Selective Inversion of the Proximal or Distal Hydroxyl Groups in *syn,syn*-3-[*N*-(Alkoxycarbonyl)amino] 1,2-Diols via Cyclic Sulfates

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The formation of cyclic sulfates (**4**) from *syn,syn*-3-[*N*-(benzyloxycarbonyl)amino] 1,2-diols provides a common intermediate to access other diastereomers via two inversion procedures. Thermolysis of the cyclic sulfates in acetonitrile normally leads to inversion of the distal hydroxyl group to form a 1,3-oxazin-2-one (**6**). Catalytic hydrogenation of the cyclic sulfates under basic conditions (NEt_3) results in inversion at the proximal hydroxyl group to form a 1,3-oxazolidin-2-one (**5**).

Recent advances[1,2] in selective pinacol cross coupling reactions using the vanadium(II) reagent, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$, have made many 1,2-diol systems readily available for the first time. An important advance in this technology is the synthesis of optically pure *syn,syn*-3-amino-1,2-diols (**3**) via the pinacol coupling of a 2-[*N*-(alkoxycarbonyl)amino] aldehyde and an aliphatic aldehyde.[1] Having developed this route to such diols, we felt it would be desirable to have available a method for selectively inverting either of the two hydroxyl groups in order to produce optically pure 1,2-*anti*-2,3-*syn*-3-amino 1,2-diols (**1**) and 1,2-*anti*-2,3-*anti*-3-amino 1,2-diols (**2**) (Figure 1).

Our approach to this problem has relied on cyclization reactions to achieve high regioselectivity. Precedent for choosing an intramolecular versus an intermolecular route to achieve high regioselectivity is well documented.[3] The intramolecular inversion of activated hydroxyl groups by the carbonyl of amide, thioureido and carbamate groups has been known for some time.[4,5] Since the *syn,syn*-3-amino 1,2-diols we wanted to convert are *N*-protected as alkyl carbamates, we reasoned that inversion of properly derivatized substrates should be possible. Activation of the hydroxyl groups by transformation into their cyclic sulfates[6] was chosen because it eliminates the need for selective activation of only one hydroxyl group. Furthermore, after inversion takes place at one carbon center, the other hydroxyl group is deactivated as the anionic sulfate ester, which can later be hydrolyzed.[7]

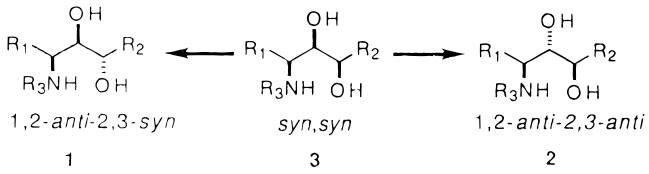
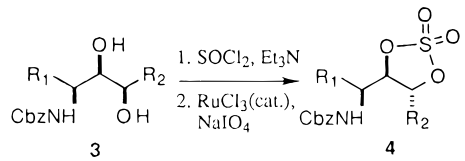


Figure 1.

Table 1



	R_1	R_2	isolated yield (%)
4a	Bn	*i*-Bu	99
4b	Bn	$PhCH_2CH_2$	92
4c	Bn	*i*-Pr	97
4d	*i*-Pr	$PhCH_2CH_2$	94
4e	*i*-Pr	*i*-Pr	89
4f	$TBDMSOCH_2$	n-$C_{14}H_{29}$	91
4g	$BnOCH_2$	n-$C_{12}H_{25}$	89

Results and Discussion

The amino diols[1] **3** were converted to cyclic sulfates **4** in excellent yield (89−99%) by modification of the Sharpless method (Table 1).[6a] Attempts to use the Alloc group in this procedure were unsuccessful due to cleavage of the allyl double bond by RuO_4.

Phytosphingosines are a class of biological molecules that contain the *anti,anti*-3-amino 1,2-diol core.[8] C_{16}-Phytosphingosine[9] was chosen as a model compound for initial study because peracetylated derivatives of all four diastereomers have been synthesized and completely

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(1) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316.

(2) (a) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (b) Takahara, P. M.; Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *Tetrahedron Lett.* **1989**, *30*, 7177. (c) Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 5924. (c) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 4506. (d) Raw, A. S.; Pedersen, S. F. *Ibid.* **1991**, *56*, 830. (e) Konradi, A. W.; Pedersen, S. F. *Ibid.* **1992**, *57*, 28.

(3) (a) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371. (b) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (c) Jager, V.; Stahl, U.; Hummer, W. *Synthesis* **1991**, 776.

(4) (a) Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannick, S. M.; Codavoci, L.; Henry, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692. (b) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331. (c) Baker, B. R.; Hullar, T. L. *J. Org. Chem.* **1965**, *30*, 4049 and references therein.

(5) (a) Sakaitanti, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150. (b) Sakaitanti, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870 and references therein.

(6) (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655. (b) Lohray, B. B.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623. (c) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

(7) Goren, M. B.; Kochansky, M. E. *J. Org. Chem.* **1973**, *38*, 3510.

(8) (a) Birk, R.; Jung, J.; Schmidt, R. R. *Liebigs Ann. Chem.* **1994**, 83. (b) Murakami, T.; Minamikawa, H.; Hato, M. *Tetrahedron Lett.* **1994**, *35(5)*, 745 and references therein.

(9) For some previous syntheses see: (a) Sugiyama, S.; Honda, M.; Higuchi, R.; Komori, T. *Liebigs Ann. Chem.* **1991**, 349. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Paola, P. *J. Org. Chem.* **1990**, *55*, 1439. (c) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 5507. (d) Kulmacz, R. J.; Schroepfer, G. J., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 3963. (e) Sugiyama, S.; Honda, M.; Komori, T. *Liebigs Ann. Chem.* **1988**, 619. (f) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961. (g) Schwab, W.; Jager, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603. (h) Gigg, J.; Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1966**, 1872. (i) Gigg, J.; Gigg, R. *J. Chem. Soc. C* **1966**, 1876. (j) Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1966**, 1879. (k) Gigg, J.; Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1966**, 1882. (l) Prostenik, M.; Majhofer-Orescanin, B.; Ries-Lesic, B.; Stanacev, N. Z. *Tetrahedron* **1965**, *21*, 651.

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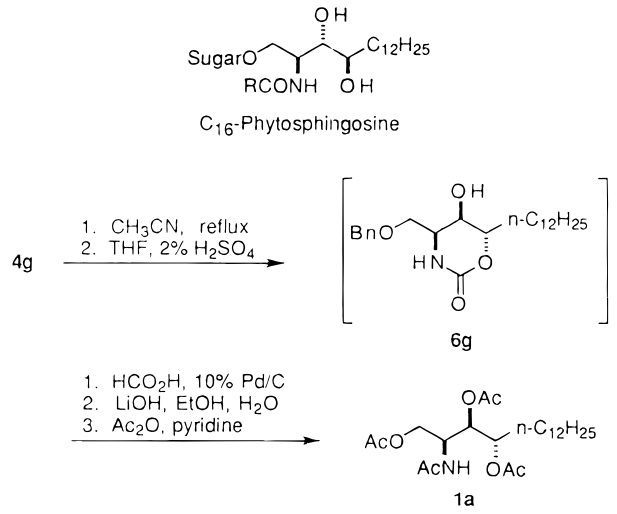
Scheme 1

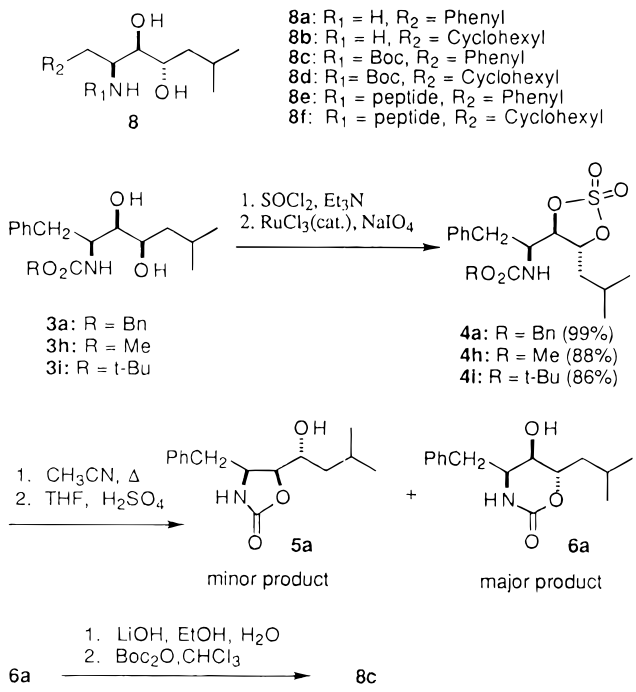


characterized,[10] allowing rapid determination of the stereochemistry obtained from the inversion reactions. To avoid the possible removal of minor isomers, the transformation of **4g** to a known phytosphingosine was performed without any purification. The cyclic sulfate **4g** was heated at reflux in acetonitrile for 5 h, hydrolyzed to remove the sulfate, hydrogenated, saponified, and acetylated to give the *syn*,*anti*-tetraacetate (**1a**) and an unknown impurity (Scheme 1). The unknown impurity was shown not to be any of the other three possible diastereomers. The tetraacetate **1a** is the diastereomer resulting from a 6-membered ring cyclization (giving **6g**).

The regioselective inversion of the hydroxyl group by this method is of practical importance because it provides effective access to 1,2-*anti*-2,3-*syn*-3-amino 1,2-diols (**1**). Although the natural phytosphingosine was not obtained in the foregoing synthesis, we realized that the stereochemistry observed is that found in an important class of pharmaceutically active compounds, namely renin inhibitors. Recently, much attention has been focused on the development of effective rennin inhibitors, and one class in particular utilizes the 1,2-*anti*-2,3-*syn*-3-amino 1,2-diol functional unit **8e** to obtain subnanomolar inhibition of human renin.[11,12] The key building block to **8e** is the dipeptide isostere **8a**, and several syntheses of this compound have been published.[12] Our synthesis of **8c** is outlined in Scheme 2.

Our approach to the synthesis of **8c** was to utilize **3a**, which is prepared in 74% yield from *N*-Cbz-L-phenylalaninal by a one-step pinacol coupling.[1] Heating of **4a** in acetonitrile, followed by hydrolysis using THF−2% aqueous H_2SO_4 (200:1), gave a mixture of **6a**/**5a** (6:1) and the byproduct *N*-benzylacetamide. The oxazinone **6a** is crystalline and the oxazolidinone **5a** is an oil, which allows the complete separation of the two regioisomers by one recrystallization. However, fractional recrystallization was required to remove all of the *N*-benzylacetamide, yielding pure **6a** in 67% yield from **4a**. The synthesis of **6a** was thus accomplished in an overall yield of 46% from L-phenylalanine and gave the desired isostere (**8a**) after basic hydrolysis (96%). The stereochemistry of **6a** was assigned by protecting **8a** with Boc_2O to provide **8c**.[12a] The stereochemistry of **5a** was confirmed by catalytic hydrogenation of the phenyl ring (5% Rh/Al_2O_3, H_2, 50 psi)[13] to give the known cyclohexyl analog **5k** (R^1 = cyclohexyl, R^2 = *i*-Bu).[12d]

Scheme 2



The formation of *N*-benzylacetamide from **4a** suggested that the intermediate "oxonium ion" **11** was reacting with

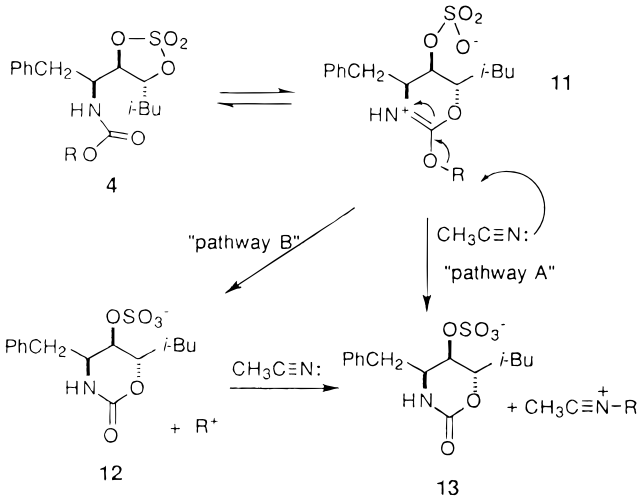
(10) Sugiyama, S.; Honda, M.; Komori, T. *Liebigs Ann. Chem.* **1990**, 1069.

(11) (a) Baker, W. R.; Condon, S. L. *Tetrahedron Lett.* **1992**, *33*, 1577. (b) Rosenberg, S. H.; Spina, K. P.; Woods, K. W.; Polakowski, J.; Martin, D. L.; Yao, Z.; Stein, H. H.; Cohen, J.; Barlow, J. L.; Egan, D. A.; Tricarico, K. A.; Baker, W. R.; Kleinert, H. D. *J. Med. Chem.* **1993**, *36*, 449. (c) Rosenberg, S. H.; Spina, K. P.; Condon, S. L.; Polakowski, J.; Yao, Z.; Kovar, P.; Stein, H. H.; Cohen, J.; Barlow, J. L.; Klinghofer, V.; Egan, D. A.; Tricarico, K. A.; Perun, T. J.; Baker, W. R.; Kleinert, H. D. *J. Med. Chem.* **1993**, *36*, 460. (d) Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. *J. Med. Chem.* **1992**, *35*, 2562. (e) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; deLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710. (f) Baker, W. R.; Fung, A. K. L.; Kleinert, H. D.; Stein, H. H.; Plattner, J. J.; Armiger, Y.; Condon, S. L.; Cohen, J.; Egan, D. A.; Barlow, J. L.; Verburg, K. M.; Martin, D. L.; Young, G. A.; Polakowski, J.; Boyd, S. A.; Perun, T. J. *J. Med. Chem.* **1992**, *35*, 1722. (g) Repine, J. T.; Kaltenbronn, J. S.; Doherty, A. M.; Hamby, J. M.; Himmelsbach, R. J.; Kornberg, B. E.; Taylor, M. D.; Lunney, E. A.; Humblet, C.; Rapundalo, S. T.; Batley, B. L.; Ryan, M. J.; Painchaud, C. A. *J. Med. Chem.* **1992**, *35*, 1032. (h) Plattner, J. J.; Marcotte, P. A.; Kleinert, H. D.; Stein, H. H.; Greer, J.; Bolis, G.; Fung, A. K. L.; Bopp, B. A.; Luly, J. R.; Sham, H. L.; Kempf, D. J.; Rosenberg, S. H.; Dellaria, J. F.; De, B.; Merits, I.; Perun, T. J. *J. Med. Chem.* **1988**, *31*, 2277. (i) Mazdiyasni, H.; Konopacki, D. B.; Dickman, D. A.; Zydowsky, T. M. *Tetrahedron Lett.* **1993**, *34*, 435. (j) Hurley, T. R.; Colson, C. E.; Hicks, G.; Ryan, M. J. *J. Med. Chem.* **1993**, *36*, 1496. (k) Stein, H. H.; Fung, A. K. L.; Cohen, J.; Baker, W. R.; Rosenberg, S. H.; Boyd, S. A.; Dayton, B. D.; Armiger, Y.; Condon, S. L.; Mantei, R. A.; Kleinert, H. D. *FEBS Lett.* **1992**, *300*(3), 301. (l) Kleinert, H. D.; Rosenberg, S. H.; Baker, W. R.; Stein, H. H.; Klinghofer, V.; Barlow, J.; Spina, K.; Polakowski, J.; Kovar, P.; Cohen, J.; Denissen, J. *Science* **1992**, *257*, 1940.

(12) (a) Pfizer Inc. EP 0438233A2 1991, 59. (b) Baker, W. R.; Condon, S. L. *Tetrahedron Lett.* **1992**, *33*, 1581. (c) Wood, J. L.; Jones, D. R.; Hirschmann, R.; Smith, A. B. *Tetrahedron Lett.* **1990**, *31*, 6329. (d) Luly, J. R.; BaMaung, N.; Soderquist, J.; Fung, A. K. L.; Stein, H.; Kleinert, H. D.; Marcotte, P. A.; Egan, D. A.; Bopp, B.; Merits, I.; Bolis, G.; Greer, J.; Perun, T. J.; Plattner, J. J. *J. Med. Chem.* **1988,** *31*, 2264. (e) Luly, J. R.; Hsiao, C.; BaMaung, N.; Plattner, J. J. *J. Org. Chem.* **1988**, *53*, 6109. (f) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277. (g) Chan, M. F.; Hsiao, C. *Tetrahedron Lett.* **1992**, *33*, 3567. (h) Kobayashi, Y.; Matsumoto, T.; Takemoto, Y.; Nakatani, K.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Chem. Pharm. Bull.* **1991**, *39*, 2550.

(13) Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; LaMont, B. I.; Lin, T.; Kawai, M.; Rich, D. H.; Veber, D. F. *J. Med. Chem.* **1985**, *28*, 1779.

Scheme 3

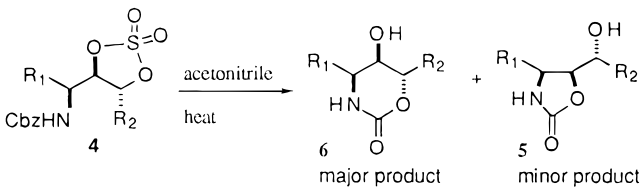


acetonitrile in one of two manners (Scheme 3). In pathway A, one can envision S_N2 attack by acetonitrile to afford the intermediate oxazinone sulfate **13**, and the nitrilium ion, which upon hydrolysis, would afford the *N*-benzylacetamide. Alternatively, pathway B shows an S_N1-type reaction that involves initial ionization of the carbon−oxygen bond in **11** resulting in the formation of a carbocation that is then trapped by acetonitrile (the Ritter reaction[14]) to form the nitrilium ion. We reasoned that if pathway A were operative in this chemistry, then changing to substrate **4h** should also work well, although somewhat slower,[15] and would produce the more easily removable *N*-methylacetamide. However, refluxing **4h** in acetonitrile for 80 h, followed by hydrolysis and NMR analysis, showed an incomplete reaction (**6a** to **4h**, 7:3). Increased reaction times or higher temperature led to extensive decomposition. These results suggested that pathway B is the primary reaction course taken in the cyclization of **4a**. This is further substantiated by the fact that when cyclic sulfate **4i** was thermolyzed, the rate of cyclization was even faster (<30 min, refluxing acetonitrile), as anticipated, based on the greater stability of the *tert*-butyl cation relative to the benzyl cation.[16] However, in this case **4i** gave a 2:1 mixture of **6a** and **5a** after hydrolysis, a significant decrease from **4a**. The regioselectivity in this reaction of **4i** can be increased by lowering the temperature and increasing the reaction time; ratio of **6a**/**5a** = 4:1 at 40 °C (12 h) and 6:1 at 20 °C (5 d).

To further examine the effect of substiuents R_1 and R_2 on the regioselectivity, several *N*-Cbz cyclic sulfates were thermolyzed (Table 2). The cyclizations follow the general pattern of providing the 6-membered ring (**6**) as the major product. When either R_1 or R_2 is isopropyl (**4c** or **4d**) the selectivity and the yield increases. However, when both R_1 and R_2 are isopropyl (**4e**) the yield of **6e** is lower. The structure of **6e** was confirmed by an X-ray crystal structure.[17]

After obtaining the results described thus far, we were interested in examining other cyclization procedures in hopes of forming the oxazolidinone **5**, which should be kinetically favored.[18] We were attracted to Sakaitani and Ohfune's work on the use of silyl carbamates as *N*-carboxylate ion equivalents.[5] Therefore, we explored their approach by converting **4i** into the *tert*-butyldimethylsilyl carbamate **4j** using *tert*-butyldimethylsilyl triflate (Scheme 4). Treatment of this product with tetra-*n*-butylammonium fluoride in THF at 0 °C followed by hydrolysis of the sulfate with THF−20% aqueous H_2SO_4 (250:1) gave the oxazolidinone **5a** exclusively (71% from **4i**). Attempts to generate the silyl carbamate from **4a** by Sakaitani and Ohfune's hydrosilylation procedure (*t*-$BuMe_2SiH$, $Pd(OAc)_2$) were unsuccessful. Driven by our desire to have procedures that would supply compounds **5** or **6** from a common intermediate, we reasoned that the *N*-carboxylate anion should be available directly from an *N*-Cbz derivative under basic hydrogenation conditions. This goal was realized when **4a** was hydrogenated on 5% Pd/C (50 psi) in THF in the presence of excess triethylamine, followed by hydrolysis in THF−20% aqueous H_2SO_4 (250:1), giving a mixture of **5a** and **6a** (12:1) that was chromatographed to afford 69% of **5a** and 6% of **6a**.

Table 2



	R_1	R_2	isolated yield (%) of **6**	isolated yield (%) of **5**	crude[a] **6**/**5**
4a	Bn	*i*-Bu	67	12	6:1
4b	Bn	$PhCH_2CH_2$	75	15	7:1
4c	Bn	*i*-Pr	89	6.0	16:1
4d	*i*-Pr	$PhCH_2CH_2$	88	6.7	13:1
4e	*i*-Pr	*i*-Pr	45	-	19:1

[a] Determined by $^{13}C\{^1H\}$ NMR.

To demonstrate the application of this new hydrogenation−cyclization procedure, the synthesis of natural phytosphingosines was reexamined. Thus, hydrogenation−cyclization of **4f** gave a protected form of natural C_{18}-phytosphingosine (**5f**) as the only detectable isomer in 71% yield (Table 3). This represents an overall yield of 38% from L-serine methyl ester hydrochloride.[1] To prove our assignment, **5f** was deprotected with HF/CH_3-CN, hydrolyzed, and then peracytlated to give the known tetraacetate of D-ribo-C_{18}-phytosphingosine (**9**).[9c,f]

As with the thermolysis reaction, the effect of substituents R_1 and R_2 on the regioselectivity was examined (Table 3). As expected, increasing the size of R_2 increased the ratio of **5** to **6**, due to blocking of the distal postion (**4a** and **4b** vs **4c**). Increasing the size of R_1 decreased the regioselectivity (**4b** vs **4d**). One of the most surprising results occurs when R_1 and R_2 are isopropyl (**4e**): an aziridine (**7e**) is formed as the major product. The aziridines **7c** and **7e** presumably result from decarboxylation due to a slow/unfavorable cyclization of the carbamate anion, followed by cyclization of the free amine.

Regioisomer assignments for **5** and **6** were arrived at by conversion to a known substrate (**5a**, **5f**, **6a**, and **6g**)

(14) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048.

(15) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 377.

(16) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York; 1987; p 407.

(17) The stereochemistry of **6e** was confirmed by X-ray analysis. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(18) Five-membered rings typically form faster than 6-membered rings. March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p 186.

Scheme 4

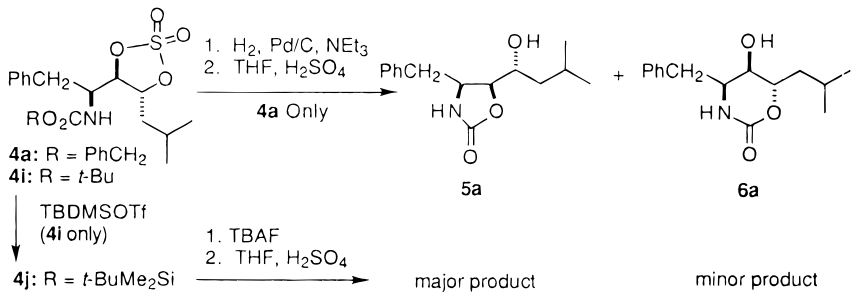
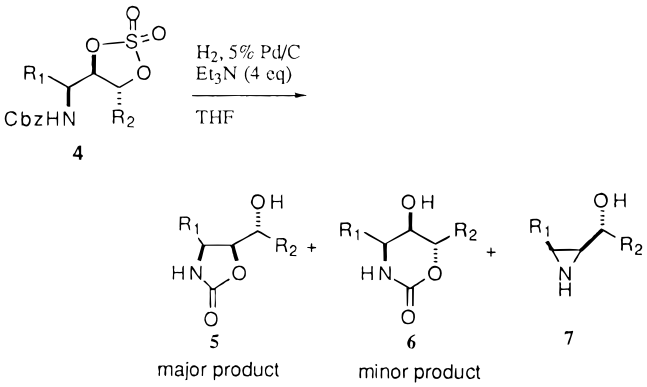


Table 3



	R_1	R_2	yield[a] (%) of **5**	yield[a] (%) of **6**	crude[b] **5**/**6**	yield[a] (%) of **7**
4a	Bn	*i*-Bu	69	6	12:1	
4b	Bn	$PhCH_2CH_2$	77	5	13:1	
4c	Bn	*i*-Pr	48	2	20:1	12
4d	*i*-Pr	$PhCH_2CH_2$	55	23	2.8:1	
4e	*i*-Pr	*i*-Pr				57
4f	$TBDMSOCH_2$	*n*-$C_{14}H_{29}$	71		>16:1	

[a] Isolated yield. [b] Determined by $^{13}C\{^1H\}$ NMR.

Table 4. Infrared Absorbance (cm^{-1}) and $^{13}C\{^1H\}$ NMR Resonance (ppm, MeOH-d_4) of the Carbonyl Group in 5 and 6

	cm^{-1} (ppm)		cm^{-1} (ppm)
5a	1745 (161.1)	**6a**	1687 (155.6)
5b	1746 (161.1)	**6b**	1686 (155.8)
5c	1745 (161.1)	**6c**	1682 (155.9)
5d	1742 (162.2)	**6d**	1692 (156.1)
5e		**6e**	1688 (156.2)
5f	1754 (162.0)	**6f**	

or X-ray crystallography (**6e**). Once several of the cyclic carbamates (**5** and **6**) were in hand we made a comparison of the physical data to see if any useful trends existed. As expected, the C=O stretch in the infrared spectra of **5** and **6** displayed a trend (Table 4).[19] The oxazolidiones (**5**) absorbed at approximately 1745 cm^{-1} and the oxazinones (**6**) absorbed at approximately 1685 cm^{-1}. Slightly unexpected was a trend in the chemical shift of the carbonyl carbon as observed by $^{13}C\{^1H\}$ NMR (Table 4): 161−162 ppm for **5** and 155−156 ppm for **6**. This information may be useful when more complicated structures fail to allow assignment by other methods.

(19) The effect of ring size on the IR absorbance of carbonyls is well known (cyclohexanone, 1715 cm^{-1}; cyclopentaone 1751 cm^{-1}; cyclobutanone 1775 cm^{-1}). Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1974; p 99.

Conclusion

We anticipate the regioselective inversion of the distal or proximal hydroxyl groups in *syn,syn*-3-amino 1,2-diols by the methodology outlined in this paper is of practical importance because it allows access to 1,2-*anti*-2,3-*syn*-3-amino 1,2-diols and/or 1,2-*anti*-2,3-*anti*-3-amino 1,2-diols from a common intermediate. This methodology also provides a direct route to 1,3-oxazin-2-ones of 1,2-*anti*-2,3-*syn*-3-amino 1,2-diols (e.g., **6**), a class of compounds not readily prepared from the unprotected diol.

Experimental Section

General Methods. For more details see ref 1. Triethylamine (Et_3N) was distilled and stored over molecular sieves prior to use. Acetonitrile (CH_3CN) was used directly from Aldrich "Sure Seal" bottles. Hexanes:ethyl acetate mixtures used for chromatography are abbrieviated as h:ea. ^1H NMR chemical shifts are reported in ppm relative to solvent resonance: $CDCl_3$, δ 7.24; $(CD_3)_2SO$, δ 2.49; CD_3OD, δ 3.30 (CD_3). Coupling constants (J) are reported in Hz. $^{13}C\{^1H\}$ NMR chemical shifts are reported in ppm relative to solvent resonance: $CDCl_3$, δ 77.0; $(CD_3)_2SO$, δ 39.5; CD_3OD, δ 49.0.

(2*S*,3*R*,4*R*)-2-[*N*-(Benzyloxycarbonyl)amino]-5-methyl-1-phenylhexane-3,4-diol (3c) was prepared from *N*-Cbz-L-phenylalaninal and isobutyraldehyde using the general procedure outlined in ref 1. The product was purified by chromatography on silica gel (75:25 h:ea) to give 4.10 g of a white solid (83%). An analytical sample was obtained by recrystallization from ethyl acetate−hexanes to give pure diol: mp 119−120 °C; R_f 0.57 (1:1 h:ea); ^1H NMR (400 MHz, $(CD_3)_2SO$, 30 °C) δ 0.68 (dd, J = 6.9, 3H), 0.79 (dd, J = 7.0, 3H), 1.73 (m, 1H), 2.66 (m, 1H), 2.85 (m, 1H), 3.14 (m, 1H), 3.30 (m, 1H), 3.77 (m, 1H), 4.22 (br, 1H), 4.42 (br, 1H), 4.95 (s, 2H), 6.93 (m, 1H), 7.13-7.35 (m, 10H); $^{13}C\{^1H\}$ NMR (100 MHz, $(CD_3)_2SO$, 30 °C) δ 16.3, 19.9, 29.4, 37.2, 37.2, 54.4, 64.7, 71.4, 74.5, 125.8, 127.5, 128.0, 128.2, 129.1, 137.4, 139.3, 155.8. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.60; H, 7.69; N, 4.08.

(3*S*,4*R*,5*R*)-3-[*N*-(Benzyloxycarbonyl)amino]-2-methyl-7-phenylheptane-4,5-diol (3d) was prepared from *N*-Cbz-L-valinal and 3-phenylpropanal using the general procedure outlined in ref 1. Chromatography on silica gel (75:25 h:ea) gave 4.40 g (83% mass rocovery) of a viscous oil that contained approximately 15−20% (by NMR) of an inseparable impurity (R_f 0.16, 7:3 h:ea). This mixture was taken to the next step where flash chromatography of the cyclic sulfite diastereomers led to purification.

Procedure for the Formation of Cyclic Sulfates 4a−i from 1,2-Diols 3a−i (adapted from the procedure of Sharpless *et al.*[6a]). Thionyl chloride (220 μL, 3.0 mmol) in CH_2Cl_2 (280 μL) was added dropwise over 10 min to a stirring solution of diol **3**[1] (2.0 mmol) and Et_3N (1.1 mL, 8.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. Stirring was continued for 5 min, at which time TLC (7:3 h:ea) indicated completion. Water (1 mL) was added, and stirring was continued for 5 min. Hexanes (8 mL) and water (10 mL) were added, and the ice bath was removed. After being stirred for an additional 5 min the aqueous layer was removed. The organic layer was washed with water (3 × 5 mL), saturated $NaHCO_3$ (5 mL), and saturated NaCl (5 mL),

dried ($MgSO_4$), and concentrated to give cyclic sulfite (pair of diastereomers by NMR and TLC) as an oil. After being dried under vacuum for 2 h, the oil was dissolved in CCl_4 (6 mL) and CH_3CN (6 mL). Water (9 mL), $RuCl_3 \cdot 3H_2O$ (6.0 mg), and $NaIO_4$ (856 mg, 4 mmol) were added with stirring at 0 °C. The reaction was monitored closely by TLC for completion (approximately 1 h). Hexanes (25 mL) and ether (25 mL) were added, the layers were separated, and the aqueous layer was extracted with hexanes (2 × 20 mL). The combined organics were washed with saturated NaCl (8 × 10 mL, or until the organic layer is nearly colorless), dried ($MgSO_4$), and concentrated to a white solid. Cyclic sulfates could be further purified by flushing through a plug of silica (7:3 h:ea) to give **4a**−**i** as a white solid or clear oil.

(2*S*,3*R*,4*R*)-2-[*N*-(Benzyloxycarbonyl)amino]-6-methyl-1-phenylheptane-3,4-cyclic Sulfate (4a): TLC of cyclic sulfite intermediate R_f 0.64, 0.68 (7:3 h:ea); yield 793 mg (92%) of a white solid; mp 111 °C dec; R_f 0.68 (7:3 h:ea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.4, 3H), 0.90 (d, J = 6.5, 3H), 1.43 (dd, J = 7.1, 12.1, 1H), 1.63−1.76 (m, 2H), 2.86 (dd, J = 8.9, 13.8, 1H), 2.99 (dd, J = 7.3, 13.8, 1H), 4.15 (q, J = 8.5, 1H), 4.44 (d, J = 8.5, 1H), 4.78, (t, J = 9.3, 1H), 5.04 (d, J = 12.3, 1H), 5.10 (d, J = 12.3, 1H), 5.24 (d, J = 6.6, 1H), 7.19−7.36 (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.2, 22.8, 25.0, 38.8, 40.2, 51.2, 67.3, 83.4, 86.9, 127.3, 127.7, 128.2, 128.5, 128.97, 129.00, 135.6, 135.9, 156.2; $[\alpha]^{20}_D$ +4.50° (*c* 3.87, $CHCl_3$). Anal. Calcd for $C_{22}H_{27}NO_6S$: C, 60.95; H, 6.28; N, 3.23. Found: C, 60.57; H, 6.05; N, 2.92.

Silylation-Inversion Procedure of 4i (adapted from the procedure of Sakaitani and Ohfune[5]). To a stirring solution of **4i** (800 mg, 2.0 mmol) and 2,6-lutidine (463 μL, 4.0 mmol) in CH_2Cl_2 (6 mL) was added *tert*-butyldimethylsilyl triflate (690 μL, 3.0 mmol) dropwise over 5 min. After 20 min, saturated NH_4Cl (10 mL) was added. The mixture was stirred and separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water (2 × 10 mL) and saturated NaCl (10 mL), dried ($MgSO_4$), and concentrated to give the crude silyl carbamate (**4j**). **4j** was dissolved in THF (10 mL) and cooled to 0 °C. A 1.0 M solution of TBAF in THF (2 mL, 2 mmol) was added over 5 min, and then the solution was stirred at 0 °C for 1 h. The solution was concentrated and chromatographed (95:5 CH_2Cl_2−methanol) through a small plug of silica to give the tetra-*n*-butylammonium sulfate intermediate (882 mg, 75%) as a clear oil. The residue was dissolved in THF[20] (40 mL) and 20% aqueous H_2SO_4 (200 μL) and stirred for 30 min at room temperature. The solution was neutralized with 20% aqueous KOH (~500 μL), dried ($MgSO_4$), concentrated, and chromatographed (95:5 CH_2Cl_2-methanol) to give **5a** (363 mg, 71% from **4i**), as a clear oil.

Thermolysis−Cyclization Procedure. A solution of **4** (1 mmol) in dry CH_3CN (60 mL) was heated. The disappearance of starting material was monitored by TLC. The solution was cooled to room temperature and concentrated. The solid was dissolved in THF (60 mL) and 2% aqueous H_2SO_4 (300 μL) and stirred for 1 h. The solution was neutralized with 20% aqueous KOH with stirring. The mixture was dried ($MgSO_4$), concentrated, and flushed through a plug of silica with ethyl acetate to give the crude products. The crude material was analyzed by ^{1}H and ^{13}C{^{1}H} NMR in CD_3OD. The isomer ratios were determined from ^{13}C{^{1}H} NMR spectra. One equivalent of *N*-benzylacetamide was obtained from the *N*-Cbz cyclic sulfates.

***N*-Benzylacetamide**: ^{1}H NMR (500 MHz, CD_3OD) δ 1.96 (s, 3H), 4.33 (s, 2H), 7.23−7.32 (m, 5H); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ 22.5, 44.2, 128.2, 128.6, 129.5, 139.9, 173.0.

Hydrogenation−Cyclization Procedure. A test tube was charged with **4** (0.40 mmol) in THF (6 mL), Et_3N (220 μL, 1.58 mmol), and 5% Pd/C (179 mg). The test tube was placed into a glass Parr bottle, and the bottle was flushed with H_2 and pressurized to 50 psi with H_2. The bottle was shaken for about 18 h, at which time TLC indicated the disappearence of starting material. The mixture was filtered through Celite with $CHCl_3$ and then concentrated. The yellow oil was dissolved in THF[20] (50 mL) and 20% aqueous H_2SO_4 (200 μL) and stirred at 25 °C for 30 min. The solution was then neutralized with 20% aqueous KOH, dried ($MgSO_4$), filtered through Celite, and concentrated to give the crude products. The crude material was analyzed by ^{1}H and ^{13}C{^{1}H} NMR in CD_3OD. The isomer ratios were determined from ^{13}C NMR spectra.

Thermolysis of 4a. Reflux for 4.5 h in CH_3CN. The oxazinone **6a** was separated from the *N*-benzylacetamide by fractional crystallization (acetone−hexanes) to provide **6a** (75 mg, 67%) as a white solid. The mother liquors were chromatographed to give **5a** (13 mg, 12%) as a clear oil.

Hydrogenation of 4a. Chromatography (95:5 CH_2Cl_2−methanol) gave **5a** (72 mg, 69%) and **6a** (6.5 mg, 6%).

(4*S*,5*S*)-4-Benzyl-5-[(1*R*)-1-hydroxy-3-methylbutyl]-1,3-oxazolidin-2-one (5a) was obtained as a viscous oil: R_f 0.35 (95:5 CH_2Cl_2−methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 0.97 (d, J = 6.6, 1H), 0.99 (d, J = 6.7, 1H), 1.42−1.57 (m, 2H), 1.89−1.97 (m, 1H), 2.67 (dd, J = 11.1, 13.3, 1H), 3.24 (dd, J = 2.9, 13.4, 1H), 3.97 (ddd, J = 2.8, 9.4, 9.6, 1H), 4.08 (ddd, J = 3.2, 7.2, 11.1, 1H), 4.33 (dd, J = 7.3, 9.2, 1H), 7.21−7.33 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 21.9, 24.4, 25.0, 37.2, 45.1, 57.9, 67.3, 83.5, 127.7, 129.8, 130.4, 139.0, 161.1; IR (film) 3410, 3300, 1745 cm^{-1}; FABMS (NBA) m/z 527 ($2MH^+$, 18), 264 (MH^+, 100), 220 (7); FAB HRMS m/z calcd for $C_{15}H_{22}NO_3^+$ 264.1600, found 264.1607.

(4*S*,5*R*,6*S*)-3,4,5,6-Tetrahydro-4-benzyl-5-hydroxy-6-(2-methylpropyl)-2*H*-1,3-oxazin-2-one (6a). An analytical sample was obtained by recrystallization from methanol: mp 188-190 °C; R_f 0.34 (95:5 CH_2Cl_2−methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 0.89 (d, J = 6.6, 3H), 0.92 (d, J = 6.7, 3H), 1.23 (ddd, 1H), 1.50 (ddd, 1H), 1.77 (m, 1H), 2.79 (dd, J = 13.1, 6.3, 1H), 3.04 (dd, J = 13.1, 8.6, 1H), 3.47 (t, J = 3.2, 1H), 3.66 (ddd, J = 3.2, 6.3, 8.6, 1H), 4.33 (dt, J = 9.8, 3.4, 1H), 7.19−7.32 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 22.1, 23.4, 25.6, 37.2, 42.3, 54.5, 64.8, 81.6, 127.7, 129.6, 130.4, 138.1, 155.6; IR (Nujol) 3381, 1687 cm^{-1}; FABMS (NBA) m/z 264 (MH^+, 100), 220 (4); $[\alpha]^{20}_D$ −66.8° (*c* 3.08, methanol). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.32; H, 7.98; N, 5.08.

(2*S*,3*R*,4*S*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-6-methyl-1-phenylheptane-3,4-diol (8c). Oxazinone **6a** (100 mg, 0.380 mmol), LiOH (273 mg, 11.4 mmol), EtOH (7 mL), and water (3 mL) were heated at reflux for 12 h. The reaction mixture was concentrated to 2 mL and extracted with ether (2 × 15 mL) and THF (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the free amino diol **8a** as a white solid (89.4 mg, 96%). The amino diol **8a** was dissolved in CH_2Cl_2 (4 mL), and a solution of di-*tert*-butyl dicarbonate (83 mg, 0.380 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 5 min. The reaction was stirred for 16 h, concentrated, flushed through silica (1:1 h:ea), and recrystallized from ethyl acetate−hexanes to give pure **8c** as a white solid (76 mg, 59%): mp 137.5−138 °C; R_f 0.45 (7:3 h:ea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, J = 6.6, 3H), 0.90 (d, J = 6.7, 3H), 1.32−1.37 (m, 2H), 1.39 (s, 9H), 1.86 (sept., J = 6.8, 1H), 2.87 (m, 2H), 3.20 (d, J = 8.2, 1H), 3.36 (m, 1H), 3.9 (br, 1H), 4.21 (m, 1H), 4.72 (d, J = 8.5, 1H), 7.18−7.29 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3, 23.9, 24.3, 28.2, 38.2, 42.1, 51.7, 69.4, 75.6, 80.3, 126.5, 128.5, 129.0, 137.9, 157.4; $[\alpha]^{20}_D$ −57.0° (*c* 3.24, $CHCl_3$) [lit.[12a] mp 139−140 °C; $[\alpha]^{20}_D$ −56.4° (*c* 1, $CHCl_3$)].

(4*S*,5*S*,6*R*)-4-(Cyclohexylmethyl)-5-(1-hydroxy-3-methylbutyl)-1,3-oxazolidin-2-one (5k, R_1 = Cyclohexyl, R_2 = Isopropyl). Using an adapted literature procedure,[13] the phenyl ring of **5a** was hydrogenated (5% Rh/Al_2O_3, H_2, 50 psi) to give the crude cyclohexyl analog. An analytical sample was obtained by chromatography (6:4 h:ea), giving **5k** as a white solid. Comparison of ^{1}H NMR to the four known diastereomers verified the stereochemical assignment of **5a**.[12d]

(20) When THF from a Na/benzophenone still is combined with 20% aqueous H_2SO_4 for the hydrolysis, we have noticed that significant quantities of polymerized THF were obtained in the products. This results from the fact that the THF is still warm. Therefore, the THF was allowed to cool to room temperature before addition of 20% aqueous H_2SO_4.

(2S,3*R*,4*S*)-2-Acetamido-1,3,4-triacetoxyhexadecane (1a). A solution of cyclic sulfate **4g** (95 mg, 0.165 mmol) in CH_3CN (15 mL) was refluxed for 4.5 h and concentrated and the residue dissolved in THF (20 mL) and 2% aqueous H_2SO_4 (100 μL) and stirred for 1 h. Na_2CO_3 (50 mg) was added, and the reaction mixture was concentrated, dissolved in ether (4 mL) and CH_2Cl_2 (10 mL), dried ($MgSO_4$), and concentrated to a solid (107 mg). The solid was dissolved in EtOH (5 mL), and HCO_2H (250 μL) along with 10% Pd/C (100 mg) were added. The mixture was stirred for 24 h, filtered, and concentrated (67 mg). The solid was dissolved in ethanol (10 mL) and 2 N NaOH (10 mL) and refluxed for 3 h. The solution was concentrated to 10 mL and extracted with CH_2Cl_2 (4 × 10 mL). The organic layer was dried ($MgSO_4$), concentrated, and dissolved in pyridine (2 mL) and acetic anhydride (2 mL). The solution was stirred for 135 min and concentrated and flushed through silica gel with h:ea (1:1) to give **1a** and an unknown impurity as a 1:1 mixture (17 mg). Comparison of the ^{1}H NMR spectra with the literature[10] clearly showed the formation of **1a**, but the impurity could not be assigned as one of the three other diastereomers.

(2S,3*S*,4*R*)-2-Acetamido-1,3,4-triacetoxyoctadecane (9). A solution of hydroxy carbamate **5f** (95 mg, 0.21 mmol) in CH_3CN (25 mL) and 48% aqueous HF was stirred for 30 min. The solution was diluted with saturated $NaHCO_3$ (25 mL) and extracted with $CHCl_3$ (4 × 50 mL). The organic layer was dried, filtered, and concentrated to give the dihydroxy carbamate as an oil. The residue was dissolved in ethanol (25 mL) and 15% NaOH (10 mL) and heated at 70 °C for 14 h. The solution was concentrated to 10 mL and diluted with saturated NaCl (50 mL). The aqueous layer was extracted with $CHCl_3$ (6 × 25 mL). The organic layer was dried ($MgSO_4$), concentrated, and dissolved in acetic anhydride (3 mL), pyridine (10 mL), and 4-(*N*,*N*-dimethylamino)pyridine (10 mg). The solution was stirred for 24 h, concentrated, and chromatographed (R_f 0.27, 1:1 h:ea) to give **9** (60 mg, 0.124 mmol, 60%). ^{1}H and ^{13}C{^{1}H} NMR spectra, were identical with the literature.[9c,e,f] The only exception was the proton reported to be at 4.69 in ref 9f; we observed this proton at 4.90, which was consistant with ref 9c,e.

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Supporting Information Available: Spectral and supporting experimental information for compounds **4b**−**i**, **5b**−**d,f**, **6b**−**e**, and **7c,e** (9 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.

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