **136** derived from **177** was converted into (±)-methyl homodaphniphyllate by a biomimetic process using a urea derivative as described previously. Furthermore, (±)-daphnilactone A (**23**) was synthesized from the unsaturated amino alcohol **136** by oxidation to the unsaturated amino acid, which was cyclized by treatment with aqueous formaldehyde at pH 7 [72] (Scheme 18.25).

A possibly biomimetic transformation of the secodaphnane to the daphnane skeleton with various Lewis acids has been investigated (Scheme 18.26) [73].

18.4.2.4 **Codaphniphylline**

(+)-Codaphniphylline, one of the C_{30} daphniphyllum alkaloids, was synthesized by a modification of Heathcock's biomimetic approach [74]. Modification was carried out by changing the tetrahydropyran to a tetrahydrofuran as in **189** (Scheme 18.27).



180 **181** **182**

Scheme 18.26

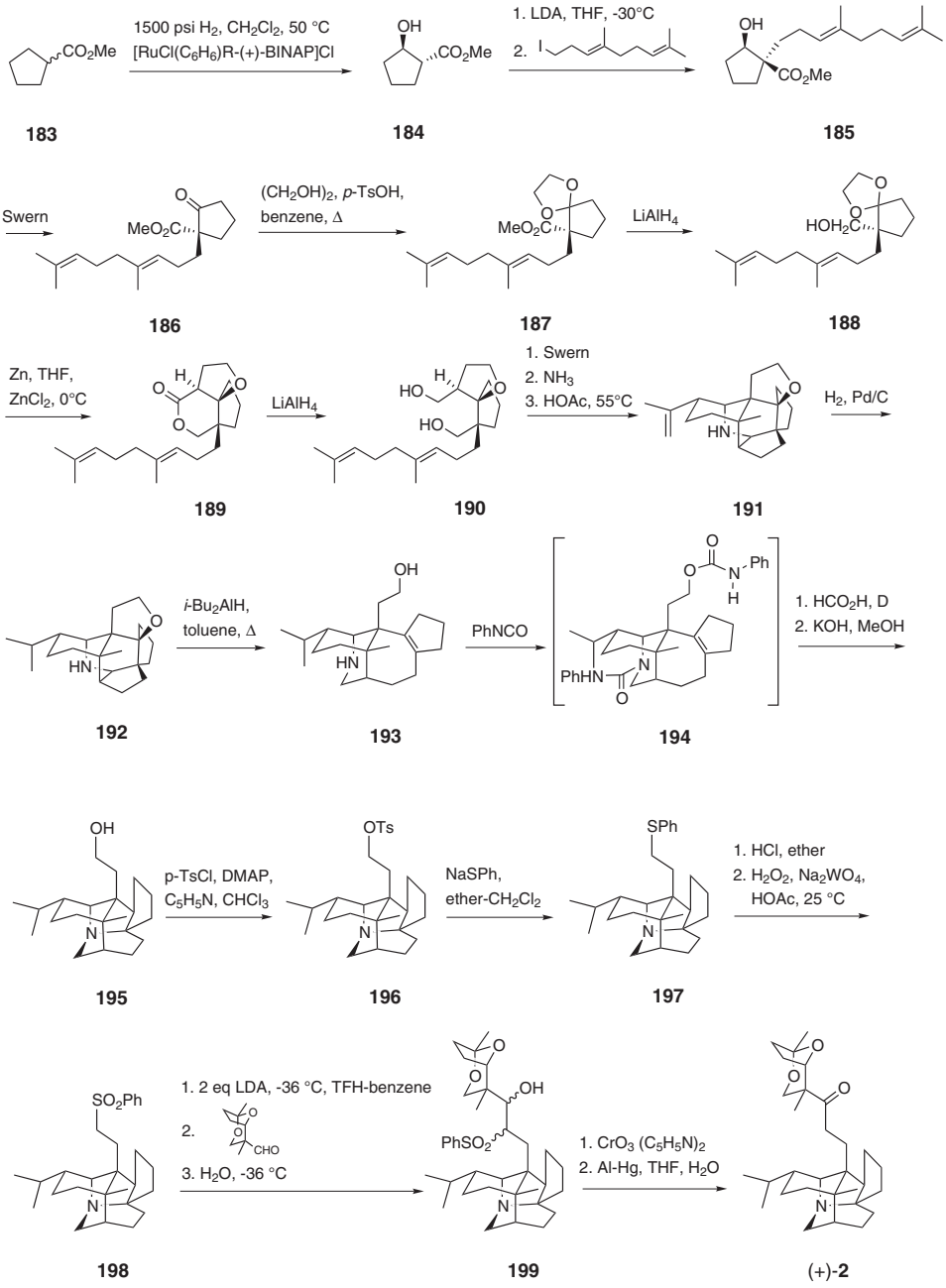
This modification resulted in a yield improvement for the pentacyclization process from 47 % to 66 %. Treatment of the amino ether **192** with diisobutylaluminum hydride in refluxing toluene accomplished Eschenmoser–Grob fragmentation and reduction of the initially formed immonium ion, to give the unsaturated amino alcohol **193** in 86 % yield. It was gratifying to find that **193** was the only product formed in this reaction. In the tetrahydropyran derivative, reduction of **192** to **193** is accompanied by about 15 % simple elimination. Displacement of the tosyl group in **196** gives sulfide **197**, which is oxidized to sulfone **198**. This material is metallated and coupled with enantiomerically pure aldehyde to secure the codaphniphylline skelton [74].

18.4.2.5 **Bukittinggine**

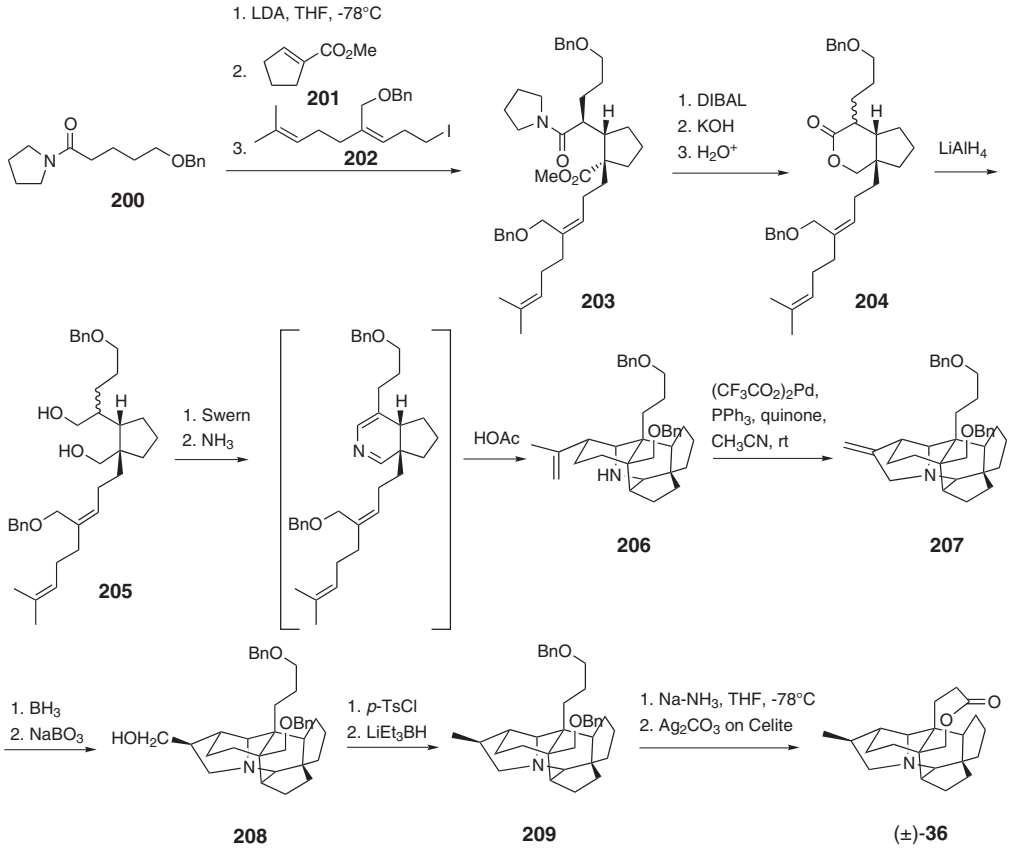
Bukittinggine possesses key structural elements of both secodaphniphylline and yuzurimine. Consequently, the biogenesis of the heptacyclic alkaloid bukittinggine, isolated from *Sapium baccatum*, may be similar to that of the daphniphyllum alkaloids. The basic secodaphnane nucleus was synthesized in one step by application of the tetracyclization process to produce dihydroxy diether **205**. The pyrrolidine ring was formed by a Pd(II)-catalyzed oxidative cyclization of **206** to give the hexacyclic amine **207**. Hydrogenation of **207** proceeded with little diastereoselectivity in establishing the final stereocenter. However, the sequence of hydroboration/oxidation, tosylation, and reduction of **207** gave **209** under excellent stereocontrol. Debenzylation of **209**, followed by regiospecific oxidative lactonization of the diol, afforded (±)-bukittinggine (Scheme 18.28) [75].

18.4.2.6 **Polycyclization Cascade**

The scope of the 2-azadiene intramolecular Diels–Alder cyclization, employed for the synthesis of the daphniphyllum alkaloids, has been further investigated by Heathcock *et al.*[76]. The protocol involves Moffatt–Swern oxidation of the 1,5-diol to the dialdehyde, and treatment of the crude methylene chloride solution with ammonia followed by solvent exchange from methylene chloride to a buffered acetic acid solution. The cyclopentyl ring, quaternary carbon and tertiary carbon centers in



Scheme 18.27 Synthesis of (+)-codaphniphylline (**2**) [74].

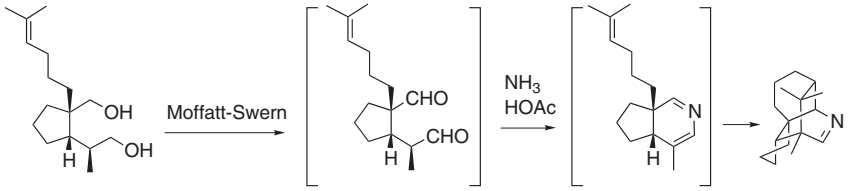


Scheme 18.28 Synthesis of (±)-bukittingine (**6**) [75].

the diol starting material all play a role in providing a selective and high-yielding cyclization (Scheme 18.29) [76].

18.5 Activities

Some daphniphyllum alkaloids, such as calyciphyllines A (**82**) and B (**83**), exhibited moderate cytotoxicity against murine lymphoma L1210 cells *in vitro* [84]. Daphniglaucin C showed inhibition of polymerization of tubulin at IC_{50} 25 mg/mL [82]. Recently, some daphniphyllum alkaloids such as daphmanidins E and F showed moderate vasorelaxant activity on rat aorta [80]. However, since the pharmacological activity of the daphniphyllum alkaloids is poorly studied, this area should be developed in future.



Scheme 18.29

18.6 Conclusions

Studies on the daphniphyllum alkaloids from 1966 to 2006 have been reviewed, with a particular focus on developments in the biomimetic synthesis of these alkaloids, and the structures of the new alkaloid types, such as daphnezomines, daphnicyclidins, daphmanidins, daphniglaucins, calyciphyllines, and daphtenidines. There are currently more than 100 daphniphyllum alkaloids of known structure. Further phytochemical investigations will bring increasing structural variation to this alkaloid group. Although the total syntheses of some of the daphnane and secodaphnane skeletons have been accomplished, the other skeletal variants remain an attractive subject. Similarly, the biosynthesis of daphniphyllum alkaloids has been only preliminarily studied, and the pathways have not been characterized with respect to the intermediates and the relevant enzymes. Widespread efforts for understanding the properties of these complex and fascinating alkaloids will result in further developments in this field.

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