Stereochemistry Associated with the Addition of 2-(Trimethylsilyl)thiazole to Differentially Protected α-Amino Aldehydes. Applications toward the Synthesis of Amino Sugars and Sphingosines[1]

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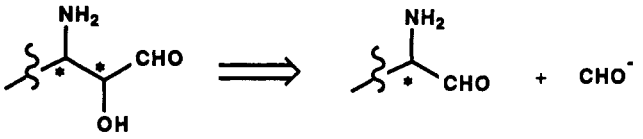
The stereochemistry and synthetic utility of the addition of 2-(trimethylsilyl)thiazole (2-TST, 1) to various N-protected α-amino aldehydes is described. The reactions of 1 with *N*-Boc-L-serinal acetonide (2) and *N*-Boc-L-threoninal acetonide (3) are essentially anti diastereoselective (ds = 85–90%) in agreement with the Felkin–Anh model for asymmetric induction, whereas the reactions with *O*-benzyl-NH-Boc-L-serinal (4) and NH-Boc-L-phenylalaninal (5) are syn diastereoselective (ds = 80%). The reversal of diastereoselectivity is interpreted on the basis of a proton-bridged cyclic Cram model for asymmetric induction. The anti adduct derived from the *N*-Boc-L-serinal acetonide (2) was subjected to thiazole-to-formyl unmasking to give a one-carbon higher homologue (i.e., the O,N-protected β-amino-α-hydroxy aldehyde **6a**). This material serves as a precursor to *ribo*- and *arabino*-4-amino-4-deoxypentoses via a further one-carbon-chain elongation with 2-TST and to a C_{20} sphingosine via Wittig olefination. The above *ribo*-amino sugar was transformed via sequential Wittig olefination and reduction into a C_{18} phytosphingosine.

The stereocontrolled assembly of β-amino-α-hydroxy aldehyde units is an important issue in the context of synthetic strategies directed toward the construction of biologically relevant target molecules such as amino sugars,[2] sphingosines,[3] and low molecular weight peptides.[4] Conceptually, the simplest strategy for this operation involves the addition of the formly anion synthon equivalent[5] to a chiral α-amino aldehyde:



In earlier work from this laboratory, we have demonstrated[6] the viability of 2-(trimethylsilyl)thiazole (2-TST, 1) as an effective source of the formyl anion synthon for the construction of 1,2-dihydroxy aldehyde fragments en route to higher carbohydrates, starting from protected α-hydroxy aldehydes (thiazole route).[1] The synthetic value of this approach is based on the high level of diastereoselectivity (anti) in the addition of 1 to the chiral aldehyde and also on the nature of the thiazole ring, which is stable to acid and base and inert toward oxidation and reduction but liberates the formyl group under very mild, neutral conditions. Since various N-protected α-amino aldehydes can be prepared[7a–c] from natural amino acids,[8] a broad class of enantiomerically pure components of the pool of chiral building blocks,[9] we have considered that the reaction between 1 and amino aldehydes[10] would provide a new and hopefully versatile approach to the asymmetric synthesis of chiral building blocks (chirons)[11] for natural products. We report herein the results[12] of the addition of 1 to model α-amino aldehydes and applications of this method to the synthesis of aminopentoses and sphingosines.

Results and Discussion

Stereochemical Studies. In contrast to the substantial levels of diastereoselectivity encountered in the numerous addition reactions of organometallic reagents to chiral alkoxycarbonyl compounds,[13] earlier reports dealing with the addition of alanes[14] and Grignard reagents[7d,15] to α-amino aldehydes have registered only a modest degree of stereocontrol. Recently, good-to-excellent diastereoselectivities have been reported by us using 2-TST (1)[12] and by others with vinylmagnesium bromide[16] and tri-

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(2) (a) Horton, D.; Wander, J. D. In *The Carbohydrates Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1980; Vol. 1B, Chapter 16. (b) Kennedy, J. F.; White, C. A. *Bioactive Carbohydrates*; Ellis Horwood: Chichester, 1983.

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(4) Rich, D. H.; Moon, B. J.; Boparai, A. S. *J. Org. Chem.* **1980**, *45*, 2288. Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263, and references therein.

(5) Ager, D. J. In *Unpoled Synthons*; Hase, T. A., Ed.; Wiley: New York, 1987; p 19.

(6) (a) Dondoni, A. *Lect. Heterocycl. Chem.* **1985**, *8*, 13. (b) Dondoni, A.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron Lett.* **1985**, *26*, 5477. For errata corrigenda see: *Ibid.* **1986**, *27*, 3796. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 835. (d) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron* **1987**, *43*, 3533. (e) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Ibid.* **1988**, *44*, 3215. (f) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1988**, 685. (g) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693.

(7) For the synthesis of amino aldehydes see: (a) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (c) Sugano, H.; Miyoshi, M. *J. Org. Chem.* **1976**, *41*, 2352. Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *22*, 3081. (d) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236. (e) Stanfield, C. F.; Parker, J. E.; Kanellis, P. J. *J. Org. Chem.* **1981**, *46*, 4797, and references therein.

(8) For a recent treatise on the use of amino acids in synthesis see: Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

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(10) For a recent account using of α-amino aldehydes as synthetic auxiliaries see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(11) Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: Oxford, 1983.

(12) For a preliminary report of this work see: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *J. Chem. Soc., Chem. Commun.* **1988**, 10.

(13) Reviews: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125. (c) For recent studies see ref 6g and Reetz, M. T.; Kesseler, K. *J. Org. Chem.* **1985**, *50*, 5434. Mead, K.; McDonald, T. L. *J. Org. Chem.* **1985**, *50*, 422. Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. Bernardi, A.; Cardani, S.; Colombo, L.; Poli, G.; Schimperna, G.; Scolastico, C. *J. Org. Chem.* **1987**, *52*, 888. Mead, K. T. *Tetrahedron Lett.* **1987**, *28*, 1019. Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1987**, 746. Reetz, M. T.; Hüllmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477. Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919.

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(15) (a) Saitoh, Y.; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980**, *21*, 75. (b) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399.

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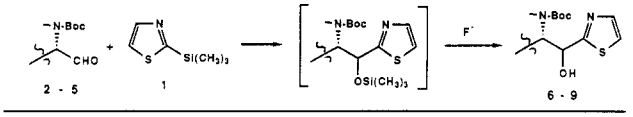
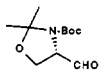
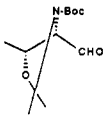
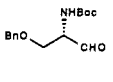
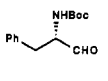
Table I

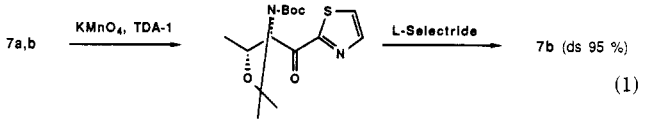


Aldehyde	Conditions	Adducts[a], ds %[b]		Yield,[c] %
 2	CH_2Cl_2, r.t	anti-(6a), 92	syn-(6b), 8	85
 3	CH_2Cl_2, 0 °C	anti-(7a), 85	syn-(7b), 15	68
 4	CH_2Cl_2, -30 °C THF, r.t.	anti-(8a), 20 33	syn-(8b), 80 67	60 55
 5	CH_2Cl_2, -30 °C THF, r.t.	anti-(9a), 20 43	syn-(9b), 80 57	74 75

[a] Th = 2-thiazolyl; Boc = *tert*-butoxycarbonyl; Bn = benzyl. [b] Diastereoselectivity ratios percent (ds %) were determined by 80-MHz ^{1}H NMR analysis (see Experimental Section) of the crude reaction mixtures. [c] Combined yield of products isolated after chromatography.

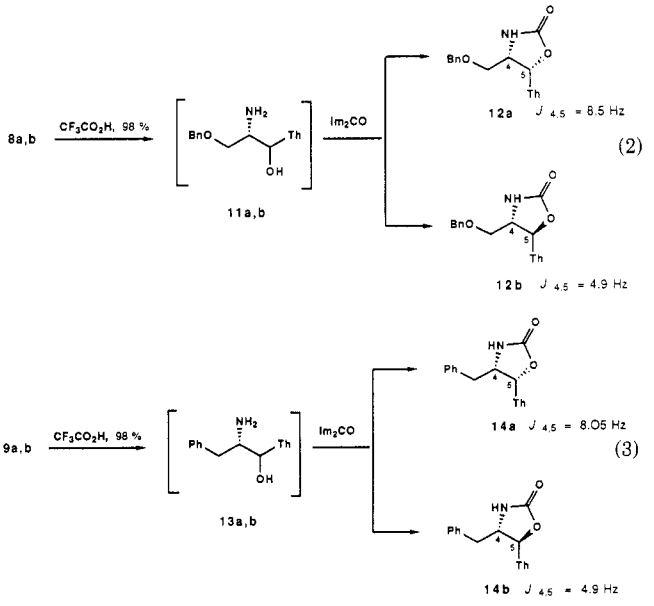
methylsilyl cyanide.[17] Since a single amino aldehyde was employed, we considered it important in the context outlined above to explore the stereochemistry of the addition of **1** with differentially protected compounds. Amino aldehydes **2–5** were selected as model systems for the initial phase of the studies and were prepared according to the literature procedures from the corresponding α-amino acids (see Experimental Section). While *N*-*tert*-butoxycarbonyl- (*N*-Boc-) L-serinal acetonide (**2**) and *N*-Boc-L-threoninal acetonide (**3**) have been shown to be configurationally stable and are available in good optical purity,[7b] the chiral integrity of *O*-benzyl-*N*-Boc-L-serinal (**4**)[7e] and *N*-Boc-L-phenylalaninal (**5**)[18] has not been established.

The reaction between equimolar amounts of 2-TST (**1**) and aldehydes **2–5** occurred smoothly at room temperature or below to give, after in situ desilylation of the resulting adducts with tetrabutylamonium fluoride, the corresponding amino alcohols **6–9**, which could be isolated by chromatography and fully characterized as mixtures of syn and anti diastereomers.[19] The results of these experiments are recorded in Table I. The relative stereochemistry of the adducts (**6a,b** and **7a,b**) derived from the reaction of **1** with oxazolidine aldehydes **2** (L-serinal) and **3** (L-threoninal), respectively, was assigned on the basis of the methyne proton coupling constants at the newly formed diastereogenic center. In analogy with that observed for the anti (J_{HH} = 5.1 Hz) and syn adducts (J_{HH} = 6.0 Hz) derived from **1** and D-glyceraldehyde acetonide,[6c,21] the coupling constants in the major anti adducts **6a** (J_{HH} = 2.8 Hz) and **7a** (broad doublet) were lower than those in the syn adducts **6b** (J_{HH} = 8.7 Hz) and **7b** (J_{HH} = 7.5 Hz). The assigned stereochemistry to *anti*-**6a** was also inferred from the X-ray structure determination of the one-carbon higher homologue obtained from it (vide infra). The major isomer **6a** has previously been converted into the minor diastereomer **6b** by inversion of configuration of the hydroxyl group via an oxidation–reduction sequence.[21] The same protocol was applied here to transform the mixture of diastereomeric amino alcohols *anti*-**7a** and *syn*-**7b** into **7b** via ketone **10** (eq 1).



(1)

The addition of 2-TST (**1**) to NH-Boc-protected amino aldehydes **4** and **5** in methylene dichloride at −30 °C afforded mixtures of amino alcohols **8a,b** and **9a,b** in good yield with reasonable syn selectivity.[20] The stereoselectivity decreased substantially by carrying out the reaction in tetrahydrofuran at room temperature. Stereochemical assignments for diastereomers **8a,b** and **9a,b** were made by conversion to oxazolidinone derivatives[22] **12a,b** and **14a,b** via the corresponding deprotected amino alcohols **11a,b** and **13a,b**, respectively. The erythro-isomers **12a** and **14a** (from anti adducts **8a** and **9a**) showed $J_{4,5}$ values much larger than those of the threo isomers **12b** and **14b** (from syn adducts **8b** and **9b**). The data are consistent with dihedral angle values measured by using Drieding molecular models (0° for **12a** and **14a** and roughly 120° for **12b** and **14b**) and are also in agreement with NMR data for related compounds[23] (eq 2 and 3).



(2)

(3)

(16) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979.
(17) Reetz, M. T.; Drewes, M. W.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 3295.
(18) See ref 7a, 14a, and: Rich, D. H.; Sun, E. T. O. *J. Med. Chem.* **1980**, *23*, 27.
(19) For syn–anti nomenclature notation and degree of diastereoselectivity designation employed in this and earlier papers, see notes 20 and 21 in ref 6g.
(20) Since the enantiomeric purity of adducts obtained from amino aldehydes **4** and **5** was not relevant in the context of this work, it was not examined.
(21) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 702.
(22) The ratio of diastereomeric oxazolidinones **12a,b** and **14a,b** were identical with those of the corresponding coupled amino alcohols **8a,b** and **9a,b**.

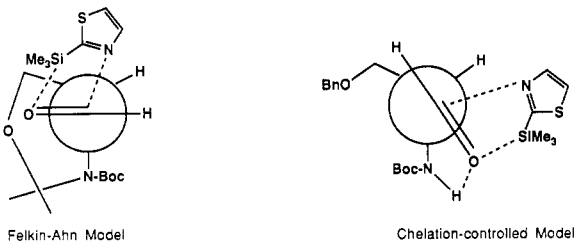
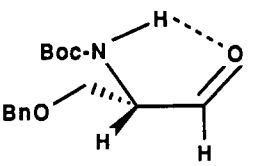


Figure 1. Transition-state models for the addition of 2-TST (1) to *N*-Boc-amino aldehydes **2** and **4**.

The results recorded in Table I clearly indicate that the diastereoselectivity of the addition of 2-TST (1) to α-aminoaldehydes **2–5** is dependent on the protection of the amino group. Thus, the anti diastereoselectivity found with the addition of **1** to *N*-Boc-oxazolidine aldehydes **2** and **3** may be ascribed to the Felkin–Anh open-chain model for asymmetric induction[24] and is also consistent with the earlier observations we have made regarding the stereoselectivity of the addition of **1** to D-glyceraldehyde and L-threose acetonides.[6c] On the basis of previous mechanistic considerations,[6c,25] the transition-state model associated with the addition of **1** to **2** is presented in Figure 1. The reversal of the diastereoselectivity observed with NH-Boc-protected amino aldehydes (syn addition) reflects some sort of chelation control in the transition state. Due to the absence of Lewis acid catalysts which generally participate in chelate structures leading to syn adducts,[26] a proton-bridged Cram cyclic model[27] is thought to account for the main stereochemical course of these reactions (Figure 1). In agreement with this hypothesis is the observation that the use of tetrahydrofuran as solvent decreases the level of diastereoselectivity as a consequence of effectively competing with the formyl group for hydrogen bonding to the NH group. The ^{1}H NMR spectra of aldehydes **4** and **5** show a sharp singlet at 9.64 and 9.61 ppm, respectively, due to the CHO proton. This suggests a tight conformation in which the dihedral angle between the aldehydic proton and the one on the α-carbon are ca. 90°, thus resulting in a minimum spin–spin coupling.[28] Aside from these mechanistic speculations, the reversal of diastereoselectivity observed is an important synthetic result since L-serine can be transformed into a *syn*- or *anti*-1,2-aminohydroxyl system by appropriate protection of the amino group. This observation considerably extends the scope of the addition of 2-TST (1) to amino aldehydes:



Homologation of L-Serinal. (i) Synthesis of L-Amino Pentoses. To demonstrate the synthetic equivalence of thiazoles **6–9** with chiral α-hydroxy-β-amino aldehydes and to test their viability in the thiazole route,[1] we decided to use the anti adduct **6a**, which can be obtained in high diastereomeric excess (Table I) and enantiomeric purity, as the model system for synthetic elaborations toward 4-deoxy-4-aminopentoses (Figure 1). Amino sugars are components of various biologically active compounds[2] such as anticancer antibiotics and biopolymers, and consequently these molecules have been the targets of several syntheses over the past few years.[2,29] Most of the traditional methods employ carbohydrate-based materials, but substantial efforts have recently been focused on the asymmetric synthesis from non-sugar precursors.[30] An increasing number of these take advantage of amino acids as chiral educts. For instance, L- and D-threonine have been transformed into protected chiral 2,3-dihydroxybutanals which have been employed for the synthesis of daunosamine and acosamine.[31] Moreover, various amino aldehydes are currently being used as heterodiene partners in cycloaddition approaches for the construction of amino sugar skeletons.[10]

The formyl deblocking of the thiazole ring was carried out by using either the unprotected alcohol **6a** or its *O*-benzyl derivative **6a′**. In both cases, the application of our one-pot unmasking protocol[6] consists of three sequential operations: N-methylation, reduction, and hydrolysis to give the corresponding aldehydes **15a** and **15a′** in high yield. This aldehyde release method tolerates the presence of the *N*-Boc function, i.e., a somewhat basic amidic nitrogen.[32] This operation should be equally applicable to other adducts of Table I to give various diastereoisomeric α-hydroxy-β-amino aldehyde units.

A further one-carbon homologation was carried out by using the *O*-benzyl-protected α-hydroxy aldehyde **15a′**. The addition of 2-TST (1) in dichloromethane at room temperature was rather unselective (ds = 60%) but became quite diastereoselective by using tetrahydrofuran[33] at 0 °C, giving rise to the *anti*-**16a** and *syn*-**16b** adducts in an 85:15 ratio and in 88% overall yield. Following the isolation of the individual isomers by flash chromatography, stereochemical assignments were made by an X-ray crystal structure determination[21] of **16b**. The anti configuration of the major isomer **16a** is consistent with the non-chelate

(23) (a) Oxazolidinones: see ref 18 and Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308. Kano, S.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1989**, *54*, 514. Rama Rao, A. V.; Murali Dhar, T. G.; Chakraborty, T. K.; Gurjar, M. K. *Tetrahedron Lett.* **1988**, *29*, 2069. (b) Oxazolidines: Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127.

(24) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 144. For a recent theoretical approach supporting the Felkin–Anh model see: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. Wu, Y.-D.; Houk, K. N. *Ibid.* **1987**, *109*, 906, 908.

(25) Similarly to that proposed earlier for the reaction of **1** with other aldehydes (ref 6g and: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1988**, *53*, 1748), it is assumed that the "spontaneous" addition of 2-TST (1) to α-amino aldehydes is a multistep process involving the formation of a thiazolium-2-ylide as a key intermediate.

(26) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609. Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. See also ref 15b and 17.

(27) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245.

(28) The same argument has been employed to explain the ^{1}H NMR spectrum of other amino aldehydes. See ref 14a.

(29) For recent reviews dealing with the synthesis of amino sugars, see: (a) Reference 13b. (b) Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35.

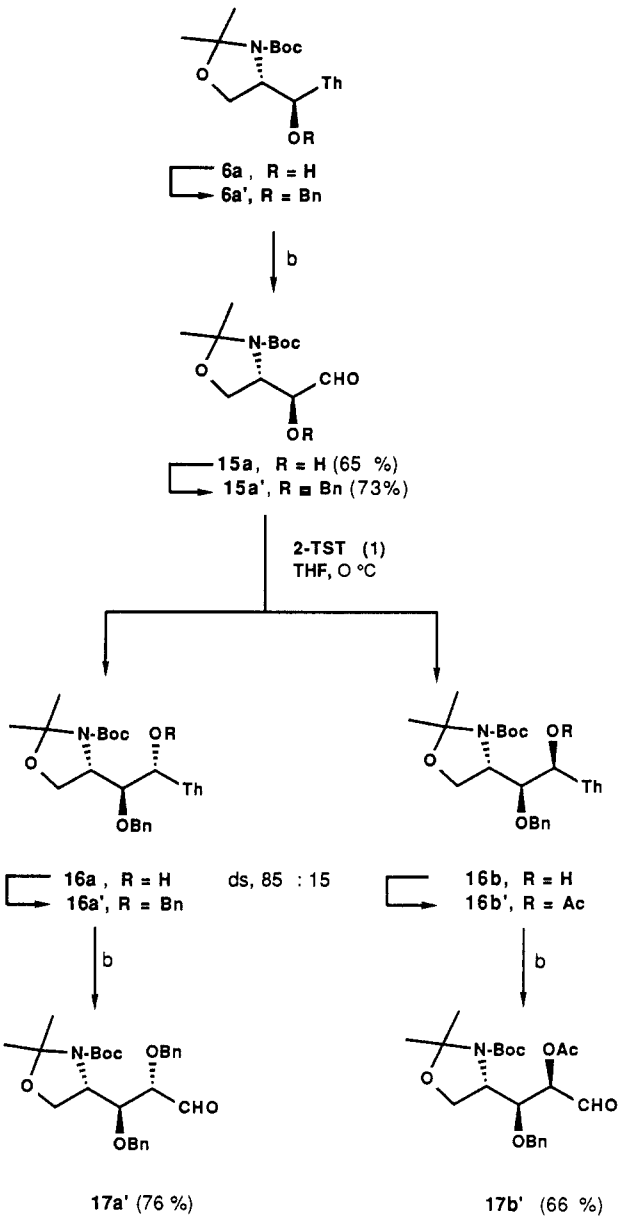
(30) For some selected recent articles see: Jäger, V.; Muller, I. *Tetrahedron* **1985**, *41*, 2997, 3519. Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261. Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269. Danishefsky, S. J.; Larson, E.; Springer, J. P. *Ibid.* **1985**, *107*, 1275. Kita, Y.; Itoh, F.; Tamura, O.; Ke, Y. Y.; Tamura, Y. *Tetrahedron Lett.* **1987**, *28*, 1431. Ha, D.-C.; Hart, D. J. *Ibid.* **1987**, *28*, 4889. Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. Banfi, L.; Cardani, S.; Potenza, D.; Scolastico, C. *Tetrahedron* **1987**, *43*, 2317. Hirama, M.; Shigemoto, T.; Ito, S. *J. Org. Chem.* **1987**, *52*, 3342. Golebiowski, A., Jacobsson, U.; Jurczak, J. *Tetrahedron* **1987**, *43*, 3063. Dai, L.; Lou, B.; Zhang, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5195. See also refs 6f and 23b.

(31) See ref 8, p 151.

(32) For another example of application of this protocol in the presence of an amidic function (i.e., the *N*-acetyl group), see ref 6f.

(33) We have observed a related solvent effect in the addition of 2-TST (1) to heptodialdo-1,5-pyranose; see ref 6d.

Scheme I[a]



[a] Th = 2-thiazolyl; Bn = benzyl; Ac = acetyl. [b] Reagents and conditions: (i) MeI (MeCN); (ii) $NaBH_4$ (MeOH, −10 °C); (iii) $HgCl_2$ (MeCN/H_2O).

Felkin–Anh model for diastereoselection[24] and is in line with the dominant stereochemical outcome observed in reactions of **1** with chiral alkoxy aldehydes.[6]

As a consequence of the thiazolyl–formyl group equivalence, compounds **16a,b** represent convenient masked aminopentoses that can be stored and handled without particular care. The deblocking of the formyl group by the usual one-pot sequence provides the O,N-protected 4-amino-4-deoxy-L-ribose (**17a'**) and 4-amino-4-deoxy-L-arabinose (**17b'**) in good yield and sufficient purity for further use. Scheme I thus represents a thiazole-mediated protocol (thiazole route)[1] for the chain elongation of amino acids to amino sugars with retention of the configuration of the amino-bearing center.

(ii) Synthesis of Sphingosines. O- and N-protected amino sugars **15a** (L-erythrose) and **17a'** (L-ribose) were considered as potential building blocks for sphingosines,[3] the molecular fragments of glycosphingolipids, which are the constituents of cell membranes. Various syntheses of sphingosines have been reported employing different strategies and starting materials.[34] Recently, the L-serine-derived aldehyde **2**, as well as its D isomer, has attracted considerable interest as precursor to the chiral hydrophilic part of sphingosines via reaction with metal acetylenes.[35]

The synthesis of D-*erythro*-C_{20}-sphingosine (**19**) was achieved[12] as outline in Scheme II. Aldehyde **15a** was subjected to Wittig reaction using *n*-hexadecanylidenetriphenylphosphorane generated in situ from the appropriate phosphonium salt and phenyllithium in the presence of an excess of lithium bromide so as to ensure trans selectivity.[36,37] This reaction led exclusively to the (*E*)-alkene **18**, which was isolated in relatively modest yield (31%) by flash chromatography.[38] The one-pot deprotection of **18** with trifluoroacetic acid–water (98:2 mixture) and acetylation of the crude reaction mixture afforded triacetyl-C_{20}-D-*erythro*-sphingosine (**19**), which showed physical properties in excellent agreement with literature values.[39]

The target compound from 4-amino sugar **17a'** was the C_{18}-phytosphingosine **22a**, one of the long-chain saturated bases that are largely diffused in plant sphingolipids[3] as well as in human brain and kidney lipids.[40] Syntheses of C_{18} and C_{20}-phytosphingosines have been mainly reported from natural carbohydrates[41] or by using stereoselective elaborations of synthetic materials.[42] There appears to be no reported case, however, that utilizes the 2(*S*) stereochemistry of L-serine as a chiral precursor.

Our strategy for the synthesis of phytosphingosine **22a** is illustrated in Scheme III. The Wittig olefination of the protected amino-L-ribose **17a'** with tridecanylidenetriphenylphosphorane afforded a single alkene, very likely the *Z* isomer **20**, in good yield.[42] Treatment of **20** with Raney Ni in refluxing ethanol affected both double-bond reduction and debenzylation, giving the O,N-protected

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(35) (a) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354. (b) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395. (c) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037. (d) Radunz, H.-E.; Devant, R. M.; Eiermann, V. *Liebigs Ann. Chem.* **1988**, *1103*.

(36) For the betaine-ylide modification of the Wittig reaction and a warning about the phenyllithium employed, see: Schlosser, M.; Tuong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311. We thank Professor R. R. Schmidt (University of Konstanz) for providing unpublished experimental details of the Wittig reaction with nonstabilized phosphoranes.

(37) For up-to-date evaluations of the mechanism and stereochemistry of the Wittig olefination, see: Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1988**, *53*, 3397. Vedejs, E.; Marth, C. F.; Ruggeri, R. *J. Am. Chem. Soc.* **1988**, *110*, 3940. Vedejs, E.; Marth, C. F. *Ibid.* **1988**, *110*, 3948.

(38) Compound **18**, showing consistent IR and NMR data, was not further purified, and no attempts were made to improve its yield.

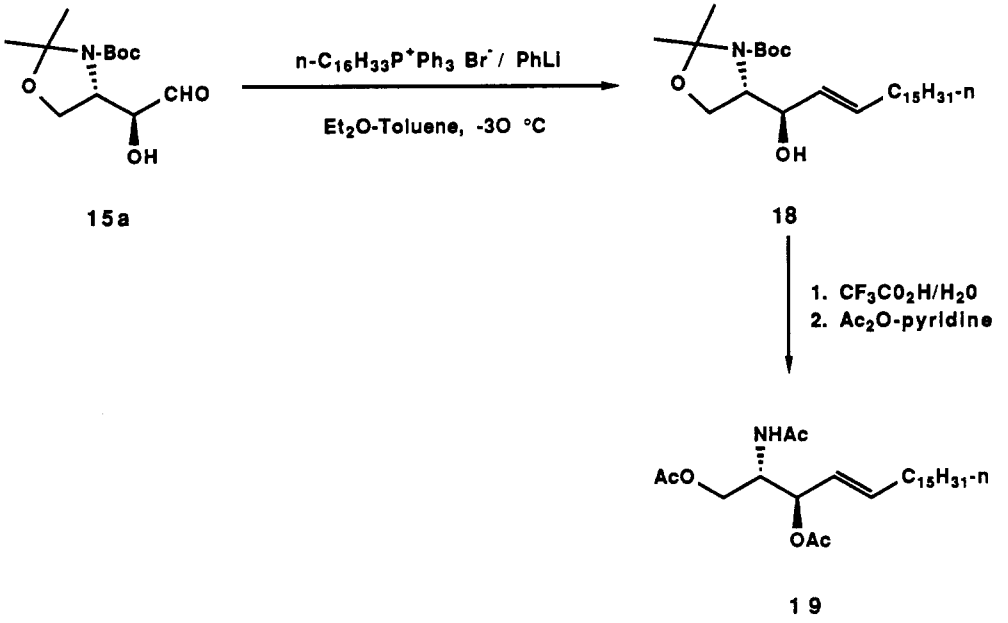
(39) See: Schmidt, R. R.; Zimmermann, P. In ref 34a.

(40) Karlsson, K. A. *Acta Chem. Scand.* **1964**, *18*, 2397.

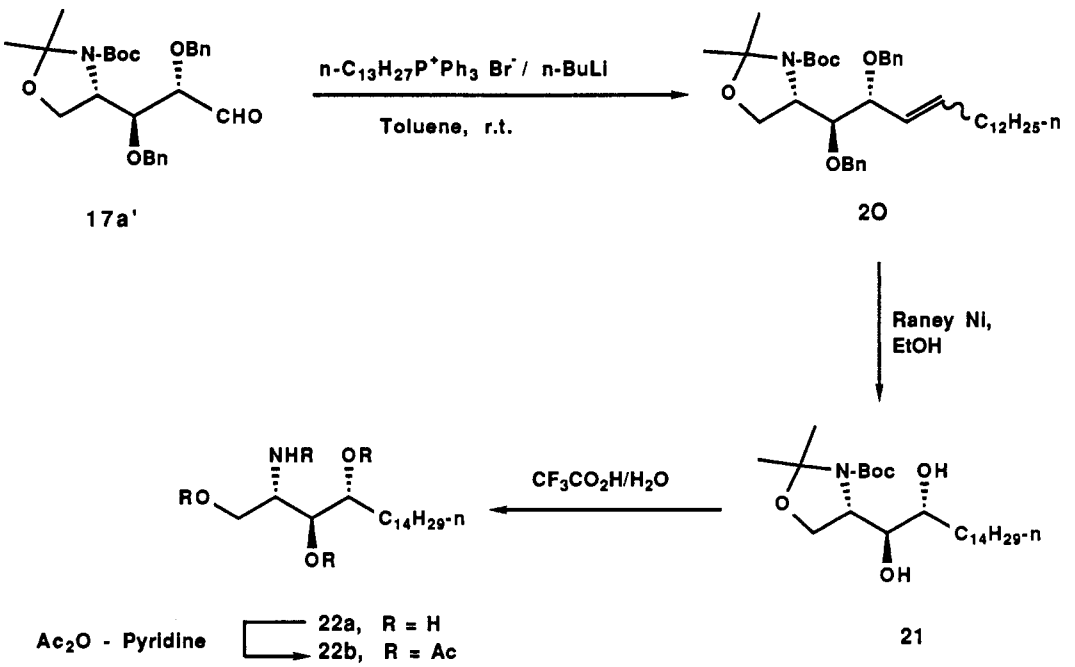
(41) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961, and references therein.

(42) From isoxazolines. See: Jager, V.; Muller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Hafele, B.; Schroter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79.

Scheme II



Scheme III



C_{18}-phytosphingosine **21**. Further deprotection of **21** with trifluoroacetic acid–water produced the target compound **22a**, which was fully characterized by comparison of its spectroscopic and physical properties, as well as of those of the tetraacetyl derivative **22b**, with literature values.[41]

The excellent agreement of the physical constants of D-*erythro*-C_{20}-sphingosine **19** and D-*ribo*-C_{18}-phytosphingosine **22** with literature values confirms the structural assignment of their precursors and indicates that the synthetic manipulations that they had been subjected to occurred with integrity of the various asymmetric centers. The synthesis of amino sugars and sphingolipid bases described above illustrates a strategy to biologically interesting compounds from L-serine, whose stereochemistry at C-2 is employed to initiate the construction of new stereocenters. This route, which is centered upon the use of 2-TST (**1**) as a formyl anion equivalent for aldehyde homologation, should be amenable to the preparation of other amino sugars and sphingosines starting from the syn adducts,[43] (i.e., the thiazole aminothreose **6b** and the thiazole aminoarabinose **16b**).

Conclusion

Our earlier studies dealing with the stereochemistry of the addition of 2-TST (**1**) to chiral aldehydes[6] has been extended to compounds bearing a protected α-amino group. The presence of the stereocenter induces a significant stereoselectivity in carbon–carbon bond formation but in opposite directions depending on the amino group protection. N,N-Diprotected compounds give anti adducts (ds = 85–90%), whereas N-monoprotected derivatives lead

(43) It is worth noting that the syn diastereomers, which are the minor products obtained from the addition of 2-TST (**1**) to aldehydes, are also available from mixtures of syn and anti adducts via our oxidation–reduction sequence. See ref 21.

to syn adducts (ds = 80%). The formyl group unmasking from the thiazole ring tolerates the presence of a suitably protected amino group. In fact, the aldehyde has been released from the anti-adduct **6a** derived from *N*-Boc-L-serinal acetonide (**2**) and 2-TST (**1**), thus demonstrating the synthetic equivalence of **1** as a formyl anion synthon for the synthesis of β-amino-α-hydroxy aldehyde fragments. The synthetic utility of these compounds is illustrated by chain elongation to homochiral aminopentoses via an iterative 2-TST-mediated homologation sequence and to sphingosines and phytosphingosines via Wittig olefination. This chemistry nicely demonstrates a useful synthetic transformation of converting natural L-amino acids into unnatural L-amino sugars and related materials.

Experimental Section

General Comments and Materials. All melting and boiling points are uncorrected. ^1H and ^{13}C NMR spectra were obtained on 80-MHz WP 80 Bruker and on 300-MHz Gemini 300 Varian spectrometers unless otherwise stated. Chemical shifts are given in parts per million downfield from tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 grating spectrometer. Elemental analyses were performed on a Model 1106 microanalyzer (Carlo Erba). All experiments were carried out with freshly distilled and dried solvents.

2-(Trimethylsilyl)thiazole (**1**),[6g,25] *N*-(*tert*-butoxycarbonyl)-*N*,*O*-isopropylidene-L-serinal (**2**),[7b] *N*-(*tert*-butoxycarbonyl)-*N*,*O*-isopropylidene-L-threoninal (**3**),[7b] *N*-(*tert*-butoxycarbonyl)-*O*-benzyl-L-serinal (**4**),[7c] and *N*-(*tert*-butoxycarbonyl)-L-phenylalaninal (**5**)[7a] were prepared according to the literature procedures. *n*-Hexadecyltriphenylphosphonium bromide and *n*-tridecyltriphenylphosphonium bromide were prepared from 1-bromo-*n*-hexadecane and 1-bromo-*n*-tridecane, respectively.[34a]

Addition of 2-(Trimethylsilyl)thiazole (1, 2-TST) to α-Amino Aldehydes 2–5. General Procedure. A. In Dichloromethane. To a stirred solution of the aldehyde (1 mmol) in dry dichloromethane (5 mL) was added dropwise a solution of 2-TST (**1**, 0.23 g, 1.5 mmol) in the same solvent (3 mL) at an appropriate temperature (Table I). After 20 h of stirring, the solvent was evaporated in vacuo, and the residue was treated with 1 M solution of tetra-*n*-butylammonium fluoride (1.5 mmol) in tetrahydrofuran (10 mL). After 1 h of stirring, the solvent was removed under vacuum, and a saturated solution of $NaHCO_3$ was added. The solution was extracted with ethyl acetate and dried over anhydrous Na_2SO_4, and the solvent was removed at reduced pressure. The residue was chromatographed through a short column (silica gel, 8:2 petroleum ether/ethyl acetate for **6**, 7:3 petroleum ether/diethyl ether for **7**, 7:3 diethyl ether/petroleum ether for **8**, and 7:3 petroleum ether/ethyl acetate for **9**) to give the mixture of syn and anti adducts **6–9** (yields and ds percent are given in Table I).

B. In Tetrahydrofuran. To a stirred solution of the aldehydes **4** and **5** (1 mmol) in dry THF (10 mL) was added dropwise a solution of 2-TST (**1**, 0.23 g, 1.5 mmol) in the same solvent (5 mL). After 15 h of stirring, water (2 mL) was added, and the mixture was treated with a 1 M solution of tetra-*n*-butylammonium fluoride (1.5 mmol). Workup as above gave the mixture of syn ad anti adducts **8** and **9** (yields and ds percent are given in Table I).

The individual diastereomers **6a** and **6b** (85% yield, ds_{anti} 92% from NMR spectrum) were separated by fractional crystallization from dichloromethane–*n*-hexane and their enantiomeric purity demonstrated by ^1H NMR spectroscopy using the chiral shift reagent Eu(hcf)$_3$ {tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III)}.

(1*S*)-2-Amino-2-*N*-(*tert*-butoxycarbonyl)-2-deoxy-2,3-*N*,*O*-isopropylidene-1-(2-thiazolyl)-L-glycitol (6a):[21] mp 168–171 °C; $[\alpha]_D = -48.3°$ (*c* 0.87, $CHCl_3$); IR (KBr) 3200, 1700 cm^{-1}.

(1*R*)-2-Amino-2-*N*-(*tert*-butoxycarbonyl)-2-deoxy-2,3-*N*,*O*-isopropylidene-1-(2-thiazolyl)-L-glycitol (6b): mp 86–87 °C; $[\alpha]_D = -0.8°$ (*c* 0.825, $CHCl_3$); IR (KBr) 3200, 1705 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3 + D_2O$) δ 1.47 (s, 3 H), 1.52 (s, 9 H), 1.61 (s, 3 H), 3.77–4.55 (m, 3 H), 5.10 (d, 1 H, *J* = 8.7 Hz), 7.34 (d, 1 H, *J* = 3.2 Hz), 7.77 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{14}H_{22}N_2O_4S$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.39; H, 7.12; N, 8.84.

The mixture of **(1*S*)-2-amino-2-*N*-(*tert*-butoxycarbonyl)-2,4-dideoxy-2,3-*N*,*O*-isopropylidene-1-(2-thiazolyl)-D-threitol (7a)** and of the 1*R* isomer **7b** (68% yield, ds_{anti} 85% from NMR spectrum) showed the following: oil; IR ($CHCl_3$) 3280, 1660 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3 + D_2O$) δ 1.17–1.65 (m, 18 H), 3.77–4.03 (m, 1 H), 4.25–4.52 (m, 1 H), 4.98 (br s, 0.85 H, anti isomer **7a**), 5.16 (d, 0.15 H, *J* = 7.5 Hz, syn isomer **7b**), 7.32 (d, 1 H, *J* = 3.2 Hz), 7.72 (d, 1 H, *J* = 3.2 Hz). Flash chromatography of the mixture (silica gel, 6:4 petroleum ether/diethyl ether) gave 0.178 g of pure anti adduct **7a**, whose NMR spectrum was as detailed above with the exception of the doublet at δ 5.16.

Anal. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.86; H, 7.37; N, 8.53. Found: C, 54.97; H, 7.30; N, 8.61.

The mixture of **(1*R*)-2-amino-3-*O*-benzyl-2-*N*-(*tert*-butoxycarbonyl)-2-deoxy-1-(2-thiazolyl)-L-glycitol (8b)** and of the 1*S* isomer **8a** (60% yield in CH_2Cl_2 and 55% yield in THF, ds_{syn} 80% in CH_2Cl_2 and ds_{syn} 67% in THF from the NMR spectrum) showed the following: oil; IR (film) 3500, 1750 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3 + D_2O$) δ 1.30–1.45 (m, 9 H), 3.55–3.78 (m, 2 H), 4.05–4.55 (m, 1 H), 4.5 (s, 2 H), 5.11 (d, 0.2 H in CH_2Cl_2 and 0.33 H in THF, *J* = 4.4 Hz, anti isomer), 5.25 (d, 0.8 H in CH_2Cl_2 and 0.67 H in THF, *J* = 3.4 Hz, syn isomer), 7.03 (m, 6 H), 7.68 (d, 1 H, *J* = 3 Hz).

The mixture of **(1*R*)-2-amino-2-*N*-(*tert*-butoxycarbonyl)-2,3-dideoxy-3-phenyl-1-(2-thiazolyl)-L-glycitol (9b)** and of the 1*S* isomer **9a** (74% yield in CH_2Cl_2 and 75% yield in THF, ds_{syn} 80% in CH_2Cl_2 and ds_{syn} 57% in THF from NMR spectrum) showed the following: oil; IR (film) 3470, 1735, 1700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3 + D_2O$) δ 1.31 (br s, 9 H), 3.0 (m, 2 H), 4.16 (m, 1 H), 5.02 (m, 1 H), 7.23 (m, 6 H), 7.68 (d, 0.8 H in CH_2Cl_2 and 0.57 H in THF, *J* = 3.2 Hz, syn isomer), 7.77 (d, 0.2 H in CH_2Cl_2 and 0.43 H in THF, *J* = 3.2 Hz, anti isomer).

Oxidation of the Mixture of the Amino Alcohols *anti*-7a and *syn*-7b. To a stirred solution of the mixture of **7a** and **7b** (85:15 ratio, 0.196 g, 0.6 mmol) and TDA-1 (tris[2-(2-methoxyethoxy)ethyl]amine, commercially available from Aldrich, 0.02 g, 0.06 mmol) in dry dichloromethane (35 mL) was added portionwise powdered $KMnO_4$ (0.14 g, 0.9 mmol), and the suspension was vigorously stirred for ca. 24 h. The reaction mixture was filtered through Celite, and the solvent removed in vacuo. The residue was chromatographed through a short column (silica gel, 7:3 petroleum ether/diethyl ether) to give the ketone **10** (0.08 g, 40%): oil; IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.36–1.76 (m, 18 H), 4.05–4.41 (m, 2 H), 7.72 (d, 1 H, *J* = 3.2 Hz), 8.02 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{15}H_{22}N_2O_4S$: C, 55.20; H, 6.80; N, 8.58. Found: C, 55.27; H, 6.64; N, 8.61.

Reduction of the Ketone 10. To a stirred and cooled (−78 °C) solution of **10** (0.08 g, 0.24 mmol) in dry THF (5 mL) was added 0.5 mL (0.5 mmol) of 1 M solution of L-Selectride (lithium tri-*sec*-butylborohydride commercially available from Aldrich) in THF, and the mixture was stirred for 2 h. The reaction was quenched with a solution of 10% NaOH (1.5 mL) and 30% H_2O_2 (0.5 mL), allowed to warm to room temperature, and stirred for 1 h. After filtration through Celite, a saturated solution of $NaHCO_3$ (20 mL) was added, and the mixture was extracted with diethyl ether (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. NMR spectrum of the residue showed a $ds_{syn} \geq 95\%$. The residue was chromatographed (silica gel, 6:4 petroleum ether/diethyl ether) to give 75 mg of the *syn*-amino alcohol **7b**: oil; IR ($CHCl_3$) 3280, 2950, 1660 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3 + D_2O$) δ 1.17–1.65 (m, 18 H), 3.77–4.03 (m, 1 H), 4.25–4.52 (m, 1 H), 5.16 (d, 1 H, *J* = 7.5 Hz), 7.32 (d, 1 H, *J* = 3.2 Hz), 7.72 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.86; H, 7.37; N, 8.53. Found: C, 54.96; H, 7.44; N, 8.59.

Oxazolidinones 12 and 14 from the Amino Alcohols 8 and 9. General Procedure. To a stirred mixture of the amino alcohol **8** or **9** obtained from the reaction in CH_2Cl_2 (0.52 mmol) was added a solution of 95:5 trifluoroacetic acid and water (2 mL). After

1 h of stirring, trifluoroacetic acid was evaporated in vacuo. The residue was dissolved in ethyl acetate (10 mL), and a saturated solution of $NaHCO_3$ (5 mL) was added. After extraction with ethyl acetate (3 × 10 mL), the organic layer was dried (Na_2SO_4), and the solvent evaporated under vacuum. To the mixture of the deprotected amino alcohols **11a,b** and **13a,b** dissolved in THF (5 mL) was added a solution of 1,1'-carbonyldiimidazole (1.06 g, 0.66 mmol) in the same solvent (3 mL). After 4–5 h of stirring, the reaction mixture was evaporated in vacuo, and a saturated solution of $NaHCO_3$ was added. After extraction with ethyl acetate (3 × 15 mL), the organic layer was dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The NMR spectrum of the residue showed the syn–anti diastereomeric ratios of amino alcohols **8** and **9**.

Chromatography (silica gel, 95:5 diethyl ether/petroleum ether) of the oxazolidinone mixture derived from **8** (ds_{syn} 80% in CH_2Cl_2) gave the threo isomer **12b** (0.113 g, 75%) and the erythro isomer **12a** (0.031 g, 20%). The threo isomer **12b**: oil; IR (film) 3480, 1860 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.68 (m, 2 H), 4.31 (m, 1 H), 4.60 (s, 2 H), 5.53 (d, 1 H, J = 4.9 Hz), 5.75 (br s, 1 H), 7.31 (m, 6 H), 7.8 (d, 1 H, J = 3.3 Hz).

Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.86; H, 4.79; N, 9.69.

The erythro isomer **12a**: oil; IR (film) 3480, 1860 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.0–4.61 (m, 5 H), 5.73 (br s, 1 H), 6.0 (d, 1 H, J = 8.5 Hz), 7.27 (m, 6 H), 7.80 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.98; H, 4.80; N, 9.59.

Chromatography (silica gel, 8:2 petroleum ether/ethyl acetate) of the mixture derived from **9** (ds_{syn} 80% in CH_2Cl_2) gave the mixture of the oxazolidinones **14a** and **14b** (96%): oil; IR ($CHCl_3$) 3470, 1785 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 2.77–3.37 (m, 2 H), 4.35 (m, 1 H), 5.53 (d, 0.8 H, J = 4.9 Hz, threo isomer **14b**), 5.75 (br s, 1 H), 6.06 (d, 0.2 H, J = 8.05 Hz, erythro isomer **14a**), 7.18–7.45 (m, 6 H), 7.8 (m, 1 H).

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.06; H, 4.69; N, 10.83.

O-Benzylation of 2-Amino-1-(2-thiazolyl)-L-glycitol (6a). To a stirred solution of the amino alcohol **6a** (0.59 g, 1.87 mmol) in dry tetrahydrofuran (30 mL) was added portionwise 50% NaH (0.1 g, 2.06 mmol) at room temperature. The reaction mixture was gently refluxed for 20 min, and then tetra-*n*-butylammonium iodide (0.06 g, 0.187 mmol) and benzyl bromide (0.25 mL, 2.06 mmol) were added sequentially. After 12 h, the solvent was concentrated at reduced pressure, saturated $NaHCO_3$ was added (20 mL), and the mixture was extracted with ethyl acetate (2 × 30 mL). After drying (Na_2SO_4), the solvent was removed in vacuo, and the residue was chromatographed (silica gel, 8:2 petroleum ether/ethyl acetate) to give the *O*-benzyl derivative **6a'** (0.57 g, 75%): oil; IR (film) 1710 cm^{-1}; ^1H NMR (80 MHz, C_6D_6) δ 1.3–1.57 (m, 15 H), 3.68 (m, 1 H), 4.07–4.71 (m, 4 H), 5.25 (br s, 1 H), 6.68 (d, 1 H, J = 3.2 Hz), 7.17 (m, 5 H), 7.60 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.43; H, 6.72; N, 6.99.

Thiazole-to-Formyl Conversion in 6a and 6a'. The alcohol **6a** or the *O*-benzyl derivative **6a'** (1.4 mmol) was treated with methyl iodide (10 equiv) in acetonitrile (30 mL). The solution was refluxed for 12 h. The solvent was removed in vacuo, and the resulting *N*-thiazolium iodide, dissolved in methanol (30 mL), was treated with sodium borohydride (2 equiv) at −10 °C. After 30 min, acetone (2 mL) was added, and the solvent was evaporated. The residue was treated with a saturated solution of $NaHCO_3$ (20 mL) and extracted with diethyl ether (2 × 30 mL). The organic layer was dried (Na_2SO_4), and the solvent removed in vacuo to give the crude thiazolidine, which was dissolved in acetonitrile (5 mL) and was thus added to a solution of $HgCl_2$ (1.2 equiv) in 4/1 acetonitrile/water (25 mL). After stirring at room temperature for 15 min, the solvent was concentrated, and diethyl ether was added (30 mL). The reaction mixture was filtered through Celite, and the solvent was removed under vacuum. The residue was treated with a saturated solution of NaCl (20 mL) and extracted with diethyl ether (2 × 30 mL). The organic layer was dried (Na_2SO_4), and the solvent removed at reduced pressure.

The aldehyde **15a** (65%) derived from the amino alcohol **6a** was used in the Wittig reaction without further purification: IR (film) 3340, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.62 (br s, 1 H).

From the *O*-benzyl amino alcohol **6a'**, chromatography of the residue on a short column (silica gel, 8:2 *n*-hexane/ethyl acetate) gave the aldehyde **15a'**[21] (0.35 g, 73%) as an oil.

Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.38; H, 7.84; N, 4.04.

Addition of 2-TST (1) to the Aldehyde 15a'. To a stirred and cooled (0 °C) solution of the aldehyde **15a'** (0.2 g, 0.57 mmol) in THF (10 mL) was added a solution of 2-TST (**1**, 0.13 g, 0.86 mmol) in the same solvent (5 mL). The usual workup (as above for **6a**) gave, after flash chromatography of the residue (silica gel, 7:3 petroleum ether/ethyl acetate), 0.153 g (63%) of the anti alcohol **16a** and 0.03 g (11%) of syn alcohol **16b** (ds_{anti} = 85%).

(1*S*)-3-Amino-2-*O*-benzyl-3-*N*-(*tert*-butoxycarbonyl)-3-deoxy-3,4-*N*,*O*-isopropylidene-1-(2-thiazolyl)-L-erythritol (16a)[21] showed the following: oil; IR (film) 3400, 1695 cm^{-1}.

(1*R*)-3-Amino-2-*O*-benzyl-3-*N*-(*tert*-butoxycarbonyl)-3-deoxy-3,4-*N*,*O*-isopropylidene-1-(2-thiazolyl)-L-erythritol (16b):[21] mp 99–102 °C.

O-Benzylation of 16a. The reaction was carried as above for **6a** starting from the alcohol **16a** (5 g, 11.5 mmol) in tetrahydrofuran (50 mL), 50% NaH (0.7 g, 13.8 mmol), tetra-*n*-butylammonium iodide (0.42 g, 1.15 mmol), and benzyl bromide (1.52 g, 12.6 mmol) in THF (20 mL). The usual workup and chromatography of the residue (silica gel, 7:3 petroleum ether/ethyl acetate) gave the *O*-benzyl derivative **16a'** (5.7 g, 95%): oil; $[\alpha]_D$ = −95.7° (*c* 2.8, $CHCl_3$); IR (film) 1695, 1500 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 1.47 (s, 6 H), 3.57–4.76 (m, 8 H), 4.86 (d, 1 H, J = 4.8 Hz), 7.28 (m, 11 H), 7.77 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{29}H_{36}N_2O_5S$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.54; H, 6.85; N, 5.41.

O-Acetylation of 16b. To a stirred solution of the alcohol **16b** (0.9 g, 3.31 mmol) in pyridine (5 mL) with a catalytic amount of (dimethylamino)pyridine was added freshly distilled acetic anhydride (0.29 mL, 3.31 mmol) at room temperature. After 15 h of stirring, the solvent was removed in vacuo, and the residue was treated with a saturated solution of $NaHCO_3$ (15 mL) and then extracted with diethyl ether (3 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent removed in vacuo. The residue was chromatographed (silica gel, 7:3 petroleum ether/ethyl acetate) to give the O-acetyl derivative **16b'** (0.95 g, 88%): mp 114–116 °C; $[\alpha]_D$ = −79.3° (*c* 1.53, $CHCl_3$); IR ($CHCl_3$) 1750, 1685 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.30–1.60 (m, 15 H), 2.10 (s, 3 H), 3.72–4.28 (m, 4 H), 4.65 (s, 2 H), 6.32 (d, 1 H, J = 4.4 Hz), 7.28 (m, 5 H), 7.33 (d, 1 H, J = 3.2 Hz), 7.80 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{24}H_{32}N_2O_6S$: C, 60.49; H, 6.77; N, 6.08. Found: C, 60.61; H, 6.89; N, 5.91.

Thiazole-to-Formyl Conversion in 16a'. The reaction was carried out as above for **6a'** (N-methylation, reduction, hydrolysis) starting from the thiazole amino sugar **16a'** (3.1 g, 5.9 mmol). After the usual workup, chromatography on a short column (silica gel, 7:3 petroleum ether/diethyl ether) gave 2.1 g (76%) of **4-amino-2,3-di-*O*-benzyl-4-*N*-(*tert*-butoxycarbonyl)-4-deoxy-4,5-*N*,*O*-isopropylidene-L-ribose (17a')**: oil; IR (film) 1700, 1665 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 1.49 (s, 6 H), 3.75–4.89 (m, 9 H), 7.29 (s, 5 H), 7.31 (s, 5 H), 9.75 (br s, 1 H).

Anal. Calcd for $C_{27}H_{35}NO_6$: C, 69.06; H, 7.51; N, 2.98. Found: C, 69.12; H, 7.55; N, 3.03.

Thiazole-to-Formyl Conversion in 16b'. The reaction was carried out as above for **16a'** (N-methylation, reduction, hydrolysis) starting from the thiazole sugar **16b'** (0.7 g, 1.48 mmol). After the usual workup, chromatography on a short column (silica gel, 7:3 diethyl ether/petroleum ether) gave 0.41 g (66%) of **2-*O*-acetyl-4-amino-3-*O*-benzyl-4-*N*-(*tert*-butoxycarbonyl)-4-deoxy-4,5-*N*,*O*-isopropylidene-L-arabinose (17b')**: oil; IR (Nujol) 1745, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 15 H), 2.20 (s, 3 H), 3.90–4.25 (m, 4 H), 4.48–4.82 (m, 2 H), 5.51 (br s, 1 H), 7.32 (m, 5 H), 9.79 (br s, 1 H).

Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.77; H, 7.44; N, 3.37.

2-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylidene-D-*erythro*-eicos-4-ene-1,3-diol (18, *O*,*N*-Isopropylidene-*N*-(*tert*-butoxycarbonyl)-C_{20}-D-*erythro*-sphin-

gosine). To a vigorously stirred suspension of hexadecyltriphenylphosphonium bromide (2.45 g, 4.33 mmol) in dry toluene (30 mL) was added a decanted solution of phenyllithium preformed from a suspension of Li (0.22 g, 31.2 mmol) in diethyl ether (0.5 mL) and bromobenzene (1.64 mL, 15.6 mmol) in the same solvent (7 mL). To this deep red ylide solution was added a solution of the aldehyde **15a** (0.4 g, 1.32 mmol) in tetrahydrofuran (6 mL) at −30 °C. After 1 h of stirring, the reaction mixture was warmed to −20 °C and treated sequentially with methanol (5 mL) and water (10 mL). The reaction mixture was warmed to room temperature, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). After drying (Na_2SO_4), the solvent was concentrated at reduced pressure, and the residue flash chromatographed (silica gel, 9:1 petroleum ether/ethyl acetate) to give 0.5 g (31%) of the protected sphingosine **18**: oil; IR (film) 3420, 2920, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + D_2O) δ 0.88 (t, 3 H, J = 6 Hz), 1.27 (s, 26 H), 1.50 (m, 15 H), 2.05 (m, 2 H), 3.75–4.37 (m, 4 H), 5.43 (m, 1 H), 5.62 (m, 1 H).

1-*O*,2-*N*,3-*O*-Triacetyl-2-amino-D-*erythro*-eicos-4-ene-1,3-diol (19, Triacetyl-C_{20}-D-*erythro*-sphingosine). To the protected sphingosine **18** (0.03 g, 0.06 mmol) was added a solution of trifluoroacetic acid (1 mL) and water (0.3 mL). After 30 min, the solvent was evaporated in vacuo, and a saturated solution of $NaHCO_3$ (10 mL) was added. The reaction mixture was extracted with ethyl acetate (2 × 20 mL), and after drying (Na_2SO_4) the solvent was removed under reduced pressure. To the residue dissolved in pyridine (10 mL) were added (dimethilamino)pyridine (0.029 g, 0.24 mmol) and acetic anhydride (0.03 mL, 0.3 mmol). After 12 h of stirring, the solvent was removed in vacuo. A saturated solution of $NaHCO_3$ (5 mL) was added to the residue, and the reaction mixture was extracted with diethyl ether (3 × 5 mL). The organic layer was dried (Na_2SO_4), the solvent was removed under vacuum, and chromatography of the residue (silica gel, 1:1 petroleum ether/diethyl ether) gave 0.025 g (95%) of triacetyl sphingosine **19**: mp 103–105 °C (from dichloromethane–petroleum ether) [lit.[34a] (Schmidt et al.) mp 104 °C]; $[\alpha]^{23}_D$ = −22.5° (*c* 1.07, CH_3COOH) {lit.[34a] $[\alpha]^{21}_D$ = −22.3° (*c* 2, CH_3COOH)}; IR ($CHCl_3$) 1740, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.6 Hz), 1.26 (s, 26 H), 1.97–2.15 (m, 11 H), 4.04 (dd, 1 H, J = 11.6 Hz, J = 3.7 Hz), 4.31 (dd, 1 H, J = 11.6 Hz, J = 5.6 Hz), 4.36–4.51 (m, 1 H), 5.22–5.47 (m, 2 H), 5.60–5.90 (m, 2 H).

3-*O*,4-*O*-Dibenzyl-2-[(*tert*-butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylidene-D-*ribo*-octadec-5-ene-1,3,4-triol (20, *O*,*N*-Isopropylidene-*N*-(*tert*-butoxycarbonyl)-*O*,*O*-dibenzyl-C_{18}-D-*ribo*-sphingosine). To a vigorously stirred suspension of tridecyltriphenylphosphonium bromide (previously dried by azeotropic distillation with benzene, 1.7 g, 3.3 mmol) in dry benzene (25 mL) was added a 1.6 M solution of *n*-butyllithium in hexane (2.1 mL, 3.2 mmol) in the same solvent (5 mL) at 0 °C. After 30 min, to the deep red solution was added a solution of the aldehyde **17a′** (1.55 g, 3.3 mmol) in benzene (5 mL). After 2 h of stirring, the reaction mixture was treated with a saturated solution of $NaHCO_3$ (30 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (20 mL). After drying with anhydrous Na_2SO_4, the solvent was removed in vacuo, and the residue chromatographed (silica gel, 9:1 petroleum ether/ethyl acetate) to give the *E*–*Z* mixture of the protected sphingosine **20** (0.44 g, 66%): oil; IR (film) 2970, 1700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.87 (br t, 3 H), 1.23 (s, 20 H), 1.47 (m, 15 H), 1.86 (m, 2 H), 1.86 (m, 2 H), 3.75–4.70 (m, 9 H), 5.17–5.88 (m, 2 H), 7.28 (m, 10 H).

2-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylidene-D-*ribo*-octadecane-1,3,4-triol (21, *O*,*N*-Isopropylidene-*N*-(*tert*-butoxycarbonyl)-C_{18}-D-*ribo*-phytosphingosine). To a solution of the protected sphingosine **20** (0.2 g, 0.31 mmol) in ethanol (20 mL) was added Raney[44] Ni (3 g). The reaction mixture was refluxed for 8 h, cooled at room temperature, and then filtered. The residue was washed several times with ethanol. The filtrate was concentrated in vacuo, and the residue chromatographed (silica gel, 8:2 petroleum ether/ethyl acetate) to give 0.09 g (70%) of the protected phytosphingosine **21**: mp 58–60 °C; $[\alpha]_D$ = +34° (*c* 0.2, $CHCl_3$); IR (KBr) 3400, 2930, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 7.2 Hz), 1.27 (s, 24 H), 1.40–1.72 (m, 17 H), 2.94 (br s, 2 H), 3.6–4.22 (m, 5 H).

Anal. Calcd for $C_{26}H_{51}NO_5$: C, 68.23; H, 11.22; N, 3.06. Found: C, 68.00; H, 11.31; N, 3.11.

2-Amino-D-*ribo*-octadecane-1,3,4-triol (22a, C_{18}-D-*ribo*-Phytosphingosine). The reaction was carried out as above for the sphingosine **18** starting from the phytosphingosine **21** (0.42 g, 0.93 mmol) and 20:1 trifluoroacetic acid/water mixture (4 mL). After 15 min, the reaction mixture was treated with dichloromethane (10 mL) and then with a saturated solution of $NaHCO_3$ (15 mL). The solid that formed was filtered and washed with water and then dried to give 0.29 g (95%) of the phytosphingosine **22a**: mp 98–100 °C (lit.[41] mp 103 °C); IR (KBr) 3340, 2940, 1740 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 0.86 (br t, 3 H, J = 7.2 Hz), 1.25 (s, 24 H), 1.59 (m, 2 H), 2.67 (dd, 1 H, J = 10.4 Hz, J = 7.2 Hz), 3.04 (t, 1 H, J = 7.2 Hz), 3.36 (br s, 5 H), 3.52 (dd, 2 H, J = 10.6 Hz, J = 3.8 Hz), 4.55 (br s, 1 H). After addition of D_2O the signal at δ 3.36 (br s, 5 H) collapsed to δ 3.33 (m, 1 H).

2-Amino-1-*O*,2-*N*,3-*O*,4-*O*-Tetraacetyl-D-*ribo*-octadecane-1,3,4-triol (22b, *O*,*N*,*O*,*O*-Tetraacetyl-C_{18}-D-*ribo*-phytosphingosine). To a stirred solution of the unprotected sphingosine **22a** (0.29 g, 0.39 mmol) in pyridine (10 mL) were added (dimethylamino)pyridine (0.45 g, 3.7 mmol) and acetic anhydride (0.55 mL, 4.6 mmol) at room temperature. After 12 h of stirring, the usual workup (see above for sphingosine **19a**) and chromatography (silica gel, 1:1 petroleum ether/diethyl ether) gave 0.27 g (60%) of phytosphingosine tetraacetate **22b**: syrup (lit.[41] mp 48 °C); $[\alpha]^{30}_D$ = 4.4° (*c* 1.12, DMF) {lit.[41] $[\alpha]^{20}_D$ = 4.9° (*c* 1, DMF)}; IR (film) 3300, 2930, 2860, 1740, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 7.2 Hz), 1.26 (s, 24 H), 1.71 (m, 2 H), 2.04 (s, 3 H), 2.06 (s, 6 H), 2.09 (s, 3 H), 4.00 (dd, 1 H, J = 11.7 Hz, J = 2.9 Hz), 4.30 (dd, 1 H, J = 11.7 Hz, J = 4.8 Hz), 4.48 (m, 1 H), 4.93 (dt, 1 H, J = 8.5 Hz, J = 3.3 Hz), 5.12 (dd, 1 H, J = 8.5 Hz, J = 3 Hz), 6.02 (d, 1 H, J = 9.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.15, 20.82, 21.10, 22.77, 23.34, 25.61, 28.32, 29.42, 29.46, 29.61, 29.79, 32.05, 47.87, 63.12, 72.37, 73.28, 170.39, 170.73, 171.49, 171.79.

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(44) Mozingo, R. *Coll. Org. Synth.*, Vol. 3, p 181.