JOC Article

Synthesis of C-17-Functionalized Spongiane Diterpenes: Diastereoselective Synthesis of (−)-Spongian-16-oxo-17-al, (−)-Acetyldendrillol-1, and (−)-Aplyroseol-14

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The diastereoselective synthesis of spongiane diterpenes (−)-spongian-16-oxo-17-al **2**, (−)-acetyldendrillol-1 **15**, and (−)-aplyroseol-14 **16** has been completed efficiently via the common intermediate **14**. Compound **14** was prepared in five synthetic steps from (+)-podocarp-8(14)-en-13-one **13**, easily available from commercial (−)-abietic acid. The key steps in the syntheses were a regioselective reduction of a 1,4-dialdehyde unit, a one-pot acetalization−acetylation, and a translactonization. The synthesis of **15** and **16** has led us to a revision of the configuration at C-17 for natural (−)-acetyldendrillol-1 and a structural reassignment for aplyroseol-14. Thus, aplyroseol-14 **16** presents an unprecedented δ-lactone-based structure for spongiane-type diterpenoids. A theoretical study including a series of ab initio calculations for the mechanism involved in the conversion of ester **22** into natural product **2** has also been carried out.

Introduction

Sponges face a variety of dangers in their environment but have very few predators. This is due to the production of allelochemicals that deter feeding and also kill off any attacking microorganism. Additionally, they are one of the richest marine sources of novel bioactive products with ecological and biomedical importance.[1] A family of sea slugs named *nudibranchia* is particularly interesting since many of its members are able to sequester secondary metabolites from sea fans and sponges through ingestion.[2] By using the concentrated toxins taken from the sponges, nudibranchs acquire the same protection. These discoveries led to the investigation of the "chemical defense" and its mechanism in vivo.[3]

Among the numerous bioactive substances isolated from sponges and nudibranchs,[1] the spongiane family[4,5] comprises a group of tetracyclic and pentacyclic metabolites characterized by the carbon framework (**1**), named the spongiane skeleton. Since they were discovered in 1974 by Minale and co-workers,[6] these compounds have attracted the interest of synthetic organic chemists and biologists because of the wide spectrum of biological activities. These include antifungal, antimicrobial, antifeedant, antiviral, and antitumor properties, as well as PLA_2 inhibition.[7] To date, there are around seventy known members of this family, which mainly differ in the extent of oxidation at C-17 and C-19 and the oxidation pattern on rings A−D.[8] Most of them possess a γ-lactone[9] (**2**−**4**) or furan ring D[5a] (**5** and **6**), but there are also examples where the D-ring system contains an anhydride,[10] a lactol,[5d,9] and even two acetylated hemiacetals (**7**−**9**).[7d,11] Another interesting subgroup of spongianes presents an extra furan ring E (**10**−**12**).[9]

During the past two decades, several syntheses of compounds with the spongiane carbon framework have been reported starting from manool,[12] methyl isocopalate,[13] labda-8(20),13,dien-15-oic acid,[14] and furfuryl al-

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49; **2002**, *19*, 1−48 and previous reviews in this series.

(2) (a) Proksch, P. *Toxicon* **1994**, *32*, 639. (b) Marin, A.; Lopez Belluga, M. D.; Scognamiglio, G.; Cimino, G. *J. Mollus. Stud.* **1997**, *63*, 431.

(3) Pawlik, J. R. *Chem. Rev.* **1993**, *93*, 1911.

(4) Connolly, J. D.; Hill, R. A. In *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 2, pp 895−899.

(5) For recent isolations of spongianes, see: (a) Fontana, A.; Mollo, E.; Ricciardi, D.; Fakhr, I.; Cimino, G. *J. Nat. Prod.* **1997**, *60*, 444. (b) McPhail, K.; Davies-Coleman, M. T. *Tetrahedron* **1997**, *53*, 4655. (c) Li, C.-J.; Schmitz, F. J.; Kelly-Borges, M. *J. Nat. Prod.* **1998**, *61*, 546. (d) Li, C.-J.; Schmitz, F. J.; Kelly-Borges, M. *J. Nat. Prod.* **1999**, *62*, 287. (e) Hyosu, M.; Kimura, J. *J. Nat. Prod.* **2000**, *63*, 422.

(6) Cimino, G.; De Rosa, D.; De Stefano, S.; Minale, L. *Tetrahedron* **1974**, *30*, 645.

(7) (a) Capelle, N.; Braekman, J. C.; Daloze, D.; Tursch, B. *Bull. Soc. Chim. Belg.* **1980**, *89*, 399. (b) González, A. G.; Estrada, D. M.; Martin, J. D.; Martin, V. S.; Perez, C.; Perez, R. *Tetrahedron* **1984**, *40*, 4109. (c) Kohmoto, S.; McConnell, O. J.; Wright, A.; Cross, S. *Chem. Lett.* **1987**, 1687. (d) Cimino, G.; Crispino, A.; Gavagnin, M.; Sodano, G. *J. Nat. Prod.* **1990**, *53*, 102. (e) Potts, B. C. M.; Faulkner, D. J.; Jacobs, R. S. *J. Nat. Prod.* **1992**, *55*, 1701. (f) Miyamoto, T.; Sakamoto, K.; Arao, K.; Komori, T.; Higuchi, R.; Sasaki, T. *Tetrahedron* **1996**, *52*, 8187.

(8) González, M. A. Synthesis of Terpenes with Spongiane, Scopadulane and Estrane Skeleton. Ph.D. Thesis, University of Valencia, Valencia, Spain, 2001.

(9) Taylor, W. C.; Toth, S. *Aust. J. Chem.* **1997**, *50*, 895.

(10) Kernan, M. R.; Cambie, R. C.; Bergquist, P. R. *J. Nat. Prod.* **1990**, *53*, 724.

(11) (a) Cimino, G.; Morrone, R.; Sodano, G. *Tetrahedron Lett.* **1982**, *23*, 4139. (b) Hambley, T. W.; Poiner, A.; Taylor, W. C. *Aust. J. Chem.* **1990**, *43*, 1861.

(12) Imamura, P. M.; González-Sierra, M.; Rúveda, E. A. *J. Chem. Soc., Chem. Commun.* **1981**, 734.

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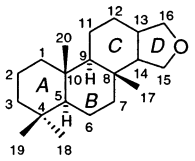
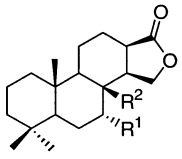
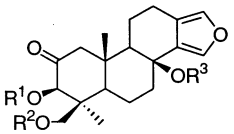


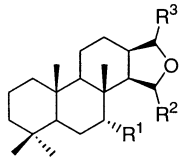
1 spongiane skeleton



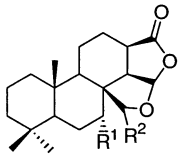
2 R^1= H;R^2= CHO
3 R^1= H;R^2= CH_2OAc
4 R^1= OAc;R^2= CH_2OAc



5 R^1= H;R^2= R^3= Ac
6 R^1= R^2= Ac;R^3= H



7 R^1= H;R^2= R^3= =O
8 R^1= H;R^2= R^3= α-OAc
9 R^1= OAc;R^2= α-OH;R^3= =O



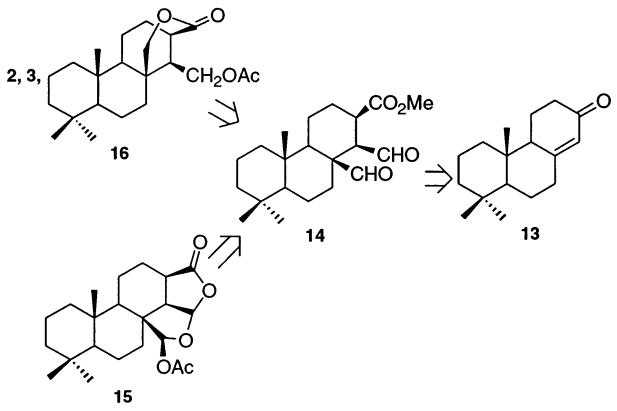
10 R^1= H,OH,OAc,OCOPr
R^2= β-OH
11 R^1= H;R^2= α-OAc
12 R^1= OAc;R^2= α-OAc

cohol[15] and using biomimetic-like polyene cyclizations,[16,17] which have led to racemic products in most cases.

Our research group has also been interested in these fascinating compounds, and during the course of our synthetic studies, we have developed several strategies, starting from either (+)-podocarp-8(14)-en-13-one[18] **13** or commercial *S*-(+)-carvone,[19] obtaining spongiane-type diterpenes in enantiomerically pure form. Podocarpenones such as **13** are versatile chiral building blocks and can be obtained in multigram quantities from commercially available (−)-abietic acid using our method.[20] This chiral starting material has been used to good advantage in terpene or steroid synthesis.[21]

In this paper, we describe the versatility of chiral synthon **13** in the synthesis of optically active C-17-functionalized tetracyclic and pentacyclic spongianes, since little synthetic attention had been paid to this group of natural spongianes. In particular, we disclose[22] the strategy for achieving the first diastereoselective synthesis of tetracyclic spongianes oxygenated at position 17 such as (−)-spongian-16-oxo-17-al **2** isolated from the nudibranch *Ceratosoma brevicaudatum*[23] and (−)-aplyroseol-14 **16** isolated from the sponge *Aplysilla Rosea* Barrois.[9] As a result of this synthetic study, we propose a revision of the structure assignment of natural aplyroseol-14 **3**, which is now represented as δ-lactone **16**. The existence of this kind of δ-lactone ring system is described for the first time in spongiane-type diterpenes. This reassignment was further confirmed by synthesizing compound **3**, having the putative structure for aplyroseol-14, as well as NOE difference experiments on lactone **16**. The preparation of the new pentacyclic spongiane (−)-acetyldendrillol-1 **15** isolated from the dorid nudibranch *Cadlina luteomarginata*,[24] and the revision of the reported stereochemistry at C-17 (**11** → **15**) is also disclosed. The study of the mechanism for the lactonization reaction, conversion of **22** into **2**, including a lower energy conformation, is also presented.

SCHEME 1



Results and Discussion

Our synthetic strategy toward the synthesis of spongianes **2**, **3**, **15**, and **16** is illustrated in Scheme 1. The versatility of our approach is based on the preparation of tricyclic ester-dialdehyde **14**, which already contains an oxygen functionality at C-17 and the full carbon backbone to obtain either tetracyclic or pentacyclic spongiane diterpenes. Subsequent elaboration of this intermediate has led us to the synthesis of tetracyclic metabolites (−)-spongian-16-oxo-17-al **2** and (−)-aplyroseol-14 **16** and pentacyclic diterpene (−)-acetyldendrillol-1 **15** by using two different approaches.

(13) (a) De Miranda, D. S.; Brendolan, G.; Imamura, P. M.; González-Sierra, M.; Marsaioli, A. J.; Rúveda, E. A. *J. Org. Chem.* **1981**, *46*, 4851. (b) González-Sierra, M.; Mischne, M. P.; Rúveda, E. A. *Synth. Commun.* **1985**, *15*, 727.

(14) (a) Nakano, T.; Hernández, M. I. *Tetrahedron Lett.* **1982**, *23*, 1423. (b) Nakano, T.; Hernández, M. I. *J. Chem. Soc., Perkin Trans. 1* **1983**, 135. (c) Nakano, T.; Hernández, M. I.; Gomez, M.; Medina, J. D. *J. Chem. Res. Synop.* **1989**, 54.

(15) Sakamoto, T.; Kanematsu, K. *Tetrahedron* **1995**, *51*, 5771.

(16) For several total syntheses of spongianes using biomimetic-like cyclizations, see: (a) Pattenden, G.; Roberts, L. *Tetrahedron Lett.* **1996**, *37*, 4191. (b) Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z.; Ribeiro, A. A. *J. Org. Chem.* **1996**, *61*, 1806. (c) Pattenden, G.; Roberts, L.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 863.

(17) For several approaches to spongianes using biomimetic-like cyclizations, see: (a) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *Chem. Lett.* **1983**, 1459. (b) Zoretic, P. A.; Shen, Z.; Wang, M.; Ribeiro, A. A. *Tetrahedron Lett.* **1995**, *36*, 2925. (c) Zoretic, P. A.; Wang, M.; Zhang, Y.; Fang, H.; Ribeiro, A. A.; Dubay G. *J. Org. Chem.* **1998**, *63*, 1162. (d) Goeller, F.; Heinemann, C.; Demuth, M. *Synthesis* **2001**, *8*, 1114.

(18) (a) Abad, A.; Arnó, M.; Cuñat, A. C.; Marín, M. L.; Zaragozá, R. J. *J. Org. Chem.* **1992**, *57*, 6861. (b) Abad, A.; Arnó, M.; Marín, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1861. (c) Abad, A.; Agulló, C.; Arnó, M.; Marín, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2193.

(19) Arnó, M.; González, M. A.; Zaragozá, R. J. *Tetrahedron* **1999**, *55*, 12419.

(20) Abad, A.; Arno, M.; Domingo, L. R.; Zaragoza, R. J. *Tetrahedron* **1985**, *41*, 4937.

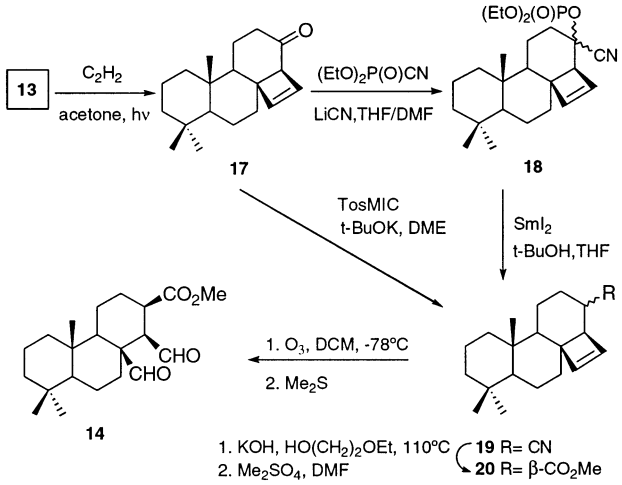
(21) (a) Abad, A.; Arno, M.; Zaragoza, R. J. *Org. Prep. Proced. Int.* **1991**, *23*, 321. (b) Abad, A.; Agulló, C.; Arnó, M.; Marín, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2987. (c) Berettoni, M.; De Chiara, G.; Iacoangeli, T.; Lo Surdo, P.; Bettolo, R. M.; di Mirabello, L. M.; Nicolini, L.; Scarpelli, R. *Helv. Chim. Acta* **1996**, *79*, 2035. (d) Arnó, M.; González, M. A.; Marín, M. L.; Zaragozá, R. J. *J. Org. Chem.* **2000**, *65*, 840.

(22) For a preliminary account of this work, see: Arnó, M.; González, M. A.; Marín, M. L.; Zaragozá, R. J. *Tetrahedron Lett.* **2001**, *42*, 1669.

(23) Ksebati, M. B.; Schmitz, F. J. *J. Org. Chem.* **1987**, *52*, 3766.

(24) Dumdei, E. J.; Kubanek, J.; Coleman, J. E.; Pika, J.; Andersen, R. J.; Steiner, J. R.; Clardy, J. *Can. J. Chem.* **1997**, *75*, 773.

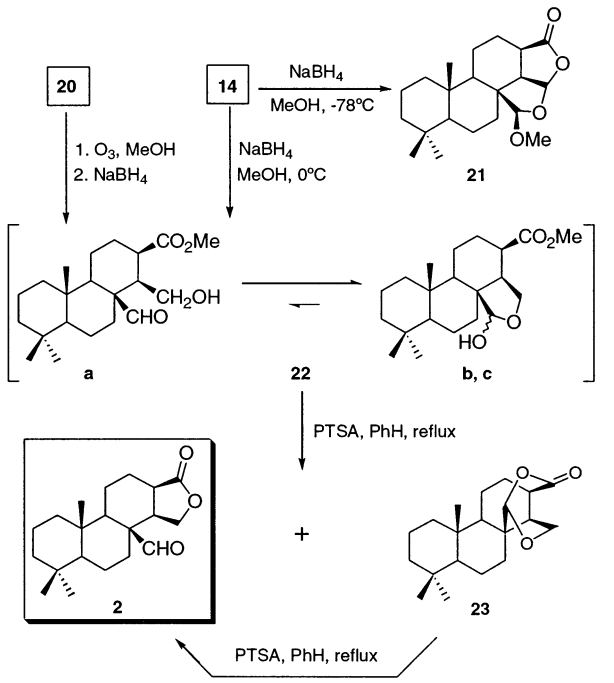
SCHEME 2



The synthetic route started with the preparation of key intermediate **14** in five steps starting from podocarpenone (+)-**13**[20] (Scheme 2). Podocarpenone **13** was transformed into ester **20** using our previously described methodology.[18c] Thus, irradiation of podocarpenone **13** in dry acetone saturated with acetylene at −40 °C gave stereoselectively photoadduct **17** in 60% yield. The homologation at C-13 of **17** can be effected by reductive cyanation using tosylmethyl isocyanide (TosMIC),[25] giving a 7:3 mixture of β- and α-nitriles **19** in 67% yield.[18b] However, the cyanophosphorylation and subsequent removal of the phosphate moiety[26] gave a better yield of nitriles **19**. Therefore, treatment of cyclobutenone **17** with $(EtO)_2P(O)CN$ and LiCN readily afforded a mixture of epimeric cyano phosphates at C-13 (**18**) in essentially quantitative yield. Subsequent treatment of the crude cyano phosphates **18** with SmI_2 and *t*-BuOH gave a mixture of nitriles **19**. Alkaline hydrolysis of both nitriles using KOH in ethylene glycol ethyl ether at 110 °C overnight, followed by in situ treatment with Me_2SO_4, furnished a 93:7 mixture of 13β-ester **20** and the corresponding α-epimer in a 91% overall yield from **17**. The alkaline treatment of nitriles **19** produces initially an equilibration process in favor of the more stable isomer (β-isomer), followed by hydrolysis of the cyano group.[27] The minor 13α-isomer can be recycled by equilibration with 2% NaOMe/MeOH at 80 °C to give a 8:2 mixture of **20** and starting material, respectively. Ozonolysis of the cyclobutene ring in **20** followed by treatment of the resultant intermediate ozonide with Me_2S provided the crude ester-dialdehyde **14** in essentially quantitative yield (ca. 98% purity), which was used without further purification. Attempts to purify **14** by chromatography over either silica gel or neutral alumina demonstrated the high tendency for lactone-hemiacetal formation and reduced the yield because of the formation of (−)-dendrillol-1 **10** (R^1 = H).

With 1,4-dialdehyde **14** in hand, our next objective was to achieve the synthesis of target spongianes **2**, **3**, **15**, and **16**. We first focused our efforts on the synthesis of tetracyclic spongiane **2** (Scheme 3). To this end, regioselective reduction of the carbonyl group at C-15 to obtain **22** followed by lactonization was required. Unexpectedly, first attempts of reduction with $NaBH_4$/MeOH at −78 °C led us to the isolation of compound **21**. This pentacyclic product probably arises from internal lactone-hemiacetalization followed by acetalization with MeOH without any reduction in the molecule oxidation state. Reduction with BH_3·THF[28] gave **22** in moderate yield (ca. 40%), but reduction using $NaBH_4$/MeOH at 0 °C afforded a 2:1 epimeric mixture at C-17 of **22** as ester-hemiacetals (**22b** and **22c**) in high yield. The corresponding ring-opened product **22a** was not detected in the ^{1}H NMR spectrum of the crude product. This fact supports the higher stability of the cyclic hemiacetals, which was further confirmed by ab initio calculations. Chromatographic separation of both epimers was unsuccessful, probably due to a rapid equilibration process between them. Parallel attempts to reduce the number of steps were carried out under reductive ozonolysis of **20** in either MeOH or CH_2Cl_2 at −78 °C, followed by treatment of the resultant ozonides with either $NaBH_4$ or BH_3·Me_2S.[29] These experiments led to complex mixtures of products with poor yields of hemiacetals **22**.

SCHEME 3



To obtain the lactone ring present in natural **2**, several lactonization conditions were tried on **22** such as 9:1 acetone/HCl, 1% H_2SO_4/AcOH, *p*-toluenesulfonic acid (PTSA)/toluene or PTSA/PhH and TFA. The best results were obtained using either PTSA in refluxing benzene for 18 h or TFA in a 2:3 (v/v) mixture of acetone/water at reflux for 60 h, giving a 3:1 mixture of (−)-spongian-16-oxo-17-al **2** and δ-lactone **23**. Both structural isomers were separated by either careful flash chromatography

(25) Van Lausen, A. M. *Lect. Heterocycl. Chem.* **1980**, *5*, S111.
(26) Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* **1989**, *30*, 3681.
(27) (a) Arnó, M.; Marín, M. L.; Zaragozá, R. J. *Magn. Reson. Chem.* **1998**, 579. (b) Marín, M. L.; Zaragozá, R. J.; Pla, F. F. Perez *Int. J. Chem. Kinet.* **1999**, *31*, 611.
(28) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786.
(29) Flippin, L. A.; Gallagher, D. W.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, *54*, 1430 and references therein.

or normal-phase HPLC, affording spongiane **2** in 65% overall yield from **14**. δ-Lactone **23** was isolated in 20% yield and can be conveniently recycled under the above-mentioned conditions to give a 3:1 mixture of **2** and **23**. Synthetic tetracyclic spongiane **2** had spectroscopic data identical to those recorded for the natural product.[23] The structure shown in Scheme 3 for compound **23** was supported by their spectroscopic data.

With the aim of clarifying the mechanism and equilibria involved in this lactonization reaction, we have carried out a series of ab initio calculations, the results from which are summarized later on.

After having successfully accomplished the synthesis of tetracyclic spongiane **2**, we studied the utility of key intermediate **14** for the synthesis of the new pentacyclic spongiane **15** (initially described with structure **11**, and therefore named 17-epiacetyldendrillol-1). Consequently, it was envisaged that the conversion of **14** into natural product **15** could be done under simple acetylation conditions, since it was clear that the internal lactone-hemiacetal formation is highly favored; although the outcome of the obtainable stereochemistry at C-17 was unknown. Predictions from AM1 semiempirical calculations showed that the orientation β-OAc is 1.2 kcal/mol more stable than the α-OAc orientation, which means that we would have a 85:15 ratio of β- to α-epimers at the equilibrium at room temperature. Moreover, this energy difference between both epimers calculated with ab initio calculations (HF/6-31G*) rises up to 6.2 kcal/mol, which clearly supports that the β-OAc orientation is favored, though the α-OAc orientation has been described for the natural product. Although the existence of other pentacyclic diterpenes possessing a 17α-acetoxy group has been reported,[23] our own calculations along with a comparison of the reported spectroscopic data for the natural product with those of similar compounds pointed out an incorrect assignment of the stereochemistry at C-17. We thought that the stereochemistry would be 17β, as in the known dendrillol-1, and therefore the natural product would be correctly named acetyldendrillol-1. To confirm our hypothesis, we studied the acetylation of dialdehyde **14**, as well as of dendrillol-1 (**10** R_1 = H; R_2 = β-OH), which was available in our group from previous synthetic work.[18a]

A variety of methods were explored for the lactone-hemiacetal formation and in situ acetylation of **14**, as well as the acetylation of dendrillol-1 (Scheme 4). Some of the results are summarized in Table 1.

As shown in Table 1, using AcOH led to no reaction below 65 °C (Table 1; entries 1, 3, 5, and 8); however, at that temperature, the lactonization-hemiacetalization of **14** worked, including also partial esterification of the obtained hemiacetals epimers at C-17 (Table 1, entry 2). Interestingly, under basic conditions and using Ac_2O as an acetylating agent, the desired product was never obtained. Dialdehyde **14** reacted to give only enol acetate **24** (Table 1; entry 4), whereas dendrillol-1 (Table 1, entries 13−15) readily yielded lactone **25**, even at low temperatures. The high yield of **25** in the presence of 4-pyrrolidinopyridine (4-PP) is somewhat surprising and probably results from a base-promoted hemiacetal ring-opening and epimerization at C-15 prior to acetylation.[30,31] The structure shown for lactone **25** was deduced from its NMR data and by comparison with similar compounds. The stereochemistry of **25** was confirmed by NOE measurements. Thus, irradiation of the H-15β signal showed enhancements with both H-7β and H-17 signals.

SCHEME 4

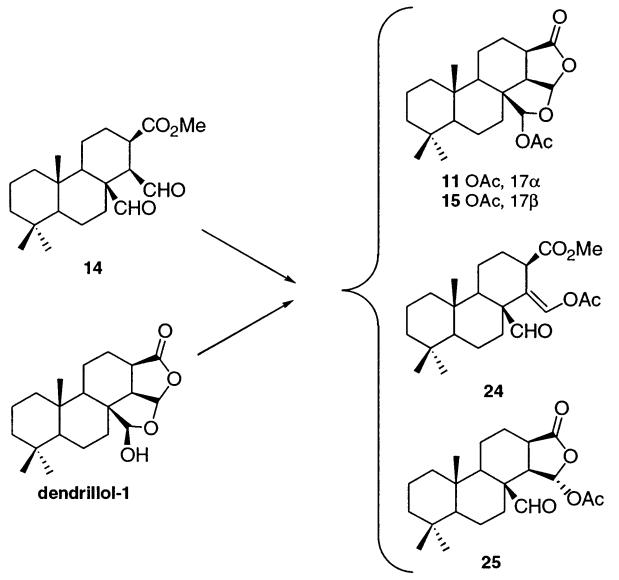


TABLE 1. Acetylation Conditions for the Reaction of 14 and Dendrillol-1

entry	SM[a]	conditions[b]	products[c,d]
1	**14**	a	NR
2	**14**	b	dendrillol-1, **11**, **15**
3	**14**	c	NR
4	**14**	d	**24**
5	**14**	e	NR
6	**14**	f	**11**, **15** (6:4 mixture), others
7	**14**	h	**15** (85%),[e] **11** (traces)
8	dendrillol-1	a	NR
9	dendrillol-1	b	NR
10	dendrillol-1	f	**11** (traces), **15** (traces)
11	dendrillol-1	g	**15**, **11**, dendrillol-1 (traces)
12	dendrillol-1	h	**15**, **11** (traces)
13	dendrillol-1	i	**25**
14	dendrillol-1	j	**25**
15	dendrillol-1	k	**25** (90%)[e]

[a] SM = starting material. [b] Reagents and conditions: (a) AcOH, 20 °C, 17 h; (b) AcOH, 65 °C, 24 h; (c) AcOH, anhydrous AcONa, 20 °C, 17 h; (d) Ac_2O, anhydrous AcONa, 65 °C, 15 h; (e) AcOH cat., Ac_2O, 40 °C, 17 h; (f) 4:1 AcOH/Ac_2O, 65 °C, 17 h; (g) AcOH, H_2SO_4 cat., 65 °C, 17 h; (h) AcOH, Ac_2O, H_2SO_4 cat., 65 °C, 17 h; (i) Ac_2O, pyridine, 35 °C, 3 h; (j) Ac_2O, pyridine, −30 °C, 3 days; (k) Ac_2O, Et_3N, 4-pyrrolidinopyridine. [c] Determined by ^1H NMR. [d] NR = no reaction. [e] After flash chromatography.

Eventually, the desired conversion was successfully optimized by using a catalytic amount of sulfuric acid (1%) in a 9:1 mixture of AcOH/Ac_2O at 65 °C for 17 h. Thus, compound **15** was obtained in 85% yield directly

(30) This fact has been reported previously for other related pentacyclic spongianes: see refs 23 and 31 and: Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1986**, *51*, 1144.

(31) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069. The use of DMAP in the benzoylation of aplyroseol-1 **10** (R^1 = H.; R^2 = β-OH) also produces the opening of the hemiacetal system, inversion of configuration at C-15, and acylation in high yield; see: Hambley, T. W.; Taylor, W. C.; Toth, S. *Aust. J. Chem.* **1997**, *50*, 391.

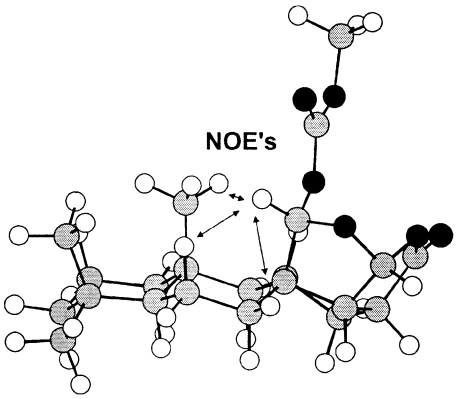


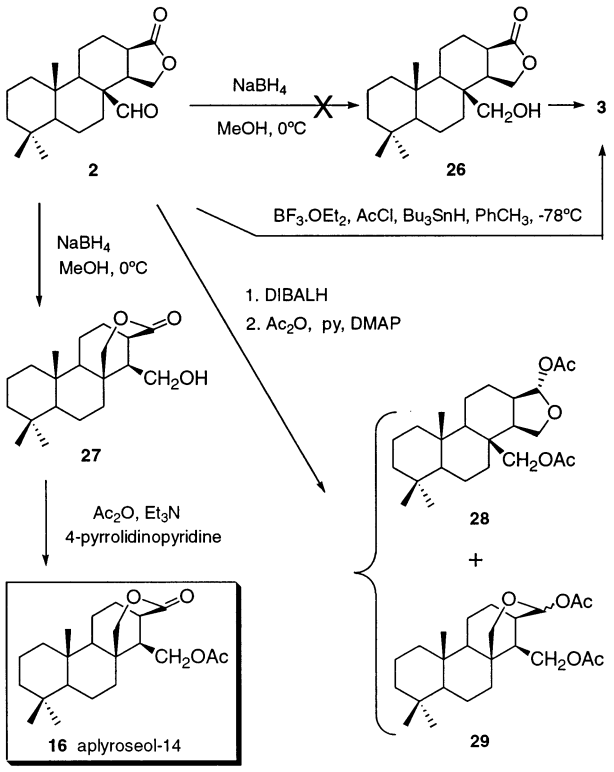
FIGURE 1. Observed NOE enhancements in compound **15** when proton H-17 was irradiated.

from either **14** (Table 1; entry 7) or from dendrillol-1 (Table 1, entry 12). The structural assignment for this compound was based on IR and NMR data, and the stereochemistry at C-17 was determined by NOE difference experiments. Thus, the NOE enhancement of the signals due to protons H-20, H-6β, and H-7β when proton H-17 was irradiated conclusively proved the 17β-acetoxy orientation (Figure 1). Synthetic pentacyclic spongiane **15** resulted in spectroscopic data identical to those recorded for the natural product, and consequently the orientation of the acetate group in the natural product was reassigned as 17β-acetoxy instead of the 17α reported by Andersen and co-workers.[24]

Following our investigations toward the functionalization at position 17, our next objective was to introduce an acetyl function at C-17 in synthetic **2** to obtain compound **3**, which contains the structure proposed for (−)-aplyroseol-14 during its isolation (Scheme **5**). At first sight, the conversion of **2** into its 17-acetyl derivative **3** seems to be straightforward by standard reduction and subsequent acetylation, but in practice this conversion proved to be quite complicated. The first attempt to form **26** by reduction of aldehyde **2** with $NaBH_4$/MeOH at 0 °C did not proceed as expected and led to alcohol **27** (90%). This compound results formally from reduction and in situ translactonization of lactone ring D from C-15 to C-17. We realized that we were handling a δ-lactone group instead of the desired γ-lactone group on the basis of IR and ^{13}C NMR data for alcohol **27** (ν_{CO} 1721 cm^{-1}; δ_{CO} 174.7). Attempts at equilibration between lactones **26** and **27** from **27** in either acidic (PTSA/PhH or toluene) or basic (KOH, *t*-BuOH) media were unsuccessful.[32]

Subsequent acetylation of **27** with Ac_2O/Et_3N in the presence of a catalytic amount of 4-PP afforded acetate **16** (89%), which surprisingly gave ^1H NMR data in agreement with those reported for the natural product aplyroseol-14.[9,33] However, its infrared band at 1732

SCHEME 5



cm^{-1}, assignable to a combination of the acetate and the δ-lactone functions, as well as its ^{13}C NMR data (δ_{CO} 173.6), clearly indicated the presence of a δ-lactone moiety. Therefore the proposed structure **3** for aplyroseol-14 was confirmed as incorrect. It is worth noting that the ^1H NMR spectrum of **27** showed an AB quartet at δ_H 4.87 and 4.18, J = 12.2 Hz, assignable to protons H-17, which rested practically unaltered after acetylation. This observation reveals that the hydroxyl group in **27** is located not at C-17 but at C-15, and consequently, the acetyl group in **16** will be at position 15. The structural assignment for compound **16** as depicted in Scheme 5 was based on ^1H and ^{13}C NMR data as well as NOE difference experiments. We confirmed that the NOE effects observed by Taylor and co-workers did not conclusively distinguish between both lactone structures, since these NOE enhancements upon irradiation of protons H-20 and H-17 as well as H-19 can be observed independently of the position of the acetyl function. In a key NOE experiment, irradiation of the H-13 signal caused the enhancement of the signals due to both protons H-15 and the acetoxyl methyl group providing further support to our assignment. The synthesis of (−)-aplyroseol-14 **16**, containing an unprecented δ-lactone-based structure, and revision of the assumed structure had thus been achieved.

To fully confirm our assignment of the structural features of (−)-aplyroseol-14, the synthesis of γ-lactone **3** initially assigned for (−)-aplyroseol-14 was carried out. To this end, several conditions for the mild reduction of aldehyde **2**, and even reductive acetylation conditions to diminish the favorable translactonization process leading to δ-lactone **27**, were evaluated. Initially, when spongianal **2** was subjected to reduction with $NaBH(OAc)_3$ in

(32) These experiments pointed out a higher stability of δ-lactone **27** versus γ-lactone **26**. However, a series of calculations at different levels have shown similar energies for both lactones without having found any conformation for δ-lactone **27** clearly more stable than any of the conformations for γ-lactone **26**.

(33) Comparison with other relevant data (^{13}C NMR) has not been possible because the authors did not provide it, probably due to the sample size. We could only compare the IR data for the carbonyl group ν_{CO} 1775 cm^{-1} for the natural product and 1732 cm^{-1} in synthetic **16**. This discrepancy may be due to a typographical error.

benzene at reflux,[34] a complex mixture of products, including unreacted starting material, was obtained. The reaction with diisopropoxyaluminum trifluoroacetate[35] failed as well. Use of sodium bis(2-methoxyethoxy)-aluminum hydride and DIBALH as reducing agents at low temperature led to mixtures of products arising from reduction without selectivity at C-16 and/or C-17 and translactonization of lactone ring D. Then, we thought that trapping the aluminum intermediate in situ with Ac_2O would probably lead to our target molecule. When **2** was treated, following Rychnovsky's protocol,[36] with a stoichiometric amount of DIBALH but using 4-PP instead of DMAP as an acetylation catalyst, a mixture of products resulting from reduction of the lactone group and acetylation, reduction at C-17, and translactonization of lactone ring D as well as unreacted **2** (50%) was obtained. By increasing the amount of DIBALH to 2.2 equiv as well as the amounts of pyridine, 4-PP, and Ac_2O, we could identify among the reaction products three double-acetylated lactols, tentatively assigned as depicted in **28** and **29** (7:3 mixture of epimers at C-16) in 15 and 50% yields, respectively.[37] Reductive acetylation to trap the corresponding stannane derivative using Kaplan's protocol (Bu_3SnH/AcCl)[38] led not to the desired acetate but unreacted starting material. In view of the poor reactivity of the aldehyde group in **2** probably due to steric effects, which even permitted the lactone reduction to take precedence over the desired reduction in some cases, we decided to use a carbonyl activator to enhance its reactivity. After much experimentation, a combination of reductive acetylation conditions reported by Kaplan and Maruoka[39] turned out to be a good reagent system for effecting the desired reductive acetylation of the aldehyde group at C-17. In fact, the combined use of $BF_3 \cdot OEt_2$, AcCl, and Bu_3SnH as a reducing agent in toluene at −78 °C gave a 1:1 mixture of acetates **3** and **16** in essentially quantitative yield, which were easily separated by preparative normal-phase HPLC. Although the favored translactonization reaction could not be completely avoided, we have found a high-yielding new procedure for the mild one-step aldehyde-to-acetate conversion. We believe that this method may be extended to other chemoselective reductive acetylations of carbonyl groups. As expected, compound **3** showed very similar ^1H and ^{13}C data to those of the naturally occurring 17-acetoxy spongiane diterpenoid as lactone **4**.[40] Isoaplyroseol-14 **3** exhibited carbonyl absorptions due to a γ-lactone (ν_{CO} 1774 cm^{-1}; δ_{CO} 178.9) and one acetate (ν_{CO} 1739 cm^{-1}; δ_{CO} 170.7). Further evidence of the assigned structure for **3** was obtained by NOE difference experiments. In particular, the NOE enhancements of the signals due to protons H-12α, H-14, and H-15α, on irradiation of proton H-13, unambiguously proved the structure of **3** as depicted.

(34) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535.
(35) Akamanchi, K. G.; Varalakshmy, N. R.; Chaudhari, B. A. *Synlett* **1997**, 371.
(36) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.
(37) A 1:9 mixture of epimers **29** was obtained in a 30% yield upon acetylation and purification of the crude obtained by reduction of **2** with $NaBH_4$/MeOH at 0 °C over 1 h.
(38) Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 4970.
(39) Ooi, T.; Uraguchi, D.; Morikawa, J.; Maruoka, K. *Org. Lett.* **2000**, *2*, 2015.
(40) Karuso, P.; Taylor, W. C. *Aust. J. Chem.* **1986**, *39*, 1629.

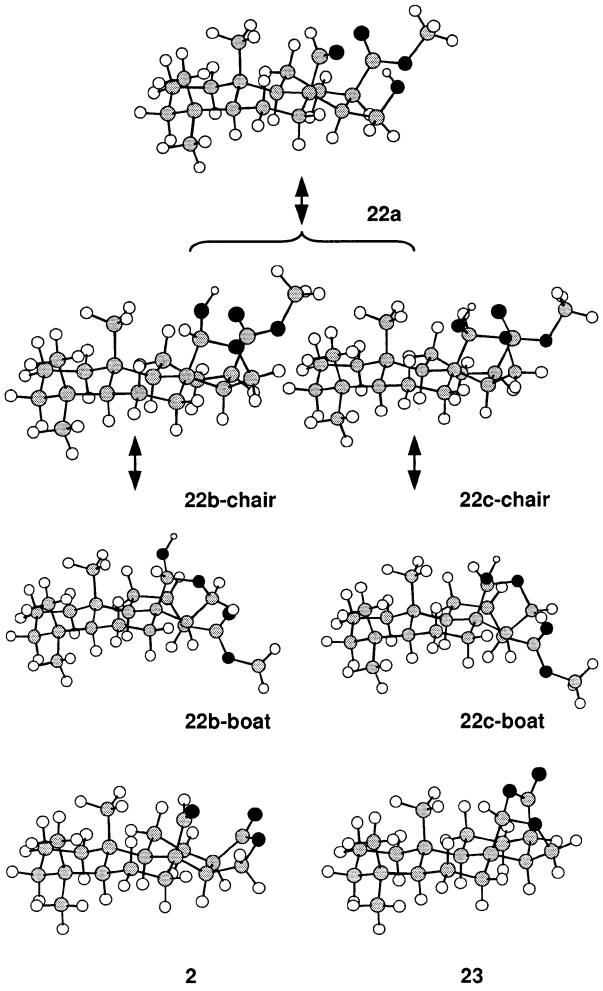


FIGURE 2. Selected conformations for compounds **2**, **22**, and **23** from ab initio calculations at the HF/6-31G* level.

Theoretical Calculations

As we have already mentioned, the experimental observations of the lactonization of ester **22** to lactones **2** and **23**, under acidic conditions, suggest a rapid equilibrium between opened form **22a** and both hemiacetals **22b** and **22c**, where the latter are more favored. Under these reaction conditions, final products **2** and **23** occur in a post-equilibrium, which is slightly driven in the direction of aldehyde **2** (Scheme 3). To provide insight into the observed equilibria and clarify the mechanism through which ester **22** is transformed into lactones **2** and **23**, we then carried out a series of theoretical studies in more detail employing ab initio calculations (HF/6-31G*). The results of the study for the observed equilibria are first presented followed by a discussion of the possible mechanism of reaction.

Starting materials **22a**−**c** along with both final products **2** and **23** have been carefully studied in a lower energy conformation basis. The most stable conformations for every compound together with other conformations of interest are presented in Figure 2. The corresponding relative energies are shown in Table 2.

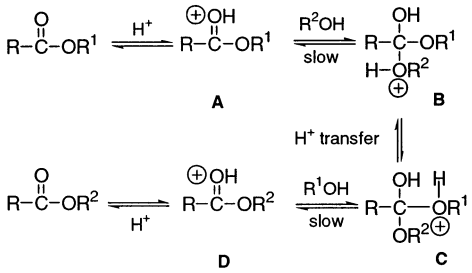
As can be seen, in our starting material, opened form **22a** shows a clear preference to have a chair conformation in ring C, which allows H-bonding between the hydroxyl

TABLE 2. Enthalpy (kcal/mol), Entropy (cal mol^{-1} K^{-1}) and Gibbs Energy (kcal/mol) for Some Stationary Points of the Intramolecular Lactonization Reaction of Ester 22 Computed (HF/6-31G*) at 25 °C

	ΔH	ΔS	ΔG
22a	4.1[a]	2.4[a]	3.4[a]
22b-chair	3.8[a]	−4.2[a]	5.0[a]
22b-boat	0.0[a]	0.0[a]	0.0[a]
22c-chair	3.0[a]	−3.3[a]	3.9[a]
22c-boat	1.1[a]	1.3[a]	0.7[a]
2	0.0[b]	0.0[b]	0.0[b]
23	−1.7[b]	−6.7[b]	0.3[b]
TSa	6.8[c]	0.1[c]	6.8[c]
TSb	0.0[c]	0.0[c]	0.0[c]
TSc	8.7[c]	7.5[c]	6.5[c]
TSd	−3.9[c]	−0.1[c]	−3.9[c]

[a] Relative to **22b**-boat. [b] Relative to **2**. [c] Relative to **TSb**.

SCHEME 6

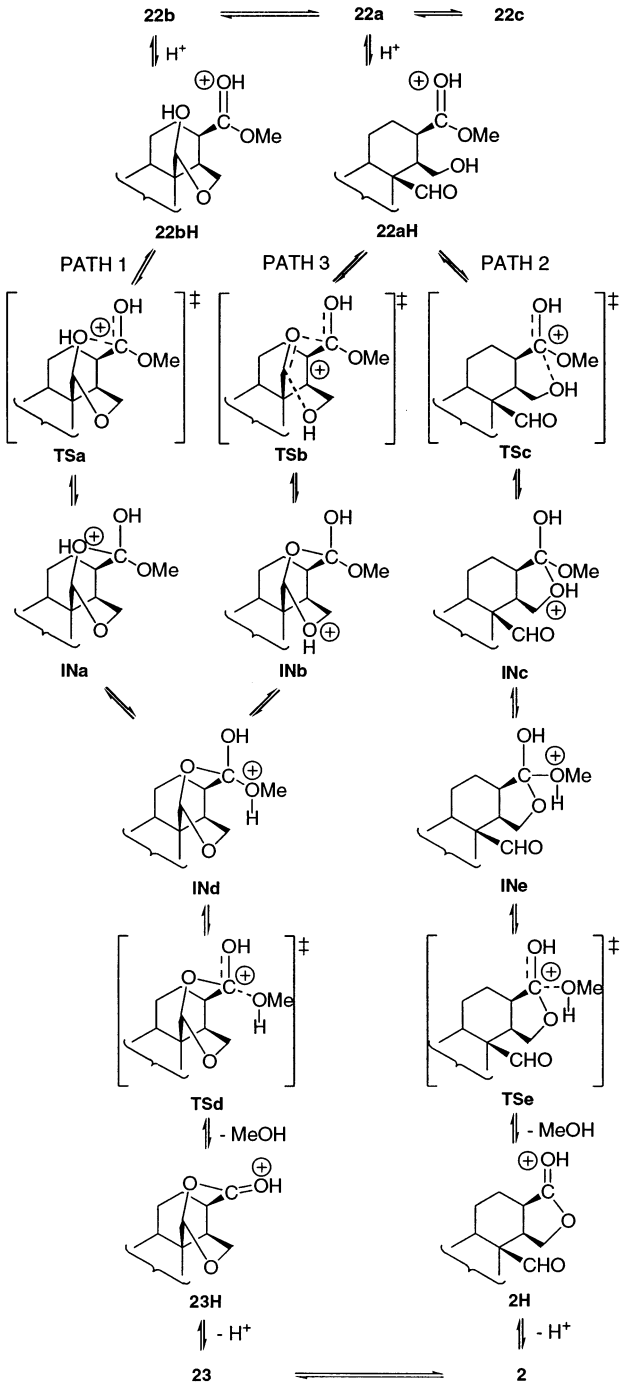


group at C-15 and the carbonyl group at C-17. On the other hand, hemiacetals **22b** (17β-OH) and **22c** (17α-OH) do prefer boat conformations in ring C (**22b**-boat, **22c**-boat), which are 5.0 and 3.9 kcal/mol (ΔG, see Experimental Section) more favorable than the corresponding chair conformations (**22b**-chair and **22c**-chair, respectively). Moreover, conformation **22b**-boat is approximately 3.4 kcal/mol energetically more favorable than opened hemiacetal **22a**. Therefore, in an equilibrium process for **22**, considering the species **22b**-boat, **22c**-boat, and **22a** at 298 K, we would obtain a 77:23:<1 ratio, respectively, which confirms a clear predominance of the cyclic forms. With respect to the final products, the most favorable conformations for both **2** and **23** (Figure 2 and Table 2) presented chair-like conformations in ring C with similar energy values, aldehyde **2** being slightly lower in energy content (0.3 kcal/mol). These calculations are in good agreement with our experimental observations.

After completing our conformational study, we were able to evaluate a plausible mechanism for this lactonization reaction. The accepted mechanism for this type of transformation, sometimes called the AAC2 mechanism, assumes a reaction profile through tetrahedral intermediates **B** and **C** (Scheme 6).[41] The rate-determining step of the reaction is either the attack of the alcohol R^2OH to the protonated ester **A**, giving species **B**, or the loss of R^1OH from **C** to afford **D**.

For the conversion of **22** into **2** and **23**, we have investigated three possible reaction pathways (Scheme 7). In the first pathway, hemiacetal **22b** is converted into acetal-lactone **23** through transitions states (TS) **TSa** and

SCHEME 7



TSd. **TSa** arises from the intramolecular attack of the hydroxyl group at C-17 to the protonated ester **22bH**, producing tetrahedral intermediate **INa**. A proton transfer in **INa** leads to intermediate **INd**, which by loss of MeOH through **TSd** and deprotonation gives **23**. In the second reaction pathway, hydroxy-ester **22a** is transformed into spongiane **2** through **TSc** and **TSe** in a manner similar to pathway one. In the last pathway, **22a** is converted into **23** through transition states **TSb** and **TSd**. **TSb** is formed in a concerted process by attack of the hydroxyl group at C-15 to the carbonyl group of the aldehyde, whose oxygen atom attacks the carbonyl group of the protonated ester at C-16. This allows both acetalization and lactonization simultaneously. Tetrahedral

(41) March J. *Avanced Organic Chemistry*, 4th ed.; Wiley & Sons: New York, 1992; p 380.

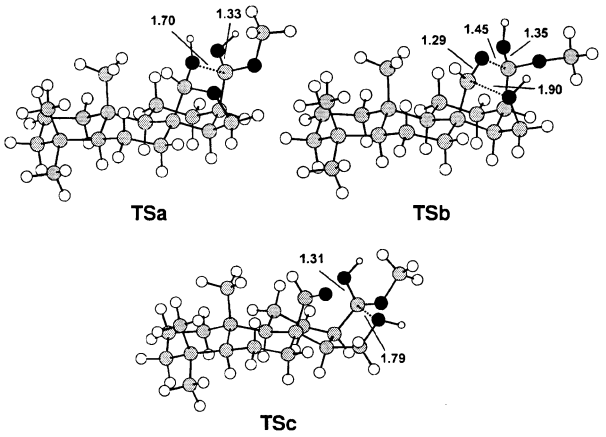


FIGURE 3. Selected geometric parameters for transition structures corresponding to the lactonization of ester **22**. Lengths of bonds (Å) involved in the reaction from ab initio calculations at the HF/6-31G* level are shown.

intermediate **INb** thus obtained evolves by proton transfer to intermediate **INd** vide supra. It is worth pointing out that hemiacetal **22c** due to geometric restrictions (17α-OH) can only lead to the final products by equilibration to either **22a** or **22b**.

With this complex equilibrium in mind, our theoretical study was then focused on calculations of the geometry and energy of the above-mentioned TSs. Some of these geometries are presented in Figure 3, while the relative energies are shown in Table 2. If we consider all of the initial TSs of the different reaction pathways (**TSa**−**c**), it is observed that ring C is in a chair conformation in all of them. This fact enhances the attack of the carbonyl group at C-17 (**TSb**), the hydroxyl group at C-17 (**TSa**), or the hydroxyl at C-15 (**TSc**) to the protonated ester group at C-16. From the energy values given, a great difference can be deduced in favor of the concerted transition state (**TSb**), which is indeed 6.8 and 6.5 kcal/mol more favorable than **TSa** and **TSc**, respectively. This fact indicated that if those TSs were involved in the rate-determining step for every proposed pathway, the mechanism that goes from **22a** to **23** through **TSb** and **TSd** would be the favored one. For this result, however, it is necessary that the energy of **TSd** is lower than that of **TSb**. Only in the case where **TSd** had its energy higher than that of **TSb** and **TSc**, therefore controlling the overall rate for this reaction pathway, would it have been necessary to calculate the energy value for **TSe**. All the attempts to get data for either **TSd** or intermediate **INd** were unsuccessful. In both cases, during the calculation process a spontaneous loss of MeOH occurred leading to **23H** without any other TS. To determine approximately the energy for **TSd**, the distance between the O of the expelled MeOH molecule and the C-16 was fixed at 1.79 Å (like in **TSc**). The energy value thus calculated for **TSd** (Table 2) is 3.9 kcal/mol lower than that of **TSb**, which confirmed **TSb** as the rate-determining TS of the whole process. According to all these statements, the calculation of the energy for **TSe** was not determined by assuming that the value of this calculation was irrelevant for the final results.

In view of these results, we can first deduce that in the equilibrium between **22b**, **22c**, and opened form **22a**, there is a clear predominance of cyclic forms **22b** and **22c**. Second, the kinetically more favorable cyclization occurs through opened acetal **22a**, via **TSb**, to furnish lactone **23**. Finally, spongiane **2** is obtained by thermodynamic equilibration of lactone **23**.

Compound Testing

The in vitro cytotoxic activity of (−)-spongian-16-oxo-17-al **2**, (−)-acetyldendrillol-1 **15**, and (−)-aplyroseol-14 **16** against HeLa and HEp-2 cells and the antiherpetic activity on Herpes simplex virus type 2 (HSV-2) shows compound **2** to be the most toxic (CC_{50}= 14.2 and 9.6 μg/mL for HeLa and HEp-2 cells, respectively).[42]

Conclusion

The utility of our sequence has been proved by preparing (−)-acetyldendrillol-1 **15** (85%, one step), (−)-spongian-16-oxo-17-al **2** (65%, two steps), and (−)-aplyroseol-14 **16** (56%, four steps) from intermediate **14**, which has permitted the reassignment of the assumed structures for acetyldendrillol-1 and aplyroseol-14 using NOE studies. The versatility of dialdehyde **14,** which was obtained in 48% overall yield in five steps from chiral podocarpenone **13**, as a key precursor of C-17-functionalized spongiane diterpenes has thus been well demonstrated. Confirmation of the incorrect structure assignment to aplyroseol-14 during its isolation was also obtained chemically by synthesizing the molecule having the proposed structure **3**, whose ^{1}H NMR spectrum was similar to, but clearly different from, that of natural aplyroseol-14. To this end, we have developed a novel reaction for conversion of aldehydes to acetates, which may find application in other synthetic problems. Biochemically, it is interesting to note the existence of δ-lactone **16**, unknown to date, which may be also involved in the biogenetic pathways of other naturally occurring spongiane-related diterpenoids.

Our predictions from calculations at the ab initio level (HF/6-31G*) are in agreement with the equilibria observed experimentally between species **22** and between **23** and spongiane **2**. In addition, these results have permitted the establishment of a plausible mechanism of reaction for the conversion of **22** into **2**.

Experimental Section

Computing Methods. The theoretical AM1 semiempirical method was carried out by MOPAC version 93 on a PC with a Pentium 166 MHz processor. Theoretical HF/6-31G* ab initio calculations were performed on a Cray-Silicon Graphics Origin 2000 with 64 processors of the Servicio de Informática de la Universitat de València and carried out with the Gaussian 98 suite of programs.[43] The stationary points were characterized by frequency calculations in order to verify that minima and transition structures have zero and one imaginary frequency, respectively.

It is a usual simplification to consider the difference of free energy (ΔG) as the difference of enthalpy without taking into account the contribution of the entropy term ($-T\Delta S$), which reduces the number of calculations to be done. However, in our particular study, the entropy term can contribute significantly to the final ΔG (see **2** and **23**) and this term has been included in our calculations.

(42) Betancur-Galvis, L.; Zuluaga, C.; Arno, M.; González, M. A.; Zaragozá, R. J. *J. Nat. Prod.* **2002**, *65*, 189.

Experimental Details. For general experimental details, see ref 21d. The reaction mixture was usually diluted with either Et_2O or AcOEt, washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. Compound **13** was prepared from commercial (−)-abietic acid using our method.[20] Compound **17** was obtained from **13**, in a manner similar to that reported.[18a] ^{1}H NMR coupling constants are given in hertz.

Methyl 8β,14β-Ethylidenepodocarpan-13β-oate (20). In a manner similar to that described in ref 18b for the preparation of 7-hydroxylated analogue of **20**, a solution of ketone **17** (400 mg, 1.47 mmol) in THF (20.6 mL) at 0 °C, LiCN in DMF (0.5 M, 8.8 mL, 4.4 mmol), and $(EtO)_2P(O)CN$ (0.72 mL, 4.4 mmol) were successively added. After the mixture was stirred for 20 min, workup gave the crude product (**18**) as a yellow oil, which was dissolved in THF (14.2 mL), and *t*-BuOH (0.14 mL, 1.47 mmol) was added. This mixture was then added to an intense blue solution of SmI_2, prepared from Sm (877 mg, 5.83 mmol) and ICH_2CH_2I (1.24 g, 4.4 mmol) in THF (15.5 mL). After 30 min, the resulting mixture was diluted with Et_2O and washed with brine containing diluted HCl and $Na_2S_2O_3$, and after workup the solid residue (480 mg) thus obtained was directly hydrolyzed and esterified without previous purification.

To a solution of crude nitriles **19** in a Teflon flask in $HOCH_2CH_2OEt$ (5.6 mL) was added 15 M aqueous KOH (1.44 mL) and the mixture was stirred and heated at 110 °C for 16 h. The mixture was cooled to room temperature, and DMF (7 mL) and Me_2SO_4 (2.7 mL) were added. After stirring for 4 h, the mixture was poured into 1.5 M aqueous HCl and extracted with Et_2O. Workup as usual gave a residue that was purified by careful column chromatography, using 98:2 hexanes−Et_2O as an eluent, to afford 13β-ester **20** as a white solid (395 mg, 85% from **17**) and its 13-epimer (28 mg, 6%). Data can be found in refs 18a and 27a.

Methyl 8β,14β-Dioxopodocarpan-13β-oate (14). Cyclobutene **20** (47 mg, 0.149 mmol) in CH_2Cl_2 (9 mL) was cooled to −78 °C, and ozone was passed into the reaction mixture until a light blue color was observed (15−20 min). Argon was then bubbled through the solution to remove excess ozone. Me_2S (1.7 mL) was added, and the reaction mixture was slowly allowed to warm to 5 °C in a refrigerator overnight. Workup gave in essentially quantitative yield crude dialdehyde **14** as a solid (52 mg, whose ^{1}H NMR was shown to have a purity higher than 95%). Dialdehyde **14** was used directly without further purification. For analytical purposes, 20 mg was filtered through a short silica column eluting with 7:3 hexane−AcOEt to afford 11 mg of **14** as a white solid: mp 141−143 °C (from CH_2Cl_2); $[\alpha]^{27}_D$ −35.8 (*c* 0.95, $CHCl_3$); IR (KBr) 2925, 2865, 1718, 1230 cm^{-1}; ^{1}H NMR (300 MHz) δ 10.02 (1H, s), 9.75 (1H, d, J = 1.3), 3.67 (3H, s), 3.21 (1H, ddd, J = 5.6, 5.6, 2.0), 2.82 (1H, ddd, J = 12.8, 3.3, 3.3), 2.51 (1H, m), 2.25 (1H, dd, J = 5.6, 1.3), 0.85, 0.78, and 0.77 (3H each, each s); ^{13}C NMR (75 MHz) δ_C 204.76 (d), 201.54 (d), 173.58 (s), 60.67 (d), 59.38 (d), 55.97 (d), 52.13 (q), 49.68 (s), 41.75 (t), 41.16 (d), 38.84 (t), 37.91 (s), 35.72 (t), 33.27 (q), 33.20 (s), 28.30 (t), 21.30 (q), 18.81 (t), 18.59 (t), 17.13 (t), 15.85 (q); MS (EI) *m*/*z* 348 (M^+, 9), 320 (57), 302 (100), 292 (61), 288 (82), 177 (78); HRMS $C_{21}H_{32}O_4$ requires 348.2301, found 348.2304.

Methyl 15,17-Epoxy-17-hydroxy-ent-isocopalan-16-oate (22). To a stirred solution of crude dialdehyde **14** (52 mg, 0.149 mmol) in MeOH (5.9 mL) at 0 °C was added $NaBH_4$ (98%, 45 mg, 1.14 mmol). The reaction mixture was stirred for 45 min and then diluted with Et_2O and washed with 1.5 M aqueous HCl. Workup afforded the crude 2:1 mixture of hemiacetals **22** (52 mg, 99%) as an amorphous solid: IR (KBr) 3500−3200, 1732, 1019 cm^{-1}; ^{1}H NMR (major isomer, 300 MHz) δ 5.23 (1H, d, J = 2.4), 3.64 (3H, s), 2.66 (1H, ddd, J = 13.2, 5.9, 3.2), 0.94, 0.85, and 0.83 (3H each, each s); ^{13}C NMR (major isomer, 75 MHz) δ_C 175.67 (s), 102.84 (d), 66.44 (t), 56.96 (d), 51.48 (q), 49.71 (d), 48.85 (s), 47.31 (d), 43.67 (t), 42.06 (t), 39.01 (d), 38.83 (t), 38.14 (s), 33.56 (q), 33.17 (s), 21.61 (q), 20.65 (t), 19.57 (t), 18.72 (t), 15.81 (t), 15.19 (q); ^{1}H NMR (minor isomer, 300 MHz) δ 5.56 (1H, d, J = 3.2), 3.65 (3H, s), 2.77 (1H, m), 0.93, 0.86, and 0.82 (3H each, each s); ^{13}C NMR (minor isomer, 75 MHz) δ_C 175.64 (s), 99.18 (d), 66.32 (t), 56.81 (d), 51.54 (q), 50.83 (d), 49.78 (d), 49.42 (s), 41.99 (t), 39.33 (d), 39.22 (t), 38.31 (s), 36.92 (t), 33.66 (q), 33.17 (s), 21.64 (q), 20.87 (t), 19.61 (t), 19.24 (t), 18.55 (t), 14.34 (q). The mixture of epimers at C-17 **22** was inseparable by chromatography and used directly in the lactone ring formation reaction.

(−)-Spongian-16-oxo-17-al (2). A solution of hemiacetals **22** (52 mg, 0.148 mmol) and PTSA (16 mg, 0.084 mmol) in benzene (16.8 mL) was refluxed for 18 h. The reaction mixture was then cooled, diluted with AcOEt, and washed with 10% aqueous $NaHCO_3$. Workup and careful flash chromatography, using hexane−AcOEt (from 95:5 to 6:4) as an eluent, gave δ-lactone **23** (9.4 mg, 20% from **14**) followed by γ-lactone **2** (30.5 mg, 65% from **14**) as a white solid. Alternatively, the same result can be achieved from the residue obtained by treatment of a refluxing solution of hemiacetals (52 mg, 0.148 mmol) in a 2:3 mixture of acetone−water (20 mL) with TFA (1.4 mL) for 60 h, after a similar workup and purification. For spongiane **2**: mp 176−178 °C (from hexane−CH_2Cl_2); $[\alpha]^{24}_D$ −59.0 (*c* 1.64, $CHCl_3$); IR (KBr) 2943, 2738, 1770, 1708, 1131 cm^{-1}; ^{1}H NMR (300 MHz) δ 9.96 (1 H, d, J = 1.5), 4.09 (1 H, dd, J = 10.0, 4.5), 4.04 (1 H, br d, J = 10.0), 2.67 (1 H, m), 2.54 (1 H, dt, J = 13.0, 3.0), 2.50 (1 H, m), 2.28 (1 H, dd, J = 7.5, 4.5), 0.85, 0.75 and 0.69 (3H each, each s); ^{13}C NMR (75 MHz) δ_C 203.83 (d), 177.71 (s), 66.87 (t), 56.56 (d), 55.88 (d), 50.81 (s), 49.00 (d), 41.77 (t), 39.03 (t), 38.53 (d), 37.80 (s), 35.65 (t), 33.37 (q), 33.25 (s), 23.08 (t), 21.43 (q), 18.75 (t), 18.62 (t), 16.34 (t), 14.89 (q); MS (EI) *m*/*z* 318 (M^+, 15), 275 (11), 218 (100), 123 (25); HRMS $C_{20}H_{30}O_3$ requires 318.2195, found 318.2193.

(−)-17β-Acetoxy-15,17-oxidospongian-16-one(acetyldendrillol-1) (15). Dialdehyde **14** (12 mg, 0.034 mmol) was dissolved in a 1% H_2SO_4 solution in acetic acid (0.7 mL), Ac_2O (42 μL, 0.44 mmol) was added and the resulting mixture was heated at 65 °C for 17 h. The brownish mixture was cooled to room temperature, and usual workup including a wash with 10% aqueous $NaHCO_3$ gave a residue which was purified by column chromatography (7:3 hexanes−EtOAc) to afford 10.9 mg (85%) of acetyldendrillol **15** as a white solid: mp 218−219 °C (from MeOH); $[\alpha]^{25}_D$ −74.7 (*c* 1.87, $CHCl_3$); IR (KBr) 1785, 1754, 1223 cm^{-1}; ^{1}H NMR (400 MHz) δ 6.29 (1 H, s), 6.11 (1 H, d, J = 6.0), 2.76 (1 H, dd, J = 11.0, 7.0), 2.65 (1 H, dd, J = 11.0, 6.0), 2.45 (1 H, br d, J = 11.5), 2.04 (3 H, s), 1.94 (1 H, dt, J = 13.5, 3.0), 0.86, 0.81 and 0.72 (3H each, each s); ^{1}H NMR (300 MHz; C_6D_6) δ 6.41 (1 H, s), 5.57 (1 H, d, J = 6.0), 2.44 (1 H, m), 2.00 (1 H, dd, J = 11.0, 7.0), 1.79 (3 H, s), 0.76, 0.65 and 0.55 (3H each, each s); ^{13}C NMR (75 MHz) δ_C 176.64 (s), 169.06 (s), 104.22 (d), 100.57 (d), 56.78 (d), 55.25 (d), 49.17 (d), 46.17 (s), 41.82 (t), 41.68 (t), 39.00 (t), 38.06 (s), 37.48 (d), 33.33 (s), 33.33 (q), 23.71 (t), 21.49 (q), 21.31 (q), 19.89 (t), 18.69 (t), 16.57 (t), 15.62 (q); MS (EI) *m*/*z* 376 (M^+, 10), 316 (100), 288 (60), 260 (41); HRMS $C_{22}H_{32}O_5$ requires 376.2250, found 376.2240.

(−)-15,16-Dideoxy-15-hydroxy-16,17-oxidospongian-16-one (27). To a stirred suspension of synthetic spongianal **2** (15 mg, 0.047 mmol) in MeOH (1.8 mL) at 0 °C was added $NaBH_4$ (17.8 mg, 0.47 mmol). After the mixture was stirred

(43) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

for 15 min, everything was dissolved and this solution was stirred at this temperature for an additional 45 min and then diluted with AcOEt. This solution was washed successively with 5% HCl, brine, and 10% $NaHCO_3$, and workup of the resulting organic extract gave a white glassy solid, which was purified by flash chromatography with hexane−AcOEt (from 5:5 to 3:7) to afford alcohol **27** (13.6 mg, 90%) as a white solid: mp 174−175 °C (from hexane−AcOEt); $[\alpha]^{27}_D$ −15.0 (*c* 0.5, $CHCl_3$); IR (KBr) 3500−3100, 1721, 1022 cm^{-1}; ^1H NMR (300 MHz) δ 4.86 (1H, dd, J = 12.2, 1.7), 4.17 (1H, dd, J = 12.2, 1.4), 3.85 (1H, dd, J = 10.9, 4.2), 3.73 (1H, dd, J = 10.9, 6.4), 2.92 (1H, br s), 1.02, 0.86 and 0.81 (3H each, each s); ^{13}C NMR (300 MHz) δ_C 174.66 (s), 75.36 (d), 61.24 (t), 58.90 (d), 56.40 (d), 51.62 (d), 41.68 (t), 40.87 (d), 39.85 (t), 37.95 (s), 37.25 (t), 35.83 (s), 33.21 (q), 33.21 (s), 31.06 (t), 21.46 (q), 19.83 (t), 18.78 (t), 18.36 (t), 15.90 (q); MS (EI) *m*/*z* 320 (M^+, 100), 302 (31), 290 (50), 123 (27); HRMS $C_{20}H_{32}O_3$ requires 320.2351, found 320.2352.

(−)-15-Acetoxy-15,16-dideoxy-16,17-oxidospongian-16-one (Aplyroseol-14) (16). To a solution of alcohol **27** (8.1 mg, 0.025 mmol) and 4-PP (98%, 0.5 mg, 0.003 mmol) as a catalyst in dry Et_3N (0.8 mL) cooled in a −20 °C bath was added Ac_2O (7 μL, 0.075 mmol), and the mixture was stirred for 1 h. Workup as usual followed by column chromatography, using 7:3 hexane−AcOEt as an eluent, yielded acetate **16** (8.4 mg, 92%) as a white solid: mp 146−148 °C; $[\alpha]^{25}_D$ −37.0 (*c* 2.0, $CHCl_3$); IR (KBr) 1760, 1739, 1232, 1215 cm^{-1}; IR ($CHCl_3$) 1732, 1237 cm^{-1}; ^1H NMR (400 MHz) δ 4.89 (1H, dd, J = 12.5, 1.5), 4.35 (1H, dd, J = 11.5, 4.4), 4.09 (1H, dd, J = 12.5, 1.0), 3.99 (1H, dd, J = 11.5, 6.8), 2.85 (1H, br s), 2.14 (1H, m), 2.05 (3H, s), 1.02, 0.86 and 0.81 (3H each, each s); ^{13}C NMR (75 MHz) δ_C 173.57 (s), 170.85 (s), 74.85 (t), 62.68 (t), 58.82 (d), 56.32 (d), 48.63 (d), 41.63 (t), 40.80 (d), 39.82 (t), 37.95 (s), 37.18 (t), 35.73 (s), 33.19 (q), 33.19 (s), 31.04 (t), 21.43 (q), 20.80 (q), 19.74 (t), 18.70 (t), 18.33 (t), 15.88 (q); MS (EI) *m*/*z* 362 (M^+, 21), 302 (100), 287 (40), 245 (29), 123 (57); HRMS $C_{22}H_{34}O_4$ requires 362.2457, found 362.2462.

(−)-17-Acetoxyspongia-16-one (Isoaplyroseol-14) (3). To a solution of aldehyde **2** (9.0 mg, 0.028 mmol) in toluene (0.4 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (30μL, 0.237 mmol), and the resulting solution was stirred for 5 min. Then, acetyl chloride (120 μL, 1.69 mmol) and Bu_3SnH (97%, 80 μL, 0.288 mmol) were successively added. The reaction mixture was stirred for 3 h at −78 °C, allowed to warm to −35 °C for 2 h, diluted with AcOEt, and washed with 10% $NaHCO_3$. The usual workup afforded a colorless oil containing tin residues that was filtered through a short silica column, using 7:3 hexane−AcOEt as an eluent, to give a mixture of acetates **3** and **16** (10.2 mg) in an approximate 1:1 ratio (by ^1H NMR analysis) in quantitative yield. This mixture was separated by preparative HPLC (μPORASIL, 7.8 × 300 mm; 8:2 hexane−AcOEt) with a flow rate of 1 mL/min. The first compound eluted (4.6 mg, 45%) was identified as γ-lactone **3**, a colorless oil which solidified upon standing: mp 132−134 °C; $[\alpha]^{23}_D$ −29.8 (*c* 0.94, $CHCl_3$); IR (NaCl) 1774, 1739, 1235 cm^{-1}; ^1H NMR (400 MHz) δ 4.51 (1H, d, J = 9.7), 4.29 (1H, d, J = 12.9), 4.10 (1H, d, J = 12.9), 4.08 (1H, dd, J = 9.7, 5.8), 2.59 (1H, dd, J = 8.1, 8.1), 2.38 (1H, m), 2.20 (1H, m), 2.06 (3H, s), 0.90, 0.86 and 0.80 (3H each, each s); ^{13}C NMR (75 MHz) δ_C 178.88 (s), 170.71 (s), 67.59 (t), 64.24 (t), 56.99 (d), 56.63 (d), 49.84 (d), 41.80 (t), 40.03 (t), 37.85 (t), 37.81 (d), 37.60 (s), 37.48 (s), 33.35 (s), 33.25 (q), 22.28 (t), 21.43 (q), 21.00 (q), 18.49 (t), 18.25 (t), 17.00 (t), 16.38 (q); MS (EI) *m*/*z* 362 (M^+, 2), 302 (100), 287 (52), 246 (29), 123 (44); HRMS $C_{22}H_{34}O_4$ requires 362.2457, found 362.2446. The second material eluted (5.4 mg, 53%) was δ-lactone **16** (aplyroseol-14, see above).

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Supporting Information Available: Representative data and experimental procedures for the preparation of **24**, **25**, **28**, and **29**; representative data for **21** and **23**; ^1H NMR spectra for **2**, **3**, **15**, **16**, **21**, and **23**; and Cartesian coordinates for **22a**, **22b**-chair, **22c**-chair, **2**, **23**, and **TSa**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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