Further Studies of the *Daphniphyllum* Alkaloid Polycyclization Cascade

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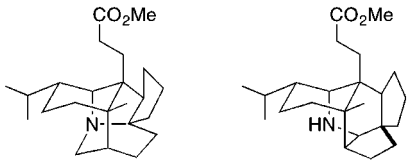
Received July 28, 2000

The scope of the 2-azadiene intramolecular Diels−Alder cyclization, previously employed for synthesis of the *Daphniphyllum* alkaloids, has been further investigated. Through a series of 1,5-diol cyclization precursors the substitution pattern of both the dienophile and the 2-azadiene were examined. From these studies it was shown that the cascade reaction is tolerant toward a variety of alkyl-substituted dienophiles. However, it was also demonstrated that this reaction is very sensitive to the substitution pattern of the 2-azadiene. Alterations made to the structure of the 2-azadiene cause either competing side reactions or complete failure of the reaction cascade.

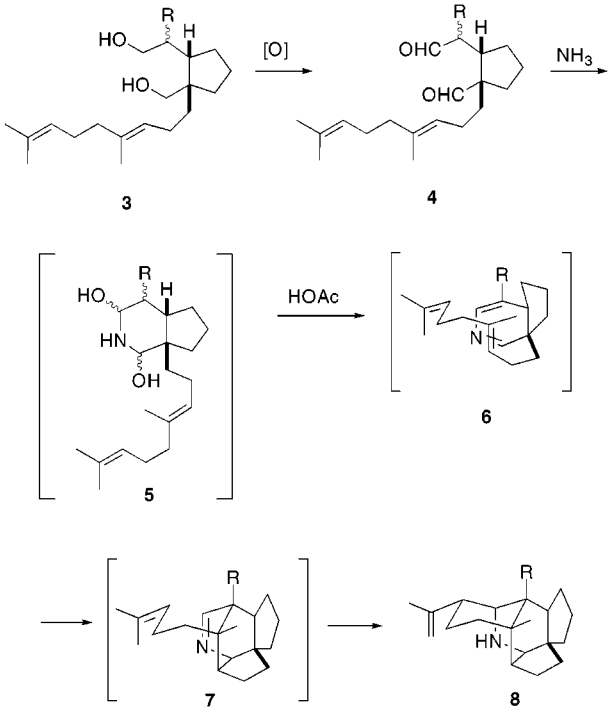
The *Daphniphyllum* alkaloids are a group of polycyclic natural products first isolated from the deciduous tree Yuzuriha (*Daphniphyllum macropodum*) in 1909.[1] Since then, over 30 *Daphniphyllum* alkaloids have been isolated and structurally characterized.[2] Methyl homodaphniphyllate (**1**) and methyl homosecodaphniphyllate (**2**) are representative members of this group of natural products and illustrate two of the pentacyclic core structures that are found.



1 **2**

During the 1980s, we developed the biomimetic approach to these alkaloids that is illustrated in Scheme 1.[3,4] This one-pot procedure begins with the oxidation of a 1,5-diol (**3**) to a dialdehyde (**4**). Treatment of the crude oxidation mixture with ammonia, followed by acetic acid and ammonium acetate, leads to the formation of an azadiene (**6**), which undergoes an intramolecular Diels−Alder cyclization to form imine **7**. Heating the acetic acid solution of imine **7** facilitates an intramolecular aza-Prins cyclization to provide pentacyclic amine **8**. This remarkable process, which forms three carbon−carbon bonds and two nitrogen−carbon bonds and establishes six stereocenters, has been used as the key step in the synthesis of five of the *Daphniphyllum* alkaloids.[3,5,6]

Scheme 1



3 **4** **5** **6** **7** **8**

In this paper, we report further studies that explore the scope and generality of the intramolecular 2-azadiene Diels−Alder cyclization.[7] By studying the cyclizations of diols **9**−**16** we hoped to examine the effect of both the

† The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as Sponsoring Member.

(1) Yagim S. *Kyoto Igaku Zasshi.* **1909**, *6*, 208.

(2) For reviews on the *Daphniphyllum* alkaloids see: (a) Yamamura, S.; Hirata, Y. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, p 41. (b) Yamamura, S.; Hirata, Y. *Int. Rev. Sci.: Org. Chem., Ser. Two* **1976**, *9*, 161. (c) Yamamura, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 29, p 265.

(3) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544.

(4) We have also reported a classical approach to these alkaloids: Heathcock, C. H.; Davidsen, S. K.; Mills, S. G.; Sanner, M. A. *J. Org. Chem.* **1992**, *57*, 2531.

(5) Heathcock, C. H.; Stafford, J. *J. Org. Chem.* **1992**, *57*, 2566.

(6) Heathcock, C. H.; Rugerri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585.

(7) For references on 2-aza dienes, see: (a) Eddaif, A.; Mison, P.; Laurent, A.; Pellissier, N.; Carrupt, P.-A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548. (b) Cheng, Y.-S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem.* **1985**, *50*, 5678. (c) Boger, D. L.; Weinreb, S. M. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987; pp 255−260. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

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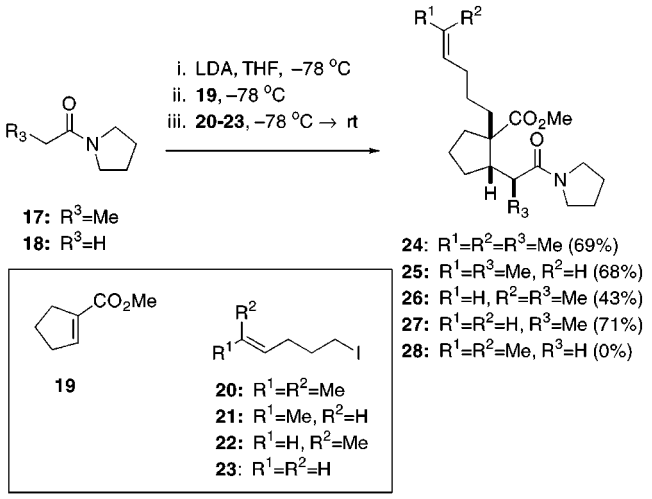
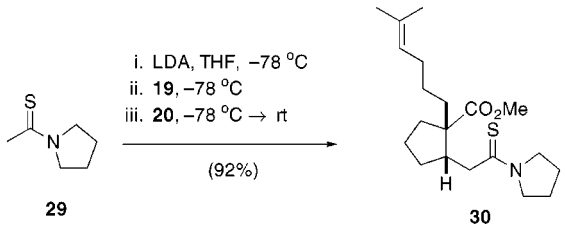
Published on Web 12/23/2000

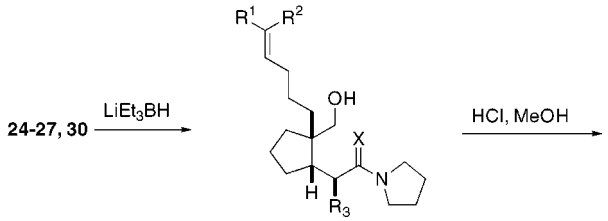
Scheme 2



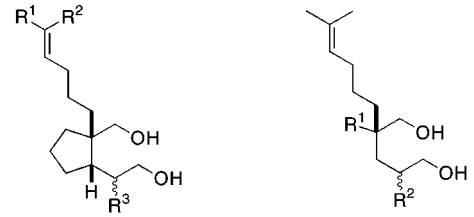
Scheme 3

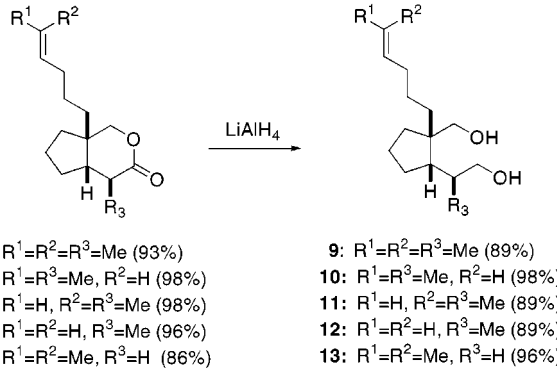


Scheme 4



substitution pattern of the 2-azadiene as well as the pendent dienophile. In addition, the dienophile tether was extended by one carbon, such that six-membered rings would be formed during the Diels−Alder cyclizations.





Results and Discussion

Synthesis of Diols 9−16. The synthesis of diols **9**−**13** began with the three-component coupling of amides **17** and **18**[8] with enoate **19**[9] and iodides **20**−**23** (Scheme 2).[6] The lithium enolate of amide **17** or **18** was treated with enoate **19**, and the corresponding Michael addition adduct was trapped with iodides **20**−**23**.[10] The desired products could be isolated in good to moderate yields in all cases except for ester-amide **28**. The stereochemical assignment of the ester-amides **24**−**27** is based on literature precedent of similar Michael reactions of amide enolates.[9,11]

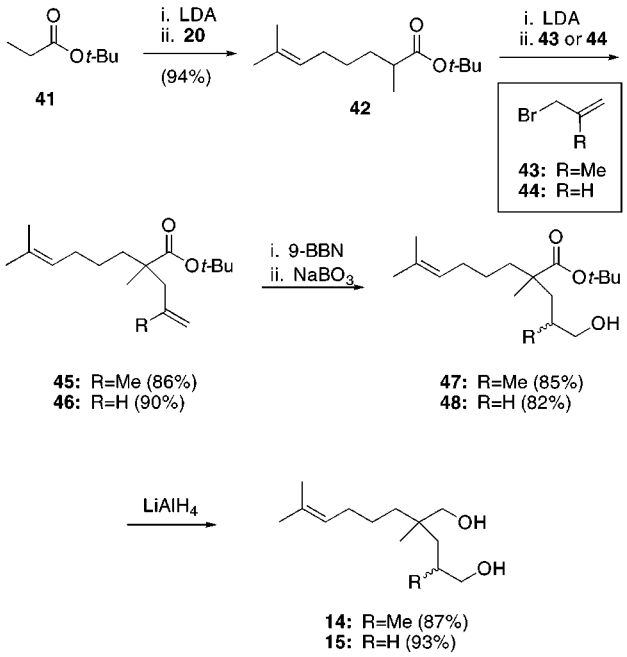
The failure to obtain ester-amide **28** by this method was not unexpected, in light of earlier work in these laboratories.[9] Although none of the desired ester-amide **28** was isolated from the reaction of the lithium enolate of **18** with enoate **19** followed by trapping with iodide **20**, products resulting from 1,2-addition were observed. However, the lithium enolate of thioamide **29**,[12] a softer nucleophile,[4,13] reacts smoothly with enoate **19**. Treatment of the resulting adduct with iodide **20** provided the desired adduct **30** in 92% yield (Scheme 3).

The conversion of amides **24**−**27** and **30** to their corresponding diols is shown in Scheme 4. Lithium triethylborohydride chemoselectively reduced the ester moiety of these substrates to provide alcohols **31**−**35** in good yields. Acid-catalyzed lactonization followed by lithium aluminum hydride reduction efficiently provided the desired diols **9**−**13**.

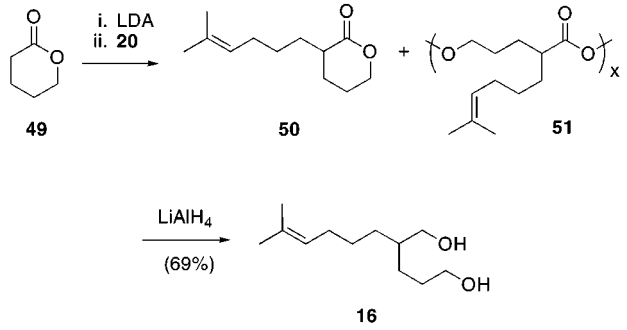
Attempts to prepare diols **14**−**16** through the three-component-coupling method described above lead to intractable mixtures of products. Rather than pursue this method, we developed the alternate approaches to these diols shown in Schemes 5 and 6. The synthesis of diols **14** and **15** began with the alkylation of the lithium enolate of *tert*-butylpropionate (**41**) with iodide **20** to provide ester **42** in high yield. Subsequent allylation of the lithium enolate of ester **42** with either 2-methylallyl bromide or allyl bromide provided esters **45** and **46**, respectively. Selective hydroboration of the terminal olefins in esters **45** and **46**, followed by oxidation lead to

(8) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132−157.
(9) Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734.
(10) Millar, J. G.; Underhill, E. W. *J. Org. Chem.* **1986**, *51*, 4726.
(11) Yamaguchi, M. *Yuki Gosei Kagaka.* **1986**, *44*, 405.
(12) (a) Oare, D. A. Doctoral Thesis, University of California at Berkeley, 1988. (b) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. O. *Org. Synth.* **1984**, *62*, 158.
(13) (a) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581, 643. (b) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (c) Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1973**, *14*, 527.

Scheme 5



Scheme 6



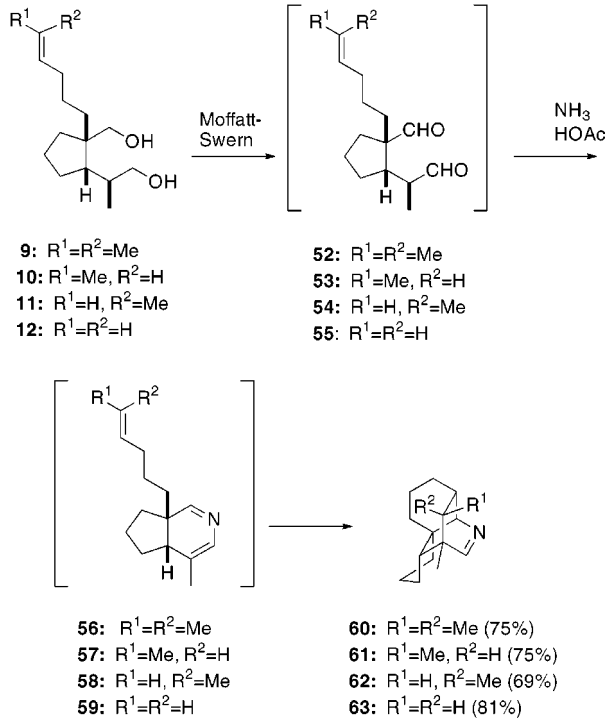
the primary alcohols **47** and **48**. Reduction of the ester function in **47** and **48** gave access to the desired diols **14** and **15**.

The synthesis of diol **16** was carried out in two steps as shown in Scheme 6. Alkylation of the lithium enolate of *δ*-valerolactone with iodide **20** provided lactone **50** in low and variable yields (25−50%). We believe that ring-opening of the lactone **50** and oligomerization to polyester **51** was responsible for the low and variable yields of **50**. Support for this hypothesis came from the observation that reduction of the crude reaction mixture with LAH provided the desired diol **16** in a reproducible 69% yield.

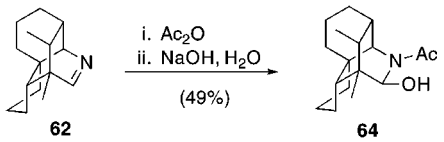
Exploration of the Azadiene Diels−Alder Cylization. With diols **9**−**16** in hand, we were prepared to commence with our studies of the scope and generality of the *Daphniphyllum* alkaloid azadiene Diels−Alder cyclization. From the onset of this project, we planned to use the biomimetic reaction protocol developed during the *Daphniphyllum* alkaloid synthesis, rather than attempting to optimize the reaction conditions for each substrate. This protocol involves Moffatt−Swern[14] oxidation of the 1,5-diol to the dialdehyde, treatment of the crude methylene chloride solution with ammonia followed by solvent exchange from methylene chloride to a buffered acetic acid solution. Following an aqueous workup,

(14) Mancusco, A. J.; Swern, D. *Synthesis* **1981**, 165.

Scheme 7



Scheme 8



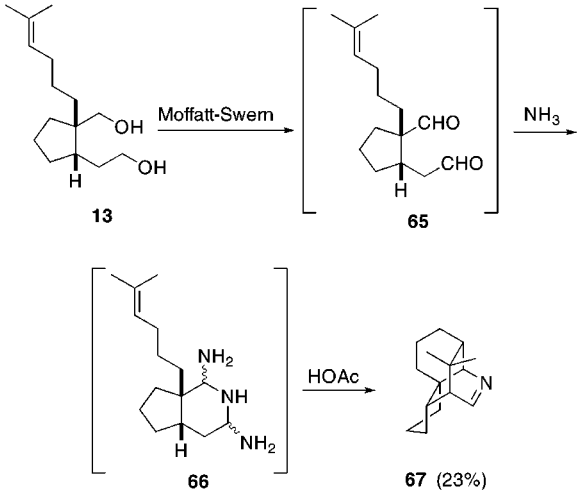
the imine products were isolated by column chromatography on silica gel. The cyclization sequences of diols **9**−**12** are shown in Scheme 7.

Oxidation of diols **9**−**12** led smoothly to the 1,5-dialdehydes **52**−**55**. These delicate molecules can be observed in the crude form by ^{1}H NMR, following an aqueous workup of the Moffatt−Swern oxidation. However, as noted above, the reaction mixtures were more routinely treated directly with ammonia, followed by solvent exchange to acetic acid. Following an aqueous workup, imines **60**−**63** were isolated in yields ranging from 69 to 81% by column chromatography on silica gel that had been pretreated with triethylamine. The structures of imines **60**−**63** were determined through ^{1}H NMR, ^{13}C NMR, ^{13}C DEPT, IR, and elemental analysis. In addition to the spectral and analytical evidence that supported the assigned structures of tetracyclic imines **60**−**63**, the structure of **62** was further confirmed by conversion into derivative **64**, the structure of which was rigorously determined by X-ray crystallography (Scheme 8).[15]

In the course of performing the cyclizations of diols **9**−**12**, we noted a definite trend in the reaction rates of these substrates (imines **60** and **61** can be formed at room temperature, whereas imines **62** and **63** require heating at 80 °C). Qualitatively, the rates of these azadiene

(15) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 147538. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Scheme 9

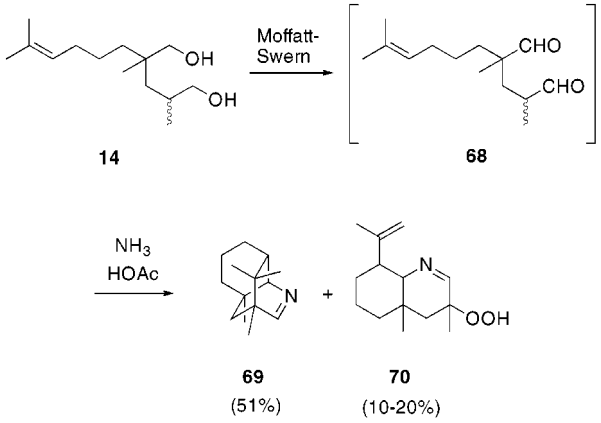


13 **65** **66** **67** (23%)

cyclizations follow the order **56** > **57** > **58** > **59**. This observation supports a rate-limiting inverse-electron-demand Diels–Alder reaction mechanism in which the more electron-rich dienophiles provide faster reaction rates. However, it was also noted that azadiene **57** cyclizes at a faster rate than azadiene **58**, even though both substrates have disubstituted dienophiles. We believe the steric congestion associated with cyclizing the *Z*-olefin of azadiene **58** is the cause of this marked decrease in reaction rate. In addition, it was noted that the olefin geometry of diols **10** and **11** is conserved during the reaction providing imines **61** and **62** respectively, further supporting a concerted mechanism for the Diels–Alder step of the cascade. These experiments also demonstrate that the cascade cyclization works well when the tether length is such that a six-membered ring is formed (the examples previously demonstrated in our *Daphniphyllum* alkaloid syntheses all give rise to five-membered rings). These cyclizations also show that the cascade succeeds with substrates having various alkyl substitution patterns on the dienophile, ranging from mono- to trisubstituted. At this point we turned our attention to the structure of the aza-diene intermediate.

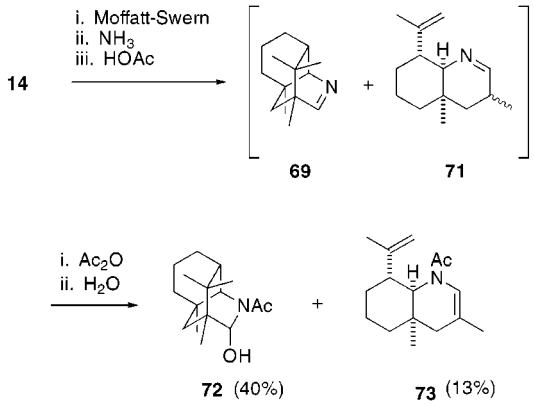
The cyclization sequence of diol **13** is shown in Scheme 9. Treatment of diol **13** under the standard cyclization conditions provided imine **67** in a rather disappointing 23% yield. This was intriguing because the only difference between diol **13** and previous diols is the methyl stereocenter alpha to one of the aldehydes. At this point attempts were then made to determine at which stage the reaction cascade was faltering. Oxidation of diol **13** under Moffatt-Swern conditions followed by an aqueous work up provided the crude 1,5-dialdehyde **65**, verifying the efficiency of this step of the cascade. Repeating the cyclization protocol and stopping after treatment of dialdehyde **65** with ammonia provided a complex mixture of products that has been assigned as the various bisaminal and bishemiaminal structural isomers related to compound **66**. Treatment of this mixture with acetic acid and ammonium acetate again provided imine **67** in low yield, along with intractable polymeric material. To check the stability of imine **67** to the reaction conditions it was taken up in D-4 acetic acid and heated for 50 h at 80 °C, at which time there was no sign of decomposition as judged by ^{1}H NMR. From these data we believe inefficient azadiene formation is responsible for the low yield in the cyclization of diol **13**.

Scheme 10



14 **68** **69** (51%) **70** (10-20%)

Scheme 11



69 **71** **72** (40%) **73** (13%)

We next turned our attention to the cyclization of diols **14**–**16**, in which the five-membered ring of diols **9**–**13** is absent. Treatment of diol **14** under the standard cyclization conditions provided the desired tricyclic imine **69** in 51% yield along with bicyclic imine-hydroperoxide **70** in 10–20% yield (Scheme 10). The structure of imine-hydroperoxide **70** was tentatively assigned on the basis of ^{1}H NMR, IR, and mass spectroscopy. This compound was very sensitive; partially decomposing when exposed to silica gel chromatography as well as on storage at 0 °C under a nitrogen atmosphere. We believe that imine-hydroperoxide **70** arises from autoxidation of the corresponding imine on exposure to air during the workup of the reaction.[16] This cyclization was particularly interesting because we had not previously been able to isolate and identify any side products from the reaction cascade.

Because of the sensitive nature of imine-hydroperoxide **70** we decided to modify the cyclization protocol in order to produce a more stable product. Attempts to treat **70** with reducing agents such as trimethyl phosphite or triphenylphosphine in order to reduce the peroxide moiety were unsuccessful, resulting in either no reaction or decomposition of the starting material. Based on these results, we decided to investigate the alternative approach shown in Scheme 11. The idea was that it may be possible to intercept the precursor to **70** by acylation of the imine nitrogen,[17] thus producing an enamide that would be less prone to autoxidation. In the event, treatment of the crude cyclization reaction mixture with

(16) Kleinman, E. F. Doctoral Thesis, University of California at Berkeley, 1980.

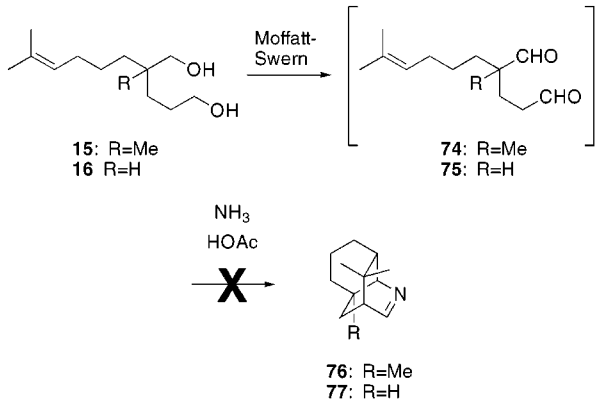
(17) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, *6*, 1173–1182.

an excess of acetic anhydride provided a mixture of amides **72** (40%) and **73** (13%). As expected, enamide **73** was not prone to autoxidation and was fully characterized. The relative stereochemistry of **73** was established by 1D and 2D (NOESY) ^{1}H NMR spectroscopy. In addition, amide **72** is a crystalline solid and its structure was unambiguously determined by X-ray crystallography.[18]

With the structures of **72** and **73** firmly established we considered the factors governing their competing formation. Initial experiments were performed to determine whether imines **69** and **71** can be interconverted. Because imine **69** was isolable it was easily resubjected to the reaction conditions and shown to be stable. As noted above, imine **71** was not easily isolable. To circumvent this difficulty the cyclization reaction was carried out for various times and the ratio of amides **72** and **73** was measured. Extending the reaction time had little effect on either the yield or ratio of amides **72** and **73**. From these data we conclude that imines **69** and **71** are both kinetic products of this reaction. Interestingly, removal of the five-membered ring of diol **9** generates a system in which the aza-Diels−Alder cyclization is only slightly more favorable than the aza-Prins cyclization. Through our efforts it has been possible to observe the 1,5-dialdehyde **68**, but we have been unable to observe the corresponding azadiene intermediate in this reaction. Therefore, it is presently unclear at which point in the cyclization cascade the paths leading to imines **69** and **71** diverge.

We also attempted the cascade cyclization with diols **15** and **16** (Scheme 12). Both of these substrates failed to produce any tractable products. This was not unexpected based on the results gained from diol **13**. Again, aldehydes **74** and **75** could be observed in their crude form, confirming the efficiency of the oxidation step in the cascade reaction. As previously discussed, we believe

Scheme 12



that inefficient aza-diene formation is responsible for the failure of these reactions.

Conclusion

From the above studies we have been able to expand the scope of the *Daphniphyllum* alkaloids cyclization, while defining some of the limitations of this cascade reaction. The cyclization is very permissive to various alkyl substitution patterns of the dienophile, but a marked decrease in rate is noted when relatively electron deficient dienophiles are employed. In addition, it has been demonstrated that the structure of the 2-azadiene is crucial. The cyclopentyl ring, quaternary carbon and tertiary carbon centers in the diol starting material all play a role in providing a selective and high-yielding cyclization.

Acknowledgment. This work was supported by a research grant from the United States Public Health Service Institute of General Medical Studies (GM46057). We are also grateful to Elf Atochem for a predoctoral fellowship supporting G.A.W.

Supporting Information Available: Experimental procedures and characterization for all new compounds reported in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001145R

(18) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 147539. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).