An Approach to Total Synthesis of (+)-Lycoricidine

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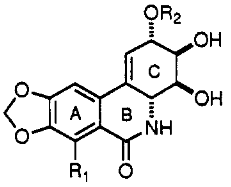
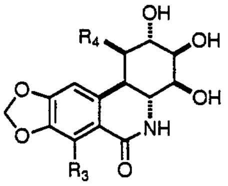
A convergent synthesis of a protected version of (+)-lycoricidine has been accomplished in 13 steps from L-arabinose. Preparation of the aminocyclitol moiety **50** employed a novel vinylsilane-terminated *N*-sulfonyliminium ion cyclization of vinylsilane aldehyde **42**. Closure of the B-ring using an intramolecular Heck reaction afforded lycoricidine derivative **58**. An unexpected cyclization of vinylsilane aldehyde **42** allowed for the stereodivergent preparation of semiprotected conduritols **43** and **45**.

Introduction

Extracts of plants of the *Amaryllidaceae* family[1] have long been used in folk medicine to alleviate a variety of ailments.[2,3] A number of *Amaryllidaceae* alkaloids of the [1,3]-dioxolophenanthridone structural class exhibit a wide range of biological activity,[1–10] including antineoplastic,[3–5] growth regulatory,[6] mitogenic,[2] and antimitotic[7] activity. This class includes narciclasine[8] (**1**) and its closely related congeners lycoricidine[9] (**2**), pancratistatin[4] (**4**), 7-deoxypancratistatin[6] (**5**), dihydronarciclasine[5] (**6**), and the glycosides kalbreclasine[2] (**3**), pancratiside[6] (**7**), and telastaside[10] (**8**).





1 R_1=OH, R_2=H
2 R_1=H, R_2=H
3 R_1=OH, R_2=β-D-glu

4 R_3=OH, R_4=OH
5 R_3=H, R_4=OH
6 R_3=OH, R_4=H
7 R_3=OH, R_4=O-β-D-glu
8 R_3=H, R_4=O-β-D-NAG

(glu=glucopyranose; NAG=N-acetylglucosamine)

Total syntheses of these alkaloids reported thus far include three syntheses of (+)-lycoricidine (Hudlicky and Olivo,[11] and Ogawa *et al.*,[12] Paulsen and Stubbe[13]), one of racemic lycoricidine (Ohta and Kimoto[14]), and one of racemic pancratistatin (Danishefsky and Lee[15]). Approaches to the alkaloids not resulting in a total synthesis include the preparation of (+)-tetrabenzyllycoricidine (Kallmerten and Thompson[16]), (±)-*cis*-dihydrolycoricidine (Keck *et al.*[17]), an A/B-ring precursor to (+)-pancratistatin (Clark and Souchet[18a]) and a pancratistatin model system (Heathcock et al.[18b]).

Reports from these laboratories have demonstrated the synthetic utility of electrophilic *N*-sulfonylimines and -iminium complexes, generated by the Kresze reaction[19] of an *N*-sulfinylsulfonamide with an aldehyde. These species have been employed in a variety of reaction types including [4 + 2]-cycloadditions,[20] inter- and intramolecular imino ene reactions,[21] amidoalkylations of olefins[22] and allyl silanes,[23] and reductive amidations.[24,25] As an extension of this work we considered the possibility of effecting *N*-sulfonyl iminium ion/vinyl silane[27] cyclizations and using this methodology as a key step in a total synthesis of lycoricidine.

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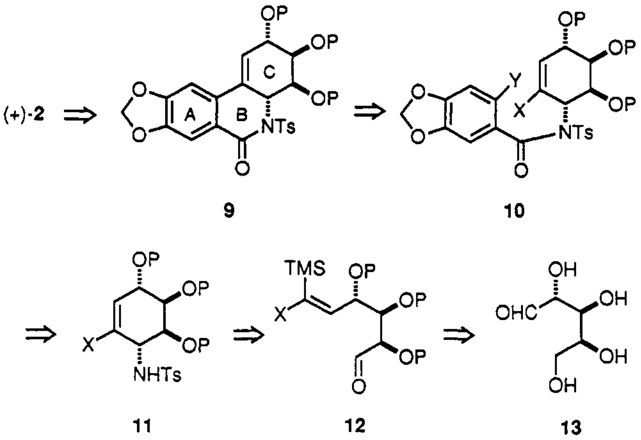
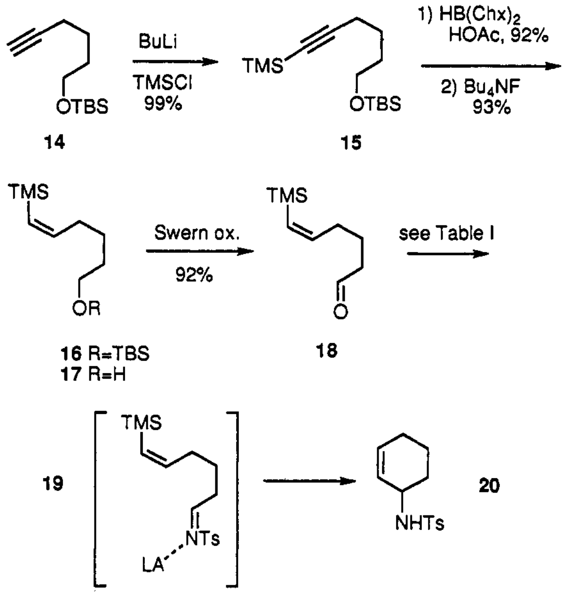
0022-3263/93/1958-4823$04.00/0

Scheme I



Scheme II



Our plan for the synthesis of (+)-lycoricidine (2) entailed closure of the B-ring late in the synthesis using an intramolecular metal mediated cross-coupling reaction[28] (i.e., 10→9) (Scheme I). Synthesis of an intermediate aminocyclitol moiety 11 would employ the proposed vinylsilane-terminated *N*-sulfonyliminium ion cyclization *via* aldehyde 12. It was not clear at the time we began the project what the stereochemical outcome of the cyclization would be, although we felt appropriate choice of oxygen protecting groups might help to influence the cyclization in favor of the desired isomer (vide infra). We planned to prepare 12 in enantiomerically pure from commercially available, inexpensive L-arabinose (13).

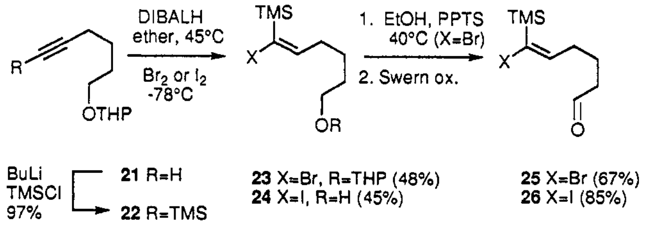
Results and Discussion

In order to test the feasibility of the key cyclization step, model vinyl silane aldehyde 18 was prepared (Scheme II). Therefore, known alkyne 14[29] was silylated in high yield to afford TMS acetylene 15. Hydroboration[30] of the TMS acetylene[15] afforded *Z*-vinylsilane 16 in isomerically pure form. Cleavage of the silyl ether protecting group to give alcohol 17 was followed by Swern oxidation[31] to afford vinylsilane aldehyde 18.

Table I. Cyclization of Aldehyde 18 to Cyclohexene 20 with TsNSO

solvent	Lewis-acid	temp (°C)	isolated yield (%)
CH_2Cl_2	BF_3–OEt_2	5	50
CH_2Cl_2	BF_3–OEt_2	0	61
benzene	BF_3–OEt_2	5	59
toluene	BF_3–OEt_2	−15	50
CH_2Cl_2	$SnCl_4$	0	55
CH_2Cl_2	$SnCl_4$	−78 to rt	47

Scheme III

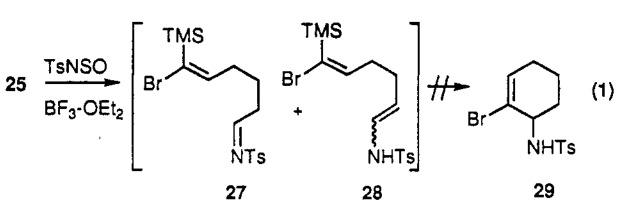


We were pleased to find that treatment of vinylsilane aldehyde 18 with *N*-sulfinyl-*p*-toluenesulfonamide (TsNSO) and BF_3–OEt_2 in fact afforded the desired allylic sulfonamide 20, presumably *via* iminium complex 19, in 50% yield as the only isolable product (Scheme II). Reaction temperature, solvent, and Lewis acids were varied with the yields remaining consistently in the 50–60% range (Table I).

Since our original route to lycoricidine (2) dictated that an appropriately substituted vinylsilane be employed (cf. Scheme I), preparation of a series of model vinylsilanes which were α-substituted was undertaken in order to test the feasibility of such a cyclization. Substituents included bromo, iodo, and phenyl.

Silylation of the known[32] acetylene 21 to TMS acetylene 22 was followed by treatment with DIBALH and bromine[33] or iodine to give the isomerically pure *Z*-(bromovinyl)silane 23 or iodo silane 24, respectively (Scheme III). Cleavage of the THP ether and Swern oxidation of the resulting alcohols gave vinylsilane aldehyde 25 and 26, respectively.

Unfortunately, treatment of (bromovinyl)silane aldehyde 25 with TsNSO and BF_3-etherate gave only a mixture of imine 27 and enamides 28 with no cyclization product 29 detected (eq 1). Similarly, treatment of iodo silane aldehyde 26 with TsNSO gave primarily recovered starting material.



The phenyl-substituted system 31 was also prepared as outlined in eq 2. Alcohol 24 was protected as THP ether 30 which could be coupled[34] with phenylmagnesium bromide in the presence of Pd(0) and subsequently converted to aldehyde 31. Once again, as with halovinyl silanes 25 and 26, treatment of 31 with TsNSO and BF_3-

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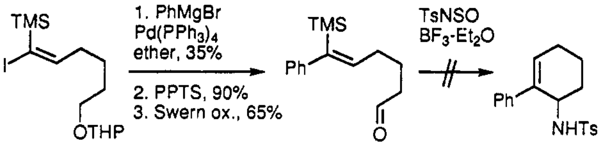
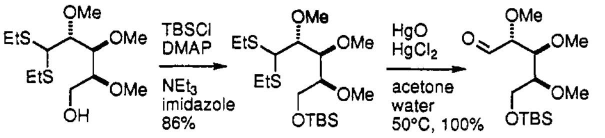


30 31 32 (2)

etherate gave none of the desired cyclization product **32**. Rather, only starting material was recovered. Although Overman has reported[35] cyclizations of (α-bromovinyl)-silanes with *N*-acyliminium compounds, it appears that these *N*-sulfonylimines may not be strong enough electrophiles to react with substituted vinylsilanes of reduced nucleophilicity.

Although our original retrosynthetic plan (Scheme I) called for the final aryl–vinyl bond to be formed *via* a cross-coupling reaction, no α-substituted vinylsilane cyclized, obviating this approach. An alternative approach was to close the B-ring using an unactivated olefin as a cyclization precursor (i.e., **12**, X = H). This approach had the added advantage of simplifying the synthesis of the C-ring component **11** (X = H). While this work was in progress, results of others[11,12] (vide infra) using a similar strategy for lycoricidine reinforced our decision to proceed in this direction.

We decided to use methyl ethers as protective groups in the initial exploratory work on the total synthesis, since the variety of potential reaction conditions which the route would entail made it difficult to envision *a priori* other protective groups which would survive all of the reactions. The simplicity of the NMR spectra of the methyl-protected intermediates was a further advantage. In addition, dithioacetal **33** (eq 3) proved to be a known compound,[36]



33 34 35 (3)

which is readily prepared in three steps from L-arabinose in good overall yield and on a large (*ca.* 50 g) scale.

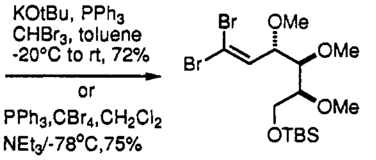
The primary hydroxy group of dithioacetal **33** was protected to afford silyl ether **34**. Deblocking of the dithioacetal of **34** to aldehyde **35** proved to be problematic. After investigation of several methods, the Corey–Erickson procedure ($AgNO_3$, NBS, lutidine)[37] was found to give moderate yields (50–70%) of aldehyde **35**. Unfortunately, the yields were variable on a multigram scale and the workup was time consuming. Alternatively, mercury salt deprotection was employed[37] which proved to be very clean and consistently high yielding on a 10–15-g scale.

At this point, a one-carbon homologation procedure was required. The Corey–Fuchs aldehyde-to-acetylene conversion[38] protocol appeared to offer a straightforward route *via* a dibromoolefin **36** to a TMS acetylene. However, only decomposition products were obtained upon subjection of aldehyde **35** to the reported reaction conditions (2 equiv of Ph_3P, CBr_4). We believe the problem here is that Ph_3PBr_2, which is a byproduct of the reaction, may be causing rapid silyl ether cleavage followed by subsequent aldehyde decomposition.[38b]

A variation of the Corey–Fuchs reaction employs metallic zinc to reduce Br_2PPh_3 with formation of $ZnBr_2$ and regeneration of PPh_3, thus lowering the amount of PPh_3 required to 1 equiv.[38] However, 1 equiv of $ZnBr_2$ is thereby generated, which can likewise cause silyl ether cleavage and subsequent decomposition. Not surprisingly, this variation also led only to disappearance of aldehyde **35** with none of the desired homologation product, or indeed any product, isolated.

We thus considered some means of generating the desired Wittig reagent which would not give rise to the undesired Br_2PPh_3 or $ZnBr_2$. Several authors have reported the preparation of the dibromomethyl phosphorane by treatment of bromoform with KOtBu in the presence of PPh_3, although the procedure apparently has found little synthetic application since the initial disclosures in the early 1960's.[39] In the event, addition of bromoform to a solution of PPh_3 and KOtBu in toluene at −20 °C, followed by addition of aldehyde **35**, afforded dibromoolefin **36** in high yield (eq 4).

35



36 (4)

Unfortunately, the yields of dibromoolefin **36** were inconsistent on a multigram scale, probably as a result of cleavage of the silyl group by alkoxide.[40] After further experimentation, a convenient variant of the Corey–Fuchs procedure was developed ($2PPh_3/CBr_4$, NEt_3, −78 °C, 5 min) which reproducibly gave 75% yields of **36** on a 5-g scale.[41]

Dibromoolefin **36** was then transformed into silylacetylene **37** using the Corey–Fuchs[38] conditions in good yield on a subgram scale (Scheme IV), but side products resulting from elimination of methoxy groups became significant on a multigram scale. A two-step conversion *via* acetylene **38** avoided this problem and gave good yields in both steps.

Catalytic hydrogenation using $Pd/BaSO_4$ was found to be the method of choice for the reduction of silylacetylene **37** to vinylsilane **39** (Scheme V). Interestingly, the *Z*/*E* selectivity of the reduction was found to be both concentration and protective group dependent. The maximum *Z*/*E* selectivity of 20:1 in the reduction of OTBS silyl-

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(37) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

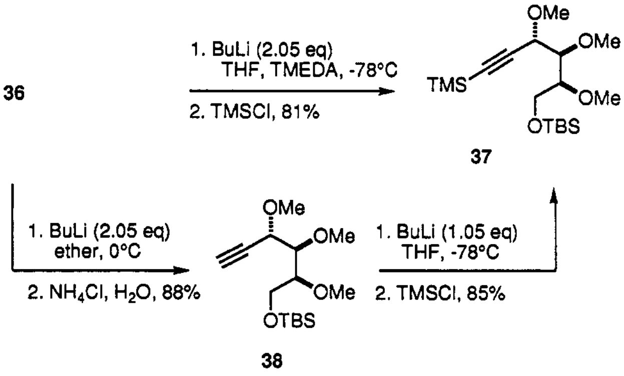
(38) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769. (b) See also, for example: Levas, É.; Raulet, D. *Bull. Soc. Chim. Fr.* **1971**, *71*, 2598.

(39) Maercker, A. *Org. React.* **1965**, *14*, 270.

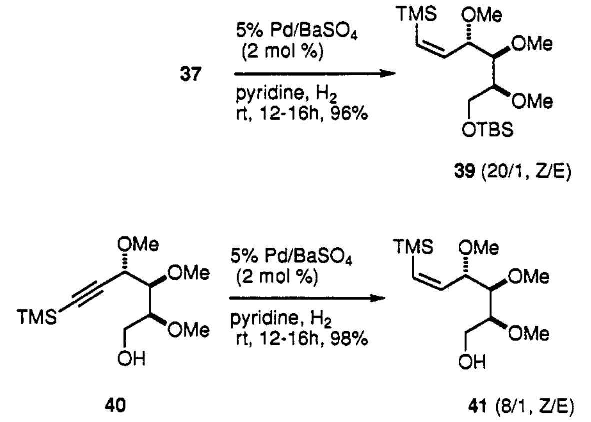
(40) The Wittig reagent is thought to slowly deprotonate the t-butyl alcohol to regenerate the alkoxide (Speziale, A. J.; Ratts, K. W. *J. Am. Chem. Soc.* **1962**, *85*, 854).

(41) Literature reports have occasionally indicated the use of triethylamine, K_2CO_3, or other additives in the Corey–Fuchs reactions. We found the use of triethylamine to give the highest and most consistent yields of olefinated products, although it is not clear precisely what function the amine is performing. The reaction was performed so as to generate 2 equiv each of the Wittig reagent and Ph_3PBr_2, but only 1 equiv of triethylamine was used. Addition of 2 equiv of triethylamine resulted in only 50–60% conversion of aldehyde to dibromoolefin by TLC analysis. Even in the presence of triethylamine, silyl group cleavage occurs to a significant extent at −78 °C within the 5-min reaction time employed, and the reaction must be quenched immediately upon determining that the starting material has been consumed in order to obtain the optimal (75%) yield.

Scheme IV

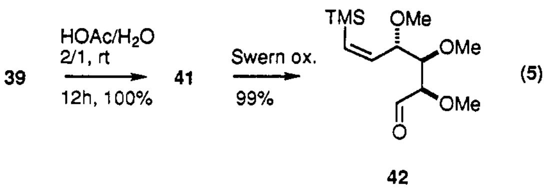


Scheme V



acetylene **37** required a concentration of *ca.* 0.22 M of substrate in pyridine. Higher dilution (0.11 M) gave no significant increase in selectivity, whereas a *Z*/*E* ratio as low as 4:1 was observed when a 0.65 M solution was used. The unprotected silylacetylene alcohol **40** gave lower selectivity in formation of **41** which was not improved at higher dilution.

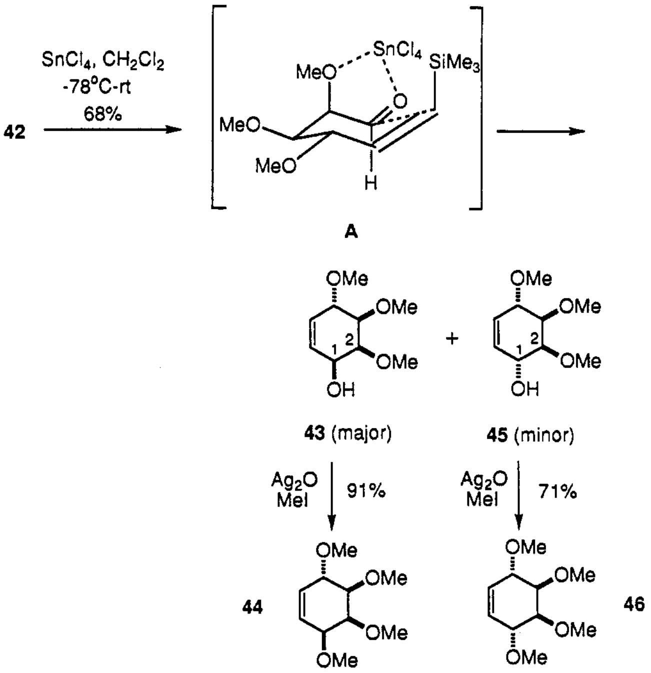
The *Z* and *E* isomers of vinylsilane **39** were inseparable by preparative TLC and were therefore used without separation. The silyl ether was cleaved under mild conditions and resulting alcohol **41** was oxidized to aldehyde **42** in excellent yield (eq 5).



(5)

At this point, with the key vinylsilane aldehyde **42** in hand, we were ready to attempt the *N*-sulfonyliminium ion cyclization. Disappointingly, treatment of vinylsilane aldehyde **42** with TsNSO and $SnCl_4$ failed to afford any of the desired aminocyclitol (cf. **11** (X = H), Scheme I). However, a mixture of products was obtained which had not incorporated the sulfonamide and which proved to be mainly the cyclitol **43** along with a smaller amount of isomer **45** (Scheme VI). This result was unexpected, since there were no literature reports of cyclizations of vinylsilane aldehydes to afford allylic alcohols.[42] We therefore examined this novel reaction in more detail.

Scheme VI



The cyclization of vinylsilane aldehyde **42** to alcohols **43** and **45** was optimized to 68% yield and a selectivity of >30:1 simply by addition of the Lewis acid to a solution of the aldehyde at −78 °C, followed by quenching of the reaction mixture upon warming to rt.[43] The stereochemistry of **43** and **45** was determined by methylation of the remaining hydroxyl group to afford the chiral and meso tetramethyl ethers **44** and **46**, respectively,[44] which were easily distinguished on the basis of their ^1H NMR and ^{13}C NMR spectra. The major isomer was thus proven to be the 1,2-*syn* epimer **43**. Obtention of the 1,2-*syn* isomer **43** as the major product in the $SnCl_4$-induced cyclization suggested that the reaction proceeded *via* a chelated chair-like transition state **A** (Scheme VI).[45]

On the basis of this reasoning, we expected that a nonchelating Lewis acid such as BF_3–OEt_2 would likely reverse the stereoselectivity of the reaction, since the pseudo-gauche interaction along the forming bond between the Lewis acid-complexed carbonyl group and the TMS group in transition state **A** (Scheme VI) or transition state **C** (Scheme VII) would be absent in transition state **B** (Scheme VII), where the two groups are antiperiplanar. This proved to be the case, with an isomer ratio of 4.3:1 of alcohols **45**/**43** being obtained upon treatment of vinylsilane aldehyde **42** with BF_3–OEt_2 at 0 °C. For reasons which are not clear, the optimal selectivity (>30:1) was achieved in the BF_3–OEt_2-induced cyclizations when the Lewis acid was added slowly (over 30 min) at rt to a solution of the vinylsilane aldehyde. More rapid addition of the Lewis acid at −78 °C, followed by quenching of the reaction mixture upon warming to rt, gave a selectivity of only *ca.* 10:1.

The cyclitol products **43** and **45** are semiprotected conduritols C (**47**) and A (**48**), respectively. Interest in

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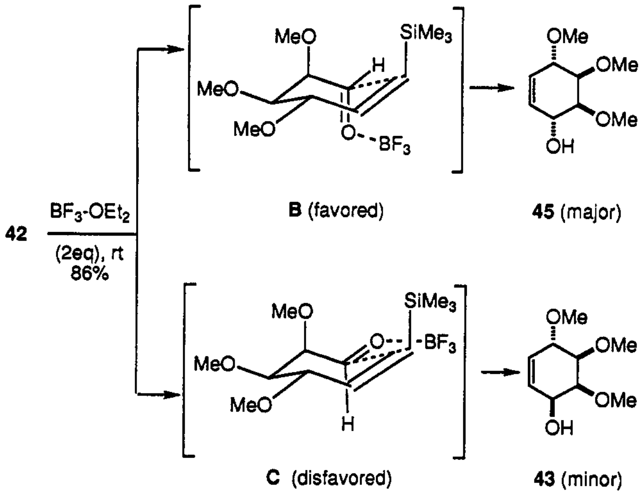
[42] One intermolecular addition of a vinylsilane with chloral had been reported at the time (Deleris, G.; Dunogues, J.; Calas, R. *J. Organomet. Chem.* **1975**, *93*, 43). The intermolecular addition of vinylsilanes to glyoxylates (Mikami, K.; Wakabayashi, H.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 4337) was reported as our preliminary publication[26b] was in press. A single example of a Lewis acid-mediated cyclization of a vinylsilane with an acetal to give an exocyclic allylic ether has been reported: Fleming, I.; Chow, H.-F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1815.

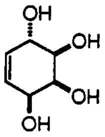
[43] Ratios of the cyclization products were determined by ^1H NMR integration of the crude mixtures, which were then separated by preparative TLC for full characterization.

[44] Meso compound **46** is known: Cambie, R. C.; Renner, N. D.; Rutledge, P. S.; Woodgate, P. D. *Synth. Commun.* **1989**, *19*, 537.

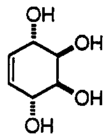
[45] Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421. For a recent review of allylic 1,3-strain in stereoselective reactions, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1.

Scheme VII



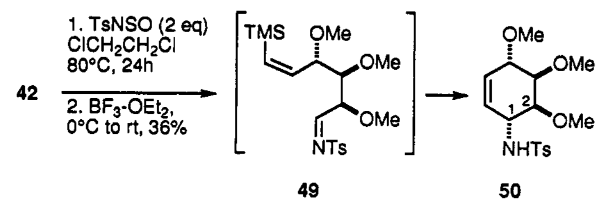


47 (conduritol C)

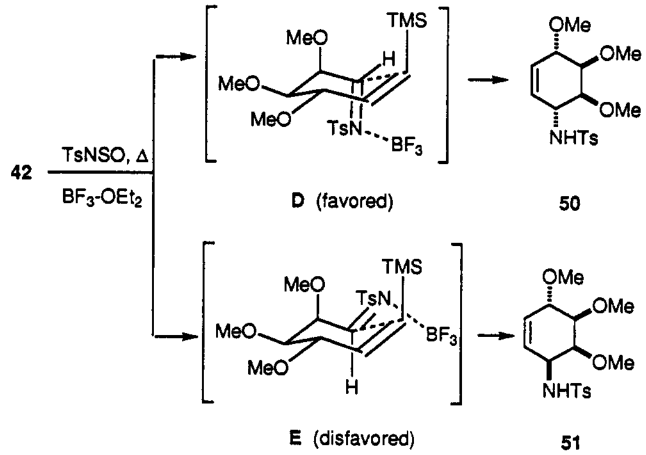


48 (conduritol A)

Scheme VIII



Scheme IX



the synthesis of both conduritols and aminoconduritols has been rapidly increasing.[46,47] Not only does this vinylsilane aldehyde cyclization reaction constitute a novel approach to the conduritols, but the stereodivergent[48] aspect of the reaction allows for the selective preparation of either conduritol A or C from the same chiral sugar-derived precursor simply by employing a chelating or nonchelating Lewis acid, respectively.[26b] This methodology could presumably be applied to different conduritols starting with pentoses other than L-arabinose.

The more rapid cyclization of the vinylsilane aldehyde relative to imine formation under Lewis acidic conditions necessitated an alternative procedure for generating the *N*-sulfonyliminium ion. *N*-Sulfinyl reagents are known to react thermally with aldehydes in the absence of Lewis acids to give *N*-sulfonylimines.[49] We therefore employed a two-step process to prepare the requisite aminocyclitol[50] whereby vinylsilane aldehyde **42** was first converted to *N*-sulfonylimine **49** under neutral (thermal) conditions (Scheme VIII).[49] The imine was then treated in situ with boron trifluoride etherate to effect cyclization to the aminocyclitol. After considerable experimentation, the optimal conditions led to only a 36% yield of the desired aminocyclitol **50** as a single stereoisomer (Scheme VIII). In all cases, cyclitol **45** was apparent by ^1H NMR and TLC analysis of the crude reaction mixtures, which indicated that imine formation had not proceeded to completion. However, heating the reaction mixture for longer times, at higher temperatures, or with a larger excess of TsNSO gave no improvement in the yield of the aminocyclitol and generally resulted in significant decomposition of the aldehyde. Imine formation under neutral conditions was also attempted using high pressure (10 kBar) and sonication. However, only trace amounts of imine were formed on the basis of the yield of aminocyclitol **50** isolated after treatment of the reaction mixtures with Lewis acid.

The 1,2-anti stereochemistry in **50** was tentatively assigned by analogy to the BF_3-OEt_2-induced cyclization of vinylsilane aldehyde **42** to cyclitol **45**. Thus, transition state **D**, with the Lewis acid-complexed N-sulfonyl iminium ion antiperiplanar to the bulky TMS group along the forming bond, avoids the pseudo-gauche interaction present in conformer **E** (Scheme IX) which leads to isomer **51**. Further support for the stereochemical assignment was obtained by *N*-methylation of aminocyclitol **50** to *N*-methylsulfonamide **52** (eq 6), which was identical to

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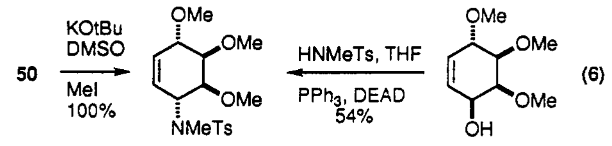
(46) (a) For reviews of conduritols, see: Balci, M.; Sütbeyaz, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715. (b) Posternak, T. *The Cyclitols*; Holden-Day, San Francisco, 1965.

(47) See, for example: (a) Johnson, C. R.; Plé, P. A.; Adams, J. P.; *J. Chem. Soc., Chem. Commun.* **1991**, 1006. (b) Johnson, C. R.; Plé, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388. (c) Takano, S.; Moriya, M.; Higashi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 177. (d) Chida, N.; Ohtsuka, M.; Nakazawa, K.; Ogawa, S. *J. Org. Chem.* **1991**, *56*, 2976 and references cited therein. (e) Miyamoto, M.; Baker, M. L.; Lewis, M. D. *Tetrahedron Lett.* **1992**, *33*, 3725. (f) Barton, D. H. R.; Augy-Dorey, S.; Camara, J.; Dalko, P.; Delauméӱ, J. M.; Géro, S. D.; Quiclet-Sine, B.; Stütz, P. *Tetrahedron* **1990**, *46*, 215 and refs cited therein. (g) Paulsen, H.; Röben, W.; Heiker, F. R. *Chem. Ber.* **1981**, *114*, 3242. (h) Chida, N.; Yamada, K.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1991**, 588. (i) Akiyama, T.; Shima, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 5573. (j) Hudlicky, T.; Luna, H.; Olivo, H. F.; Anderson, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans 1* **1991**, 2907. (k) Ley, S. V.; Yeung, L. L. *Synlett* **1992**, 997. (l) Carless, H. A. J.; Oak, O. Z. *J. Chem. Soc., Chem. Commun.* **1991**, 61 and refs cited therein. (m) Marco-Contelles, J.; Martinez, L.; Martinez-Grau, A.; Ponzuilo, C.; Jimeno, M. L. *Tetrahedron Lett.* **1991**, *32*, 6437. (n) Le Drian, C.; Vionnet, J.-P.; Vogel, P. *Helv. Chim. Acta* **1990**, *73*, 161 and refs cited therein.

(48) For some other recent examples of Lewis acid-mediated stereodivergence, see: Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 999. Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 3211. Nishigaichi, Y.; Takuwa, A.; Jodai, A. *Tetrahedron Lett.* **1991**, 2383. Yamada, J.-I.; Abe, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6118. Nakai, T.; Mikami, K.; Kawamoto, K.; Loh, T.-P. *J. Chem. Soc., Chem. Commun.* **1990**, 1161.

(49) cf. Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393.

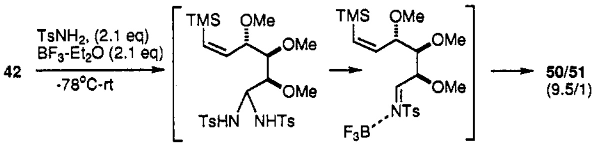
(50) (a) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709. (b) Although Mitsunobu reactions are known to proceed with both retention and inversion of stereochemistry (Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670 and refs cited therein), the retention products are special cases and are usually the result of ionization of the intermediate phosphonium species or the result of neighboring group participation. Ionization of the phosphonium ion intermediate to the corresponding allyl cation is unlikely to occur in this case because of the electron-withdrawing methoxy groups (See, for example, ref 45a,b). Allylic (vs ipso) substitution products have also been known to occur in Mitsunobu reactions, but the allylic substitution product of the reaction of alcohol **43** would be epimeric to compound **52**.



52 43 (6)

the product of Mitsunobu reaction of alcohol **43** and N-methyl-p-toluenesulfonamide.[50,51]

At this point, we became aware of a recent report[25d] which described the preparation of N-sulfonyl imines derived from ketones and nonenolizable aldehydes under relatively mild Lewis acidic conditions, although no examples using enolizable aldehydes were described. We employed a variation of this procedure in the hope of generating the N-sulfonyliminium ion prior to direct cyclization of the vinylsilane aldehyde. In the event, treatment of a mixture of vinylsilane aldehyde **42** and p-toluenesulfonamide with BF_3–OEt_2 at 78 °C, followed by warming of the reaction mixture to rt, afforded aminocyclitols **50** and **51** in a 9.5:1 ratio. The desired aminocyclitol **50** could be isolated consistently from the mixture in at least 65% yield (eq 7).



53 54 (7)

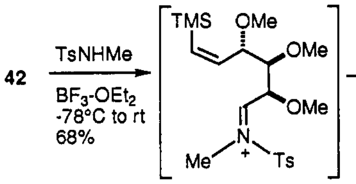
The reaction apparently proceeds *via* bis(sulfonamide) adduct **53**, which eliminates to iminium complex **54**. Rapid disappearance of aldehyde **42** at low temperature occurred with concomitant formation of a UV-active compound as detected by TLC analysis of the reaction mixture. This compound diminished as the temperature rose past 0 °C and disappeared altogether after the reaction was maintained at room temperature, with simultaneous appearance of aminocyclitol. On one occasion, we isolated bis(sulfonamide) **53**, although hydrolysis to the aldehyde and $TsNH_2$ occurred during chromatography on silica gel and it was difficult to totally purify the compound.

Interestingly, this procedure also worked well using N-methyl-p-toluenesulfonamide, which stereoselectively afforded aminocyclitol **52** in good yield as a single isomer (eq 8). A unique aspect of this reaction is that it probably proceeds *via* an N-methyl-N-sulfonyliminium ion rather than a Lewis acid-coordinated iminium ion.

Table II. Heck of Cyclizations of *N*-Acylsulfonamide 56 Using Pd (DIPHOS/DMF)

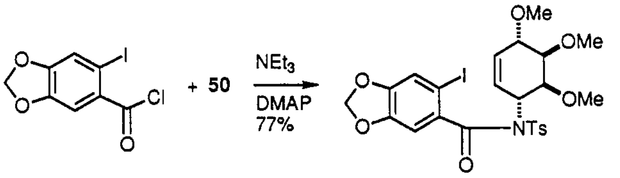
entry	base	temp (°C)	time (h)	yield (%)		
				58	**60**	**50**
1	TIOAc	140	13	50	45[a]	–
2	TIOAc	100	16	54	40[a]	–
3	TIOAc	68	36	50	45[a]	–
4	Ag_2CO_3	120	14	51	–	25
5	Ag_2CO_3	80	36	–	–	–
6	AgOAc	140	24	25(58)[b]	–	–
7	AgOAc	140	48	29(73)[b]	–	–
8	Bu_4NOAc	140	16	–	50[a]	50[a]

[a] Yield estimated by ^1H NMR analysis. [b] (Yield) based on recovered starting material.



(8)

In our very early planning for synthesis of lycoricidine, we had considered the possibility of forming the aryl–vinyl bond of the alkaloid *via* an intramolecular Heck reaction.[52,53] However, stereochemical considerations (vide infra) led us to abandon this strategy in favor of the cross-coupling approach outlined in Scheme I. However, while the work described here was well underway, Ogawa,[12] and later Hudlicky,[11] reported using such a Heck reaction for closure of the lycoricidine B-ring in very similar systems. Since we had aminocyclitol **50** in hand, we decided to explore construction of the lycoricidine framework using such an approach. Although both Ogawa and Hudlicky used an aryl bromide in their Heck reactions, we decided that an aryl iodide might allow the proposed cyclization to be run under milder conditions. Thus, coupling of 6-iodopiperonyl chloride (**55**)[54] and aminocyclitol **50** afforded N-acylsulfonamide **56** (eq 9).



55 56 (9)

Cyclization of **56** using variations of the Ogawa procedure (Table II, entries 1–3) afforded the desired phenanthridone **58** in about 50% yields (Scheme X). Interestingly, the only isolable byproduct was cyclitol acetate **60**. Use of Ag_2CO_3 as base instead of TlOAc also gave **58** in about the same yield (entry 4), but the deacylation product **50** was produced instead of acetate **60**. If tetrabutylammonium acetate was used, only **50** and **60** were formed (entry 8). It is clear from these results that the counterion of the base (Tl^+,Ag^+,Bu_4N^+) plays a key role in determining the outcome of the reaction, although what that role is remains unclear.

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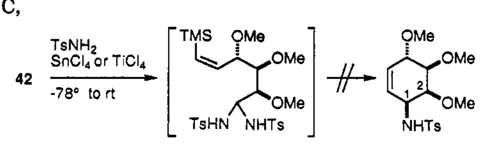
(51) All attempts to selectively prepare the 1,2-*syn* aminocyclitol **i** by the use of chelating Lewis acids ($TiCl_4$, $SnCl_4$) were unsuccessful. Vinylsilane aldehyde **42** was treated with and $TsNH_2$ and $TiCl_4$ or $SnCl_4$ at −78 °C,



53 i

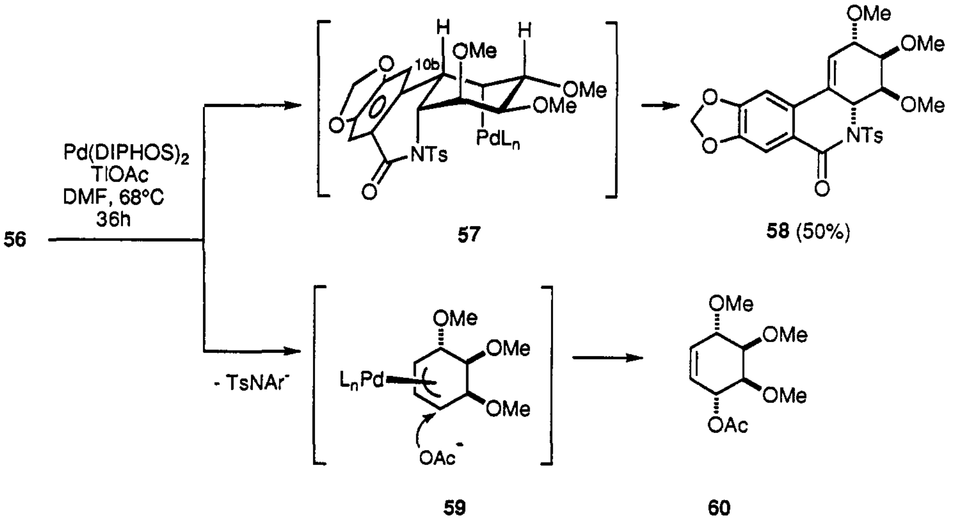
followed by warming of the reaction mixture to rt, but only the bis(sulfonamide) adduct **53** was apparent by TLC analysis. In one case, the reaction mixture was heated at 40 °C for 16 h, but only a trace of the 1,2-anti isomer **50** was detected.[26c]

(52) For reviews of the Heck reaction, see: Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, p 833. Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. Heck, R. F. *Org. React.* **1982**, *27*, 345.

(53) For recent examples of intramolecular Heck reactions, see: (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) Zhang, Y.; O'Conner, B.; Negishi, E. *J. Org. Chem.* **1988**, *53*, 5588. (c) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003. (d) Negishi, E.; Zhang, Y.; O'Conner, B. *Tetrahedron Lett.* **1988**, *29*, 2915. (e) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919 and refs cited therein.

(54) Prepared from the known acid: Kobayashi, S.; Kihara, M.; Hashimoto, T.; Shingu, T. *Chem. Pharm. Bull.* **1976**, *24*, 716.

Scheme X



The success by us, as well as by Ogawa[12] and Hudlicky,[11] in forming a phenanthridone like **60** is surprising if one considers the accepted mechanism and stereochemistry of the Heck reaction.[52] Thus, one would expect *syn*-1,2-addition of a palladated aromatic to the olefin moiety of **56** to afford tricycle **57** (Scheme X). However the next step, which should be a *syn*-β-elimination of palladium hydride, is precluded in **57**, and apparently an unusual, but not totally unprecedented,[55] anti-elimination occurs to yield **58**. The regioselectivity of this mode of PdH elimination may be favored by the acidity of the hydrogen at C-10b.

The acetate **60** must be formed by displacement of the allylic tosylamide group[56] to give the chiral π-allyl palladium complex **59** (Scheme X). Attack of acetate anti to the palladium would then afford **60**, whose identify was confirmed by saponification of the acetyl group to afford the previously synthesized alcohol **45**. Attack of the acetate ion at the other allylic position would be disfavored by a 1,2-*syn*-interaction with the neighboring methoxy group.[57]

We have therefore been able to develop in 13 steps an efficient route to the ring system of (+)-lycoricidine (**2**) starting from L-arabinose. We are currently investigating the use of oxygen protecting groups other than methyl and hope to use the methodology described here in total synthesis of several alkaloids of this class.[57]

Experimental Section

General Methods. All chemicals were purchased from Aldrich Chemical Co. Reactions were run under an atmosphere of nitrogen or argon. When extractions were performed, the organic phase was washed with saturated NaCl solution as the final extraction step and dried over anhydrous $MgSO_4$. Concentrations were done under reduced pressure on a rotary evaporator. Flash chromatography[59] and dry column flash chromatography[60] were performed using EM Science silica gel 60. Preparative TLC was performed using EM Science silica gel 60 PF_{254}.

Preparation of TMS-Acetylene 15. n-BuLi (30 mL, 1.6 M in hexanes, 48 mmol) was added over 15 min to acetylene **14** (8.2 g, 37 mmol) in 100 mL of THF at −78 °C, followed after 5 min by TMSCl (6.1 mL, 5.2 g, 48 mmol). The reaction mixture was allowed to warm to rt and then was poured into saturated $NaHCO_3$ solution and extracted three times with ether. The combined organic extracts were dried and concentrated in vacuo to afford TMS-acetylene **15** (10.5 g, 99%) as an oil, which was used without further purification: IR (film) 2160 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.6 (2H, m), 2.2 (2H, m), 1.55 (4H, m), 0.87 (9H, s), 0.1 (9H, s), 0.03 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 107.2, 84.1, 62.3, 31.4, 25.4, 24.5, 19.0, 17.7, −0.5, −6.0; CI MS *m/z* 285, 269, 227, 211, 171, 147, 133.

Synthesis of Vinylsilane 16. Cyclohexene (8.5 mL, 6.9 g, 84.4 mmol) was added over 10 min to a solution of BH_3–THF (42 mL, 1 M in THF, 42 mmol) in 120 mL of THF at 0 °C, followed after 1 h by TMS-acetylene **15** (6.0 g, 21.1 mmol) in 10 mL of THF. After stirring for 12 h at rt, the reaction mixture was cooled to 0 °C and 5 mL of 1-hexene was added, followed after 1 h by 5 mL of HOAc. After 2 h at rt, the reaction mixture was poured into saturated $NaHCO_3$ solution and extracted three times with ether. The combined organic extracts were dried and concentrated in vacuo. Dry column flash chromatography of the mixture using hexanes gave vinylsilane **16** (5.6 g, 92%) as an oil: IR (film) 1240, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.3 (1H, dt, J = 7.2, 13.8 Hz), 5.5 (1H, d, J = 13.8 Hz), 3.6 (2H, t, J = 6 Hz), 2.15 (2H, m), 1.4–1.6 (4H, m), 0.9 (9H, s), 0.1 (9H, s), 0.08 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.1, 129.0, 62.6, 32.8, 32.1, 25.6, 25.5, 17.7, −0.4, −6.0; CI MS *m/z* 287, 271, 229, 199, 189, 147, 133.

Formation of Alcohol 17. Bu_4NF-$3H_2O$ (3.8 g, 12 mmol) was added to a solution of silyl ether **16** (2.9 g, 10.0 mmol) in 50 mL of THF at 0 °C. The reaction mixture was stirred for 12 h at rt and then was poured into aqueous NH_4Cl and extracted three times with ether. The combined organic extracts were dried and concentrated in vacuo. Dry column flash chromatography of the concentrate using gradient elution (5%, 10% ethyl acetate in hexanes) gave alcohol **17** (1.6 g, 93%) as an oil: IR (film) 3300, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.4–6.2 (1H, dt, J = 7.4, 14.1 Hz), 5.5 (1H, d, J = 14.1 Hz), 3.6 (2H, t, J = 6.3 Hz), 2.15 (2H, m), 1.35–1.65 (4H, m), 0.1 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.9, 129.1, 61.8, 32.7, 31.7, 25.4, −0.4; CI MS *m/z* 173, 157, 139, 103, 91.

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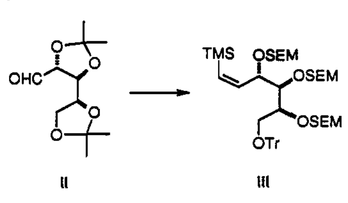
(55) For other examples of apparent trans β-hydride eliminations, see: (a) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259. (b) Reference 53c. (c) Amos, P. C.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1987**, 510.

(56) For an example of a displacement of an allylic sulfonamide by palladium, see: Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1992**, *57*, 2528.

(57) Conduritol acetates have been used previously in palladium-mediated allylic alkylations: Barton, D. H. R.; Dalko, P.; Gero, S. D. *Tetrahedron Lett.* **1991**, *32*, 2471. See also ref 47b.

(58) Attempts to demethylate **58** with BBr_3 were unsuccessful. However, we have successfully converted L-arabinose derived bis(ketal) **ii** to SEM-protected vinylsilane **iii** in seven steps.[25c]



ii iii

(59) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(60) Harwood, L. M. *Aldrichim. Acta* **1985**, *18*, 25.

(61) Hori, T.; Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1456.

Preparation of Aldehyde 18. DMSO (4.7 mL, 5.2 g, 66 mmol) in 10 mL of CH_2Cl_2 was added over 10 min to a solution of oxalyl chloride (2.4 mL, 3.5 g, 28 mmol) in 100 mL of CH_2Cl_2 at −78 °C, followed after 15 min by alcohol **17** (2.4 g, 14 mmol) in 10 mL of CH_2Cl_2, maintaining the reaction temperature below −65 °C. After 15 min, NEt_3 (12 mL, 8.4 g, 83 mmol) was added. The reaction mixture was allowed to warm to rt, poured into 100 mL of water, and extracted three times with CH_2Cl_2. The combined organic extracts were washed twice with water, dried, and concentrated in vacuo. Dry column flash chromatography of the residue using 1% ethyl acetate in hexanes gave aldehyde **18** (2.2 g, 92%) as an oil: IR (film) 2700, 1720, 1600, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.8 (1H, t, J = 1.7 Hz), 6.15–6.35 (1H, dt, J = 7.3, 14.1 Hz), 5.55 (1H, dt, J = 1.3, 14.0 Hz), 2.45 (2H, m), 2.15 (2H, m), 1.7 (2H, m), 0.05 (9H, s); ^{13}C NMR (200 MHz, $CDCl_3$) δ 202.3, 147.6, 130.3, 42.7, 32.1, 21.3, −0.5; CI MS m/z 171, 169, 155, 129, 116, 111.

***N*-Tosyl-1-amino-2-cyclohexene (20).** BF_3–OEt_2 (0.008 mL, 8.5 mg, 60 mmol) was added to a solution of aldehyde **18** (102 mg, 0.60 mmol) and *N*-sulfinyl-*p*-toluenesulfonamide[61] (260 mg, 1.2 mmol) in 5 mL of CH_2Cl_2 at 5 °C. The reaction mixture was stirred for 2 h at 5 °C, for 4 h at rt, and then was poured into saturated $NaHCO_3$ solution and extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. Preparative TLC of the crude product mixture using 25% ethyl acetate in hexanes gave sulfonamide **20** (76 mg, 50%) as a white solid: IR ($CDCl_3$) 3360, 3250, 2910, 1320, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, m), 7.3 (2H, m), 5.8 (1H, m), 5.35 (1H, m), 4.4 (1H, m), 3.8 (1H, m), 2.4 (3H, s), 1.9 (2H, m), 1.4–1.8 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.3, 131.4, 129.6, 127.0, 126.9, 48.9, 30.2, 24.4, 21.5, 19.2; CI MS m/z 252, 172, 155, 139, 96.

Synthesis of TMS-Acetylene 22. Acetylene **21**[32] (18.8 g, 100 mmol) was silylated as described in the preparation of **15** to afford TMS–acetylene **22** (24.6 g, 97%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 4.56 (1H, m), 3.65–3.9 (2H, m), 3.3–3.55 (2H, m), 2.25 (2H, t, J = 6.6 Hz), 1.4–1.9 (10H, m), 0.1 (9H, s).

Preparation of (Bromovinyl)silane 23. A solution of DIBALH (14.4 mL, 1 M in hexanes, 14.4 mmol) and TMS-acetylene **22** (1.45 g, 5.74 mmol) in 60 mL of ether was heated for 12 h under reflux. The reaction mixture was cooled to −78 °C, and pyridine (3.0 mL, 2.9 g, 37 mmol) was added, followed by Br_2 (1.0 mL, 3.1 g, 19.5 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was stirred for 15 min at −78 °C and then was allowed to warm to rt. The reaction mixture was poured into 100 mL of 1 N NaOH and extracted three times with ether. The combined organic extracts were washed once each with 5% aqueous HCl and saturated $NaHCO_3$ solution and then were dried and concentrated in vacuo. Dry column flash chromatography of the concentrate using 2% ethyl acetate in hexanes gave (bromovinyl)silane **23** (0.93 g, 48%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 6.75 (1H, t, J = 7.9 Hz), 4.55 (1H, m), 3.7–3.95 (2H, m), 3.3–3.55 (2H, m), 2.1 (2H, m), 1.4–1.9 (10H, m), 0.3 (9H, s).

Formation of Aldehyde 25. A solution of THP ether **23** (164 mg, 0.50 mmol) and ca. 25 mg of PPTS in 5 mL of ethanol were heated at 40 °C for 12 h and then concentrated in vacuo. The residue was diluted with ether, poured into saturated $NaHCO_3$, and extracted three times with ether. The combined organic extracts were dried and concentrated in vacuo. The concentrate was purified by preparative TLC using 25% ethyl acetate in hexanes to afford the corresponding alcohol (126 mg, 100%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 6.75 (1H, t, J = 6.8 Hz), 3.65 (2H, m), 2.1 (2H, m), 1.4–1.7 (4H, m), 0.25 (9H, s).

The alcohol (138 mg, 0.55 mmol) was oxidized as described in the preparation of **18** to give aldehyde **25** (92 mg, 67%) as an oil after preparative TLC using 15% ethyl acetate in hexanes: ^1H NMR (200 MHz, $CDCl_3$) δ 9.8 (1H, t, J = 1.4 Hz), 6.7 (1H, t, J = 8.0 Hz), 2.5 (2H, dt, J = 1.4, 7.2 Hz), 2.1 (2H, m), 1.7 (2H, m), 0.25 (9H, s).

Synthesis of (Iodovinyl)silane 24. A solution of DIBALH (2.0 mL, 1 M in hexanes, 2.0 mmol) and TMS-acetylene **22** (200 mg, 0.79 mmol) in 5 mL of ether was heated for 16 h under reflux. The reaction mixture was cooled to −78 °C, and I_2 (500 mg, 1.97 mmol) in 5 mL of ether was added. The reaction mixture was stirred for 1 h at −78 °C and for 15 min at 0 °C and then was poured into cold 5% aqueous HCl and extracted three times with ether. The combined organic extracts were washed once each with 1 N NaOH and 1 M $Na_2S_2O_3$ and then were dried and concentrated in vacuo. Flash chromatography of the mixture using 10% ethyl acetate in hexanes afforded alcohol **24** (106 mg, 45%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 7.15 (1H, t, J = 7.9 Hz), 3.65 (2H, t, J = 6.1 Hz), 2.1 (2H, m), 1.7–1.4 (4H, m), 0.3 (9H, s).

Aldehyde 26. Alcohol **24** (106 mg, 0.36 mmol) was oxidized as described in the preparation of **18** to afford aldehyde **26** (90 mg, 85%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 9.75 (1H, s), 7.1 (1H, t, J = 8.1 Hz), 2.45 (2H, t, J = 6.7 Hz), 2.1 (2H, m), 1.7 (2H, m), 0.25 (9H, s).

Preparation of THP Ether 30. A solution of alcohol **24** (0.73 g, 2.45 mmol), 3,4-dihydro-2*H*-pyran (1.2 mL, 1.1 g, 12.7 mmol), and ca. 50 mg of PPTS in 15 mL of CH_2Cl_2 was stirred for 16 h, poured into saturated $NaHCO_3$ solution, and extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. Preparative TLC of the residue using 10% ethyl acetate in hexanes gave THP ether **30** (0.90 g, 96%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 7.15 (1H, t, J = 8.6 Hz), 4.5 (1H, m), 3.65–3.9 (2H, m), 3.35–3.6 (2H, m), 2.1 (2H, m), 1.4–1.9 (10H, m), 0.25 (9H, s).

(Phenylvinyl)silane 31. A mixture of PhMgBr (0.34 mL, 3 M in ether, 1.0 mmol), iodide **30** (196 mg, 0.51 mmol), and $Pd(PPh_3)_4$ (59 mg, 0.051 mmol, 10 mol %) in 14 mL of 2.5:1 ether/THF was heated under reflux for 16 h. The reaction mixture was cooled to rt and then was quenched by the dropwise addition of methanol. The reaction mixture was poured into water and extracted three times with ether. The combined organic extracts were dried and concentrated in vacuo. Preparative TLC of the residue (2% ethyl acetate in hexanes) gave the (phenylvinyl)silane (58 mg, 35%) as an oil and TMS-acetylene **22** (52 mg, 40%): ^1H NMR (200 MHz, $CDCl_3$) δ 7.35–7.0 (5H, m), 6.1 (1H, t, J = 7.1 Hz), 4.6 (1H, m), 3.7–3.95 (2H, m), 3.35–3.6 (2H, m), 2.3 (2H, m), 1.4–2.0 (10H, m), 0.15 (9H, s).

The (phenylvinyl)silane (58 mg, 0.17 mmol) was deprotected as described in the preparation of **25** to give the corresponding alcohol (39 mg, 90%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.15–7.3 (3H, m), 7.05 (2H, m), 6.05 (1H, t, J = 7.6 Hz), 3.7 (1H, m), 2.3 (2H, m), 1.45–1.7 (4H, m), 0.15 (9H, s).

The alcohol (39 mg, 0.16 mmol) was oxidized as described in the preparation of **18** to give aldehyde **31** (25 mg, 65%) as an oil after preparative TLC using 10% ethyl acetate in hexanes: ^1H NMR (300 MHz, $CDCl_3$) δ 9.8 (1H, t, J = 1.6 Hz), 7.15–7.35 (3H, m), 7.0 (2H, m), 6.05 (1H, t, J = 7.4 Hz), 2.5 (2H, dt, J = 1.6, 7.3 Hz), 2.3 (2H, m), 1.8 (2H, m), 0.15 (9H, s).

Preparation of Silyl Ether 34. A solution of alcohol **33** (18.1 g, 61 mmol), TBSCl (11 g, 73 mmol), imidazole (9.9 g, 146 mmol), and ca. 500 mg of DMAP in 15 mL of DMF was stirred for 16 h at rt and then was poured into saturated $NaHCO_3$ and extracted four times with ether. The combined organic extracts were washed three times with water, dried, and concentrated in vacuo. Dry column flash chromatography of the concentrate using gradient elution (1, 2.5, and 5% ethyl acetate in hexanes) yielded silyl ether **34** (22 g, 86%) as an oil: IR (film) 2900, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.0 (1H, d, J = 7.9 Hz), 3.95–3.8 (2H, m), 3.7–3.6 (1H, dd, J = 3.8, 11.3 Hz), 3.6–3.4 (1H, m), 3.5 (3H, s), 3.46 (3H, s), 3.3 (3H, s), 3.25–3.15 (1H, m), 2.8–2.5 (4H, m), 1.2 (6H, t, J = 7.4 Hz), 0.8 (9H, s), 0.0 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 84.1, 81.6, 79.6, 60.8, 60.6, 60.3, 57.0, 53.0, 25.5, 24.0, 14.00, 13.95, −5.9, −6.0; CI MS m/z 412, 397, 381, 351, 319, 287, 263, 245, 233.

Conversion of Dithioacetal 34 to Aldehyde 35. $HgCl_2$ (57 g, 210 mmol) was added with vigorous stirring to a suspension of dithioacetal **34** (18.2 g, 44 mmol) and HgO (57 g, 263 mmol) in 400 mL of 9/1 acetone/water. The reaction mixture was heated at 50–55 °C for 1 h, allowed to cool to rt, and filtered through Celite. The solvent was removed in vacuo, and the residue was diluted with CH_2Cl_2. The mixture was filtered through Celite, and the filtrate was extracted once each with saturated KI solution, water, and saturated NaCl. The solvent was removed in vacuo to yield aldehyde **35** (13.5 g, 100%) as an oil, which was used without purification: IR (film) 1720, 1450, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.6 (1H, d, J = 1.7 Hz), 3.75 (1H, dd, J = 2.7, 11.5 Hz), 3.64 (1H, m), 3.55 (2H, m), 3.34 (3H, s), 3.19 (6H, s), 3.13 (1H, m), 0.72 (9H, s), −0.11 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.7, 86.1, 80.1, 79.7, 60.3, 59.6, 57.1, 25.3, 17.7, −6.1, −6.2; CI MS m/z 307, 275, 259, 243, 233, 217, 175.

Preparation of Dibromoalkene 36. Procedure A. $CHBr_3$ (2.4 mL, 7.0 g, 28 mmol) was added rapidly dropwise to a solution of KOtBu (3.2 g, 28 mmol) and PPh_3 (7.3 g, 28 mmol) in 100 mL of toluene at −20 °C, followed after 15 min by aldehyde **35** (2.13 g, 6.95 mmol) in 15 mL of toluene. The cooling bath was removed and the reaction mixture was allowed to warm to rt. After 30 min the reaction mixture was diluted with 200 mL of ether, filtered through Celite, and concentrated in vacuo. Dry column flash chromatography of the concentrate using gradient elution (hexanes; 1 and 2.5% ethyl acetate in hexanes) yielded dibromoalkene **36** (1.73 g, 72%) as an oil: IR (film) 1605, 1445 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.45 (1H, d, *J* = 8.7 Hz), 4.0 (1H, d, *J* = 8.6 Hz), 3.75 (1H, d, *J* = 11.8 Hz), 3.6 (1H, d, *J* = 11.3 Hz), 3.3 (3H, s), 3.25 (3H, s), 3.20 (3H, s), 3.16 (2H, m), 0.8 (9H, s), −0.1 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.7, 91.0, 80.7, 80.5, 60.9, 60.5, 57.6, 56.7, 25.9, 25.5, 17.8, −5.8, −6.0; CI MS *m/z* 463, 399, 319, 293, 271, 245, 233, 189.

Procedure B. PPh_3 (15.2 g, 58 mmol) was added to CBr_4 (9.6 g, 29 mmol) in 120 mL of CH_2Cl_2 at 0 °C, followed after 15 min by NEt_3 (2.0 mL, 1.5 g, 15 mmol). The reaction mixture was stirred for 5 min at 0 °C and then was cooled to −78 °C, and aldehyde **35** (4.5 g, 15 mmol) in 10 mL of CH_2Cl_2 was added rapidly dropwise, maintaining the reaction temperature below −70 °C. After 2 min, the reaction mixture was poured into 200 mL of saturated $NaHCO_3$ solution with vigorous stirring. The resulting mixture was extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated to dryness in vacuo. The solid residue was stirred vigorously with 500 mL of hexanes for 12 h, the solid was filtered off, and the filtrate was concentrated in vacuo. Dry column flash chromatography of the crude product using gradient elution (hexanes, 1 and 2% ethyl acetate in hexanes) yielded dibromoalkene **36** (10 g, 75%).

TMS-Acetylene 37. Procedure A. n-BuLi (6.8 mL, 1.6 M in hexanes, 10.8 mmol) was added dropwise at −78 °C to a solution of dibromoalkene **36** (2.0 g, 4.3 mmol) and TMEDA (2 mL) in 12 mL of THF, followed after 75 min by TMSCl (0.85 mL, 0.72 g, 6.7 mmol). The reaction mixture was stirred for 3 h at −78 °C and for an additional 3 h at rt, poured into saturated $NaHCO_3$, and extracted three times with ether. Preparative TLC of the concentrate using 5% ethyl acetate in hexanes yielded TMS acetylene **37** (1.3 g, 81%) as an oil: IR (film) 1455, 1245 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.12 (1H, d, *J* = 3.1 Hz), 3.85 (1H, dd, *J* = 2.7, 11.2 Hz), 3.66 (1H, dd, *J* = 4.1, 11.2 Hz), 3.55 (3H, s), 3.40 (3H, s), 3.35 (3H, s), 3.45–3.3 (2H, m), 0.88 (9H, s), 0.14 (9H, s), 0.02 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 103.0, 91.9, 87.2, 80.9, 71.1, 61.4, 60.7, 57.8, 56.6, 25.5, 17.8, −0.67, −0.74, −5.9; CI MS *m/z* 375, 343, 327, 311, 285, 271, 255, 239, 213, 189.

Procedure B. BuLi (12.3 mL, 1.6 M in hexanes, 19.4 mmol) was added over 10 min to a solution of dibromoalkene **36** (4.5 g, 9.6 mmol) in 100 mL of ether at 0 °C. After 5 min, the reaction mixture was quenched by the dropwise addition of saturated NH_4Cl solution, poured into water, and extracted three times with ether. The combined organic extracts were dried and concentrated in vacuo. Dry column flash chromatography of the mixture using gradient elution (1 and 2% ethyl acetate in hexanes) gave acetylene **38** (2.6 g, 88%) as an oil: IR (film) 3260, 2100, 1455 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.2 (1H, m), 3.9 (1H, dd, *J* = 2.9, 11.1 Hz), 3.7 (1H, dd, *J* = 4.2, 11.2 Hz), 3.6 (3H, s), 3.35–3.5 (7H, m), 2.45 (1H, d, *J* = 2.2 Hz), 0.9 (9H, s), 0.05 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 81.5, 80.8, 80.3, 74.8, 70.2, 60.7, 60.6, 57.5, 56.5, 25.4, 17.7, −6.1, −6.2; CI MS *m/z* 303, 271, 255, 245, 239, 213, 189, 97.

n-BuLi (10.5 mL, 1.6 M in hexanes, 16.8 mmol) was added over 10 min to a solution of acetylene **38** (4.9 g, 16 mmol) in 100 mL of THF at −78 °C, followed after 2 min by TMSCl (2.1 mL, 1.8 g, 16.8 mmol). The reaction mixture was stirred for 15 min at −78 °C, allowed to warm to rt, poured into saturated $NaHCO_3$, and extracted three times with ether. The combined organic extracts were dried and concentrated in vacuo. Dry column flash chromatography of the residue using 2% ethyl acetate in hexanes gave TMS-acetylene **37** (6.0 g, 85%).

Hydrogenation of Acetylene 37 to Vinylsilane 39. A suspension of TMS acetylene **37** (6.0 g, 16 mmol), 5% Pd/$BaSO_4$ (0.68 g, 2 mol %), and 75 mL of pyridine was stirred for 20 h under 1 atm of H_2. The mixture was diluted with ether and filtered through a short column of silica gel using ether as eluant. The solvent was removed in vacuo. Dry column flash chromatography of the mixture using 2% ethyl acetate in hexanes yielded vinylsilane **39** as an inseparable mixture of *Z*/*E* isomers (5.8 g, 96%, *Z*/*E* 20:1) as an oil. (*Z*)-**39**: IR (film) 1595, 1450, 1245 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.4 (1H, dd, *J* = 9.5, 14.5 Hz), 5.8 (1H, d, *J* = 14.5 Hz), 4.0 (1H, d, *J* = 10.7 Hz), 3.9 (1H, dd, *J* = 2.1, 11.3 Hz), 3.7 (1H, dd, *J* = 4.2, 11.3 Hz), 3.4 (3H, s), 3.38 (3H, s), 3.3 (3H, s), 3.4–3.25 (1H, m), 3.2 (1H, dd, *J* = 2.0, 8.5 Hz), 0.9 (9H, s), 0.1 (9H, s), 0.0 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.7, 133.4, 83.0, 80.6, 79.4, 60.8, 60.5, 57.4, 55.9, 25.2, 17.5, −0.5, −6.1, −6.3; CI MS *m/z* 377, 345, 329, 313, 297, 241, 233, 209, 189.

Alcohol 41. TBS ether **39** (5.2 g, 13.7 mmol) was stirred for 12 h in 50 mL of 2/1 acetic acid/water. The solvent was removed in vacuo, and the residue was poured into saturated $NaHCO_3$ and extracted three times with ether. The combined organic extracts were dried and concentrated in vacuo. Dry column flash chromatography of the concentrate using 25% ethyl acetate in hexanes yielded alcohol **41** (3.6 g, 100%) as an oil: IR (film) 3450, 2805, 1080 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.4 (1H, dd, *J* = 9.6, 14.6 Hz), 5.85 (1H, d, *J* = 14.6 Hz), 4.0 (1H, dd, *J* = 2.4, 9.7 Hz), 3.9 (1H, dt, *J* = 3.9, 11.9 Hz), 3.65 (1H, m), 2.1 (1H, dd, *J* = 3.9, 8.7 Hz), 0.1 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.6, 134.1, 83.4, 80.5, 79.9, 61.3, 60.0, 57.8, 56.3, 0.2; CI MS *m/z* 263, 231, 215, 199, 183, 167, 157, 143, 127.

Preparation of Aldehyde 42. A solution of DMSO (7.8 mL, 8.6 g, 110 mmol) in 10 mL of CH_2Cl_2 was added to a solution of oxalyl chloride (4.0 mL, 5.8 g, 46 mmol) in 120 mL of CH_2Cl_2 at −78 °C, followed after 5 min by alcohol **41** (4.0 g, 15.2 mmol) in 10 mL of CH_2Cl_2, maintaining the reaction temperature below −65 °C. After 10 min, NEt_3 (19 mL, 14 g, 138 mmol) was added. The reaction mixture was allowed to warm to rt and then was concentrated in vacuo. The residue was poured into water and extracted three times with hexanes. The combined organic extracts were washed three times with water, dried, and concentrated in vacuo. Kugelrohr distillation of the crude product (50–60°/1.7mm) yielded aldehyde **42** (3.9 g, 99%) as an oil: IR (film) 1725, 1100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.51 (1H, d, *J* = 1.5 Hz), 6.05 (1H, dd, *J* = 9.5, 14.6 Hz), 5.7 (1H, d, *J* = 14.6 Hz), 3.8 (1H, dd, *J* = 4.1, 9.5 Hz), 3.65 (1H, dd, *J* = 1.5, 5.4 Hz), 3.25 (3H, s), 3.23 (3H, s), 3.3–3.2 (1H, m), 3.1 (3H, s), −0.1 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.2, 144.6, 135.5, 85.0, 84.9, 80.1, 59.9, 58.4, 56.0, −0.4; CI MS *m/z* 261, 229, 213, 201, 197, 187, 182, 169, 157, 143.

Preparation of Cyclitol 43. $SnCl_4$ (0.83 mL, 1 M in CH_2Cl_2, 0.83 mmol) was added to aldehyde **42** (108 mg, 0.42 mmol) in 6 mL of CH_2Cl_2 at −78 °C. The reaction mixture was allowed to warm to rt over 3 h and then was poured into saturated $NaHCO_3$ solution. The resulting mixture was shaken with Rochelle's salt solution and extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. Preparative TLC of the residue using 50% ethyl acetate in hexanes afforded cyclitol **43** (54 mg, 68%) as an oil: $[\alpha]^{28}{}_{D}$ = +147.7° (*c* = 1.53, $CHCl_3$); IR (film) 3400, 2900, 1100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8 (2H, d, *J* = 1.2 Hz), 4.2 (1H, m), 4.0 (1H, dt, *J* = 1.4, 6.1 Hz), 3.8 (1H, dd, *J* = 1.8, 4.0 Hz), 3.6 (3H, s), 3.5 (3H, s), 3.45 (3H, s), 3.5–3.4 (1H, m), 2.7 (1H, d, *J* = 11.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 130.6, 126.1, 82.6, 78.2, 77.1, 66.9, 59.5, 58.0, 57.2; CI MS *m/z* 187, 171, 157, 139, 125, 114, 100, 97.

Preparation of Cyclitol 45. BF_3–OEt_2 (0.051 mL, 59 mg, 0.41 mmol) in 2 mL of CH_2Cl_2 was added over 30 min to aldehyde **42** (98 mg, 0.38 mmol) in 5 mL of CH_2Cl_2 at rt. The reaction mixture was stirred for 5 min and then was poured into saturated $NaHCO_3$, and the mixture was extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. Preparative TLC of the concentrate using 50% ethyl acetate in hexanes yielded cyclitol **45** (60 mg, 86%) as an oil: $[\alpha]^{28}{}_{D}$ = +6.1° (*c* = 1.96, $CHCl_3$); IR (film) 3400, 2900, 1100 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.6 (2H, m), 4.2 (1H, m), 3.7 (1H, m), 3.5 (1H, m), 3.37 (3H, s), 3.36 (3H, s), 3.4–3.3 (1H, m), 3.3 (3H, s), 3.2 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 131.0, 126.1, 81.2, 77.3, 76.1, 67.2, 58.3, 57.9, 57.2; CI MS *m/z* 189, 171, 167, 157, 139, 125, 100, 97.

Tetra-*O*-methylconduritol C (44). Cyclitol **43** (140 mg, 0.69 mmol) was methylated as described in the preparation of **46**. Preparative TLC using 50% ethyl acetate in hexanes yielded tetra-*O*-methylconduritol C (**44**) (127 mg, 91%) as an oil: IR (film) 2900, 1100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7 (1H, dt, *J* = 2.2, 10.4 Hz), 5.55 (1H, dqr, *J* = 1.6, 10.4 Hz), 3.95 (2H, m), 3.75 (1H, m), 3.5 (3H, s), 3.4 (3H, s), 3.35 (3H, s), 3.3 (3H, s), 3.1 (1H, dd, $J = 1.8, 7.9$ Hz); ^{13}C (50 MHz, $CDCl_3$) δ 127.3, 126.8, 83.4, 78.6, 78.4, 77.0, 60.7, 57.7, 57.5, 56.6; CI MS *m/z* 203, 171, 155, 139, 125, 114, 99, 88.

Tetra-*O*-methylconduritol A (46). A suspension of cyclitol **45** (98 mg, 0.49 mmol) and Ag_2O (0.56 g, 2.4 mmol) in 4 mL of MeI were stirred for 2 d at rt. Excess MeI was removed in vacuo, the residue was diluted with ether and filtered through Celite, and the filtrate was concentrated in vacuo. Preparative TLC of the residue using 50% ethyl acetate in hexanes yielded tetra-*O*-methylconduritol A (**46**) (70 mg, 71%) as an oil: IR (film) 2900, 1100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9 (2H, m), 3.83 (2H, m), 3.5 (2H, m), 3.4 (6H, s), 3.37 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 128.0, 78.7, 76.3, 58.4, 57.1; CI MS *m/z* 203, 171, 139, 125, 114, 99, 88.

Synthesis of Aminocyclitol 50. Procedure A. A solution of aldehyde **42** (107 mg, 0.41 mmol), TsNSO (179 mg, 0.82 mmol), and 1.5 mL of CH_2Cl_2 was degassed three times using the freeze-thaw procedure, heated at 80 °C for 24 h, and then cooled to 0 °C, and BF_3–OEt_2 (0.10 mL, 117 mg, 0.82 mmol) was added. After 15 min, the reaction mixture was allowed to warm to rt, poured into saturated $NaHCO_3$ solution, and extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. Preparative TLC using 50% ethyl acetate in hexanes gave aminocyclitol **50** (51 mg, 36%) as an oil which crystallized upon long standing: IR ($CDCl_3$) 3370, 3260, 2240, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (2H, m), 7.3 (2H, m), 5.8 (1H, m), 5.45 (1H, m), 4.5 (1H, d, $J = 7.1$ Hz), 3.95 (1H, m), 3.85 (1H, m), 3.55 (1H, m), 3.45 (4H, m), 3.42 (3H, s), 3.4 (3H, s), 2.45 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 137.6, 129.7, 129.2, 127.0, 126.2, 78.9, 77.9, 76.3, 58.1, 57.8, 57.6, 51.3, 21.5; CI MS *m/z* 342, 310, 278, 253, 214, 154, 139, 98; HRMS calcd for $C_{16}H_{23}NO_5S$ 341.1297, found 341.1315.

Procedure B. BF_3–OEt_2 (1.5 mL, 1.7 g, 12.1 mmol) was added to a suspension of aldehyde **42** (1.5 g, 5.8 mmol) and $TsNH_2$ (2.1 g, 12.1 mmol) in 60 mL of CH_2Cl_2 at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, was allowed to warm to rt over 1 h, and was stirred for an additional 1 h at rt. The reaction mixture was poured into saturated $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. The residue was dissolved in 10 mL of CH_2Cl_2 and 10 mL of hexanes was added. The precipitate ($TsNH_2$) was filtered off and the filtrate was concentrated in vacuo. Dry column flash chromatography of the mixture using gradient elution (10 and 20% ethyl acetate in CH_2Cl_2) gave aminocyclitols **50** (1.4 g, 73%) and **51** (153 mg, 8%). **51**: IR ($CDCl_3$) 3350, 1320, 1160 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (2H, m), 7.3 (2H, m), 5.7 (1H, m), 5.35 (1H, dt, $J = 1.6, 10.0$ Hz), 5.25 (1H, d, $J = 9.9$ Hz), 4.05 (1H, m), 3.9 (1H, m), 3.6 (1H, m), 3.45 (3H, s), 3.42 (3H, s), 3.38 (3H, s), 3.35 (1H, dd, $J = 1.8, 6.5$ Hz), 2.4 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 138.5, 129.6, 127.7, 127.4, 126.9, 82.5, 76.9, 76.6, 59.6, 58.0, 57.3, 51.6, 21.4; CI MS *m/z* 341, 310, 278, 253, 171, 154, 139, 98.

***N*-Methyl Aminocyclitol 52. Procedure A.** BF_3–OEt_2 (0.31 mL, 350 mg, 2.5 mmol) was added to a solution of aldehyde **42** (260 mg, 1.0 mmol) and *N*-methyl-*p*-toluenesulfonamide (389 mg, 2.1 mmol) in 30 mL of CH_2Cl_2 at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, was allowed to warm to rt over 1 h, and was stirred for an additional 1 h at rt. The reaction mixture was poured into saturated $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. Preparative TLC of the residue using 50% ethyl acetate in hexanes gave aminocyclitol **52** (242 mg, 68%) as a solid: IR ($CDCl_3$) 2215, 1320, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, m), 7.3 (2H, m), 5.85 (1H, m), 5.35 (1H, dd, $J = 2.6, 10.1,$ Hz), 4.8 (1H, m), 3.8 (1H, m), 3.65 (1H, m), 3.5 (3H, s), 3.45 (1H, dd, $J = 2.3, 7.8$ Hz), 3.3 (3H, s), 2.7 (3H, s), 2.4 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 136.8, 130.3, 129.3, 128.0, 127.4, 77.0, 76.5, 75.3, 58.8, 57.4, 57.3, 56.5, 30.0, 21.4; CI MS *m/z* 356, 324, 292, 267, 228, 186, 139, 112.

Procedure B. KOtBu (4.7 mg, 0.042 mmol) was added to a solution of aminocyclitol **50** (12 mg, 0.035 mmol) in 2 mL of DMSO. The reaction mixture was stirred for 10 min at rt, and MeI (0.007 mL, 15 mg, 0.11 mmol) was added. The reaction mixture was stirred for 12 h, and poured into water, and the mixture was extracted three times with ether. The combined organic extracts were washed twice with water, dried, and concentrated in vacuo. The resulting oil was purified by preparative TLC using 50% ethyl acetate in hexanes to afford aminocyclitol **52** (12 mg, 100%).

Procedure C. DEAD (0.065 mL, 72 mg, 0.41 mmol) was added to a solution of PPh_3 (107 mg, 0.41 mmol) and alcohol **43** (52 mg, 0.28 mmol) in 5 mL of THF. After stirring the reaction mixture for 12 h at rt, the solvent was removed in vacuo, and the residue was purified by preparative TLC to afford aminocyclitol **52** (53 mg, 54%).

Synthesis of Amide 56. A solution of 6-iodopiperonylic acid[54] (1.1 g, 3.9 mmol) in 5 mL of thionyl chloride and 5 mL of benzene was heated under reflux for 3 h, cooled to rt, and concentrated in vacuo. The residue was diluted with 20 mL of CH_2Cl_2 and aminocyclitol **50** (0.89 g, 2.6 mmol), NEt_3 (1.1 mL, 0.79 g, 7.8 mmol), and ca. 50 mg of DMAP were added. The reaction mixture was stirred at rt for 36 h, poured into saturated $NaHCO_3$ solution, and extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. Dry column flash chromatography of the concentrate using 35% ethyl acetate in hexanes gave *N*-acylsulfonamide **56** (1.24 g, 77%) as an oil: IR ($CDCl_3$) 1680, 1470, 1350 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.9 (2H, m), 7.3 (2H, m), 7.05 (1H, m), 6.75 (1H, m), 6.15 (1H, m), 5.95 (2H, m), 5.75 (1H, m), 4.85 (1H, m), 4.2 (1H, m), 3.4–3.6 (10H, m), 2.4 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$), δ 170.5, 149.3, 147.9, 145.0, 136.0, 134.2, 132.3, 129.7, 129.4, 129.1, 122.9, 118.6, 109.7, 102.0, 78.0, 75.7, 75.4, 59.6, 59.2, 57.0, 56.9, 21.4; CI MS *m/z* 616, 584, 552, 527, 460, 334, 275, 170.

Phenanthridone 58. A suspension of *N*-acylsulfonamide **56** (310 mg, 0.50 mmol), TlOAc (384 mg, 1.0 mmol), and Pd-$(DIPHOS)_2$ (91 mg, 0.10 mmol, 20 mol %) in 5 mL of DMF in a resealable tube was degassed at 1 mmHg and rt for 5 min. The reaction mixture was heated at 68 °C for 36 h, cooled to rt, diluted with ethyl acetate, and filtered through Celite. The filtrate was poured into water and extracted three times with ethyl acetate. The combined organic extracts were washed three times with water, dried, and concentrated in vacuo. Preparative TLC of the residue using 20% ethyl acetate in CH_2Cl_2 gave semipurified product. Preparative TLC of the mixture using 10% ethyl acetate in hexanes afforded phenanthridone **58** (122 mg, 50%): IR ($CDCl_3$) 2230, 1670, 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (2H, m), 7.3 (2H, m), 7.3 (1H, s), 6.9 (1H, s), 6.07 (1H, dd, $J = 1.9, 2.3$ Hz), 6.05 (1H, d, $J = 1.2$ Hz), 6.02 (1H, d, $J = 1.2$ Hz), 4.95 (1H, m), 4.52 (1H, dd, $J = 2.2, 4.35$ Hz), 4.15 (1H, dt, $J = 2.1, 6.4$), 3.7 (1H, dd, $J = 2.3, 6.4$ Hz), 3.6 (3H, s), 3.55 (3H, s), 3.5 (3H, s), 2.4 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 152.6, 148.4, 144.2, 137.7, 134.0, 129.9, 129.3, 128.1, 126.8, 122.0, 107.8, 102.9, 102.1, 78.7, 78.0, 77.4, 59.1, 59.0, 58.3, 57.9, 21.6; CI MS *m/z* 488, 456, 424, 399, 334, 301, 269, 244, 157, 139.

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Supplementary Material Available: NMR spectra of all new compounds (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.