only starting material was isolated.

(v) Coupling Reaction of 1,2-Diiodotetrachlorobenzene under Ullmann[29] Conditions. Copper powder (0.5 g, 7.06 mmol) was placed in a glass ampule attached to a vacuum line and flame heated. 1,2-Diiodotetrachlorobenzene (0.5 g, 1.07 mmol) was added and the ampule sealed off and removed from the vacuum line. The sealed ampule with its contents under vacuo was heated at 180–200 °C for 24 h. The contents were then washed with ether (until colorless) and filtered, and the ether was removed under vacuo. A brown solid was obtained.

IR and mass spectral analysis indicated the product to be perchlorofluorene-9-spirocyclohexa-2′,5′-diene. Detailed mass spectrum of products (mass number, m/z of clusters,* assignment, % intensity of base cluster): 711, $C_{18}Cl_{14}^+$, 7.2; 681, $C_{18}Cl_{13}^+/C_{12}Cl_8I_2^+$, 48.8; 640, $C_{18}Cl_{12}^+$, 68.3; 609, $C_{18}Cl_{11}^+$, 8.8; 590, $C_{12}Cl_9I^+$, 65.1; 570, $C_{18}Cl_{10}^+$, 37.6; 555, $C_{12}Cl_8I^+$, 79.9; 536, $C_{18}Cl_9^+$, 4.7; 500, $C_{18}Cl_8^+$, 36.6; 468, $C_6Cl_4I_2^+/C_{18}Cl_7^+$, 60.3; 428, $C_{12}Cl_8^+/C_{18}Cl_6^+$, 100; 393, $C_{12}Cl_7^+/C_{18}Cl_5^+$, 21.2; 356, $C_{12}Cl_6^+/C_{18}Cl_4^+$, 65.0; 341, $C_6Cl_4I^+$, 20.1; 321, $C_{12}Cl_5^+/C_{18}Cl_3^+$, 20.3; 286, $C_{12}Cl_4^+/C_{18}Cl_2^+$, 40.2; 250, $C_{12}Cl_3^+/C_{18}Cl^+$, 24.6; 214, $C_{12}Cl_2/C_6Cl_4^+/C_{18}^+$, 52.1; 177, $C_{12}Cl^+/C_6Cl_3^+$, 37.9; 127, I^+, 17.2.

*Mass number, m/z, assignment of highest peak within the respective clusters. Mass spectra run on a Kratos MS50 in the EI mode.

Acknowledgment. The authors thank the reviewers for their very useful comments and suggestions. Thanks are extended to the UNB Research Fund and the UNB Faculty Development Fund.

Registry No. Perchlorotriphenylene, 137695-68-2; 1,2,3,4-tetrachloronaphthalene–bis(hexachlorocyclopentadiene) adduct, 80789-64-6; triphenylene, 217-59-4; hexachlorocyclopentadiene, 77-47-4; 1,2,3,4-tetrachloronaphthalene, 20020-02-4; perchlorofluorene-9-spirocyclohexa-2′,5′-diene, 102611-22-3; 1,2-diidotetrachlorobenzene, 40707-59-3.

A Convergent Synthetic Approach to a Chiral, Nonracemic CDEF Analogue of Nogalamycin

Htwe Yin,[1] Richard W. Franck,* Shun-Le Chen, Gary J. Quigley, and Louis Todaro†

Department of Chemistry, Hunter College, 695 Park Ave., New York, New York 10021, and Hoffman-LaRoche, Nutley, New Jersey 07110

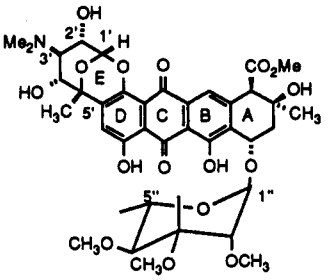
Received June 7, 1991

An approach to the synthesis of the CDEF rings of nogalamycin is described. The synthesis involves two key cycloadditions: (1) The regioselective addition of (2*S*)-2,3-*O*-cyclohexylideneglyceronitrile oxide with furan to yield the furoisoxazoline **7** and (2) the regioselective Bradsher cycloaddition of **7** with isoquinoline salt **8**, induced by a pressure of 6 kbar, to attach the amino sugar moiety to the aromatic ring.

Nogalamycin (**1**) and its congeners are notable members of the anthracycline family.[2] Nogalamycin was isolated from *Streptomyces nogalater* var, nogalater sp. n. by Wiley et al.[3] It has a nogalose unit attached to ring A at C-7 and an amino sugar joined to the aromatic ring D via a glycosidic and a C–C bond, forming a benzoxocin ring system. The structure of nogalamycin, with the exception of the A-ring stereochemistry and the configuration of the amino glucose residue, was determined by Wiley et al.[4] The absolute stereochemistry of nogalamycin was established by Arora using X-ray crystallography in 1982.[5] Other recently reported anthracyclines, with the nogalamycin-type *DEF*-benzoxocin, are decilorubicin,[6] arugomycin,[7,8] and viriplanin.[9]

Nogalamycin is active against Gram-positive microorganisms, L1210 leukemia and KB cell carcinoma in vitro.[2] It has broad spectrum activity and less cardiotoxicity compared to daunomycin, adriamycin, and related compounds.[2,4] Despite its promise, nogalamycin's unacceptable toxicity precluded its clinical use.[2] A semisynthetic derivative, 7-*con*-*O*-methylnogarol **2** showed superior antitumor activity in comparison to the parent compound **1**.[2,10] Crystallographic studies,[11] modeling and NMR work[12] have confirmed a proposal by Arora that the chromophore intercalates into DNA, with the amino sugar and nogalose interacting in major and minor grooves, respectively.[5]

Although the total synthesis of nogalamycin has not yet been achieved, a number of synthetic model studies have been reported[13–20] and the syntheses of both (+)- and (±)-7-*con*-*O*-methylnogarol **2** have been described.[19,21–24]



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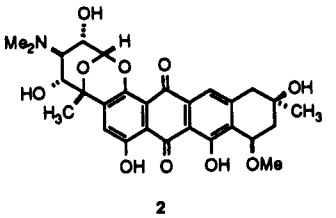

2

In this paper, we describe an approach to the synthesis of *CDEF*-benzoxocin model of nogalamycin, **3**, using the

† Hoffman-LaRoche.

(1) The synthetic chemistry is taken entirely from the Ph.D. dissertation of H.Y., CUNY, 1990, and was supported by NIH CA 39351 and PSC/CUNY grants (R.W.F.). The crystallography laboratory at Hunter College is supported by NIH GM 41359 (G.J.Q.) and NIH RR 03037. Portions of this work were presented at the Northeast Regional Meeting of the American Chemical Society, June 18–21, 1989; Abstract no. 190.

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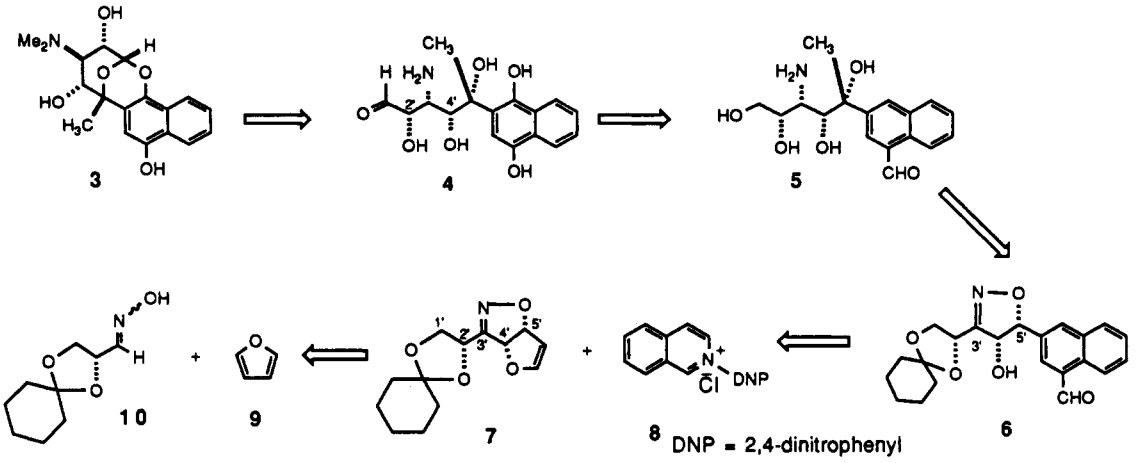
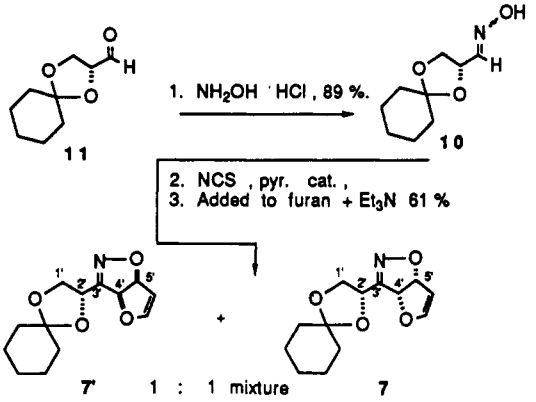
Scheme I



Bradsher cycloaddition of an isoquinolinium salt as the method for combining the amino sugar and aromatic sections, based upon the retrosynthetic analysis shown in Scheme I. The desired ultimate spontaneous cyclization of acyclic **4** to **3** has been described in similar systems. Our group had previously demonstrated the practicality of the naphthaldehyde to hydroquinone conversion (**5** to **4**) in a related series,[25] and the generality of the Bradsher cycloaddition represented by **7** + **8** yielding **6** was also well-established.[26] Heterocycle **7** promised to be readily available via nitrile oxide–furan cycloaddition. Thus $C_{2'}$ and $C_{4'}$ of **7** (nogalamycin numbering) would establish $C_{2'}$ and $C_{4'}$ in **4**, while a precedented stereoselective reduction of the imine at $C_{3'}$ of **6** should produce the desired stereochemistry at $C_{3'}$ of **4**. There would remain only the introduction of the *C*-methyl at the future $C_{5'}$ of **4** to establish the entire side-chain precursor of the *C*-glycoside.

Scheme II



Results and Discussion

The furoisoxazoline **7** was easily prepared by the known furan–nitrile oxide cycloaddition method,[27-30] using cyclohexylidene glyceraldehyde[31] (**11**) as the chiral pool source for the nitrile oxide. The hydroximic acid chloride ultimate precursor of the required nitrile oxide was produced via chlorination of aldoxime **10**. The nitrile oxide was then prepared in situ using triethylamine as the base (Scheme II). There was obtained a 1:1 mixture (determined by NMR) of two isomers of the product, furoisoxazoline **7** and its epimer **7'**. No diastereoselectivity in the cycloaddition reaction was expected, because the stereogenic center in the nitrile oxide was quite remote from the developing centers.[32] The two isomers were not separable. The furoxan dimer of nitrile oxide was observed as the byproduct in about 15% yield.[33]

The Bradsher cycloaddition of furoisoxazolines **7** and **7'** and *N*-(2,4-dinitrophenyl)isoquinolinium chloride (IsoQ) **8** in anhyd. methyl alcohol with anhyd calcium carbonate did not take place under our standard conditions at ambient pressure.[26] Therefore the cycloaddition was per-

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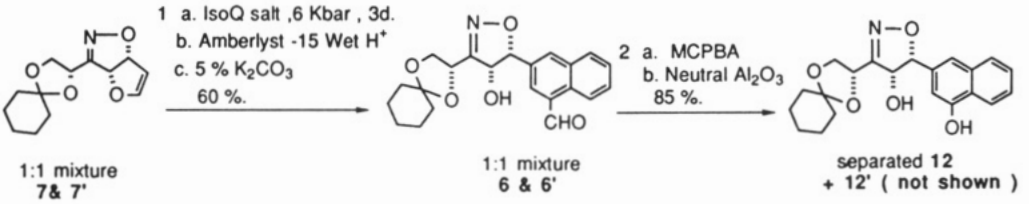
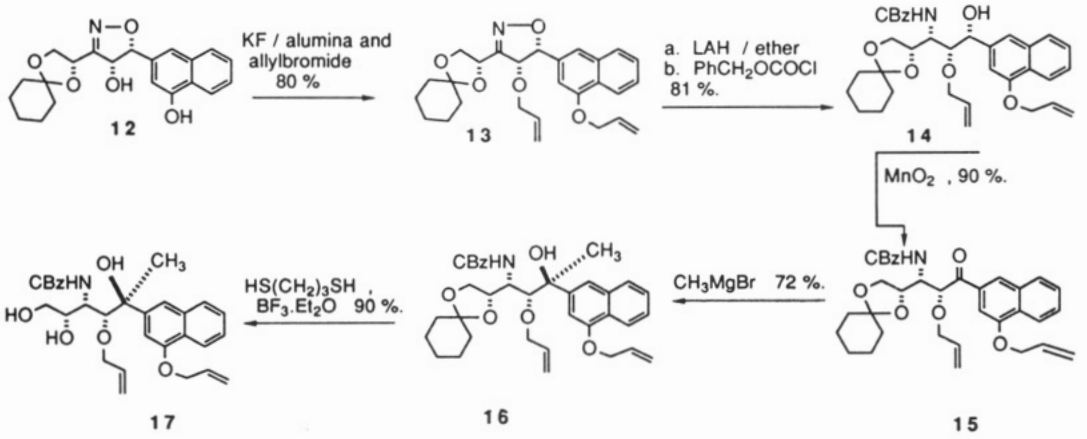
(33) We did not use 3-methylfuran which would have had the correct carbon complement because the cycloaddition product would have been 6-methylfuroisoxazoline rather than 6a-methylfuroisoxazoline.[27,28]

Scheme III



Scheme IV



formed at 6 kbar[34] using 5-nitroisoquinoline as a soluble acid scavenger in place of suspended $CaCO_3$. The choice of soluble base was critical because more basic amines catalyzed the addition of methanol to the isoquinolinium salt at C-1, forming an unreactive pseudobase. After a 3-day reaction period, workup via acid hydrolysis and base-catalyzed aromatization of the initial cycloadduct[26] afforded the desired naphthaldehydes **6** and **6′** in 55–60% yield (Scheme III).

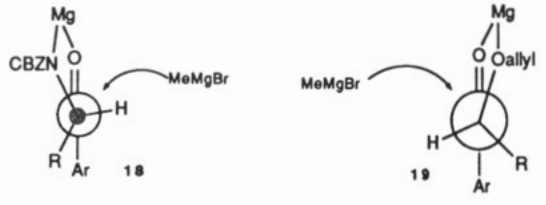
The Bradsher cycloaddition was regioselective,[35] yielding only one pair of diastereoisomers, epimeric at C-4′ and C-5′, arising from the mixture of furoisoxazolines, **7** and **7′**, used. The two naphthaldehydes **6** and **6′** were only partially separable. A third naphthaldehyde, which was the diol deprotected version of **6** or **6′**, was obtained in less than 5% yield.

The naphthaldehydes **6** and **6′** were converted to naphthols by Baeyer–Villiger oxidation to produce naphthyl formates which were then cleaved by alumina treatment.[25] The two isomers of naphthol **12** and **12′** were easily separated at this stage because one isomer was completely soluble in CH_2Cl_2 whereas the other isomer was essentially insoluble. A crystal structure of the insoluble isomer showed that it possessed the (4*R*,5*R*)-isoxazolyl and (5*S*)-dioxolyl stereocenters required for a nogalamycin synthesis.

Both hydroxyls of naphthol **12** were protected as ethers using allyl bromide and potassium fluoride impregnated alumina (80% yield).[36] These mild conditions prevented the formation of the C-4′ alkoxide which then undergoes a second-order Beckmann fragmentation of the isoxazoline[37] (Scheme IV).

Based on studies of the stereoselectivity of isoxazoline reduction with different reducing agents,[37,38] the delivery of hydride via LAH reduction was predicted to take place from the anti face of the substituents of isoxazoline **13** to give the desired syn amino alcohol since the approach by hydride to the syn face is hindered by the naphthalene and allyl ether functions. In fact, the reduction of isoxazoline **13** gave one stereoisomer in quantitative yield. The stereochemistry of the new center could not be assigned at this stage, but was proven later. The amino group of the reduced product was protected as its *N*-(benzyloxy)-carbamate **14**, using benzyl chloroformate and sodium bicarbonate in ether/water.[39] The benzylic OH of naphthyl ether **14** was oxidized to the crucial ketone **15** with activated MnO_2 in anhyd $CHCl_3$ at reflux.

At this stage, the synthesis required the introduction of a methyl group from the *si*-face of the ketone. As illustrated in the Newman projections **18** and **19**, were chela-



tion to occur between the β-amido group and the carbonyl, as in **18**, the methyl group should be delivered to the desired face to produce the tertiary alcohol with the natural configuration, while chelation between the α-ether and the carbonyl, as in **19**, would direct the methyl to the undesired face. An ambiguous precedent for face selectivity in a related polyfunctional system was described[20,21] in the successful nogarol synthesis where Terashima et al. had added an aryllithium to a methyl ketone similar to ketone **15** via a reactive geometry related to **19**. However, in contrast to the NHCBZ function in **15**, their amino function was completely protected as an *N*-methyl-*N*-meth-

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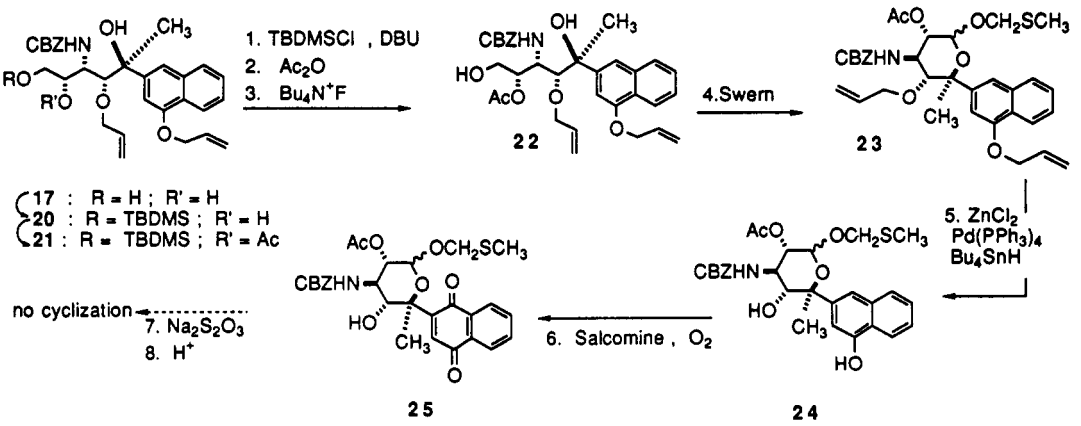
Scheme V



oxycarbonyl without an acidic NH subject to deprotonation that might serve as a chelating ligand for lithium. Furthermore, the stereochemistry of aryllithium addition was shown to be inverted in the presence of $CeCl_3$. Earlier work by Garner had shown that *N*-BOC groups could be linked to aldehyde carbonyls by Zn chelation,[40] and subsequent to our own experiments, Yamamoto et al. have demonstrated Mg chelation effects with NHBOC alaninal.[41]

Thus, the key reaction with methyl Grignard was performed via inverse addition in the hope that NH deprotonation and subsequent carbonyl–metal–N chelation would be more favorable than carbonyl–metal–*O* chelation. In the event, an 85–88% yield of a major methylated product and less than 5% of a minor isomer were observed. After removal of the cyclohexylidene protecting group of the 1,2-diol, using propane-1,3-dithiol–BF_3·Et_2O in dichloromethane, the major isomer **17** was found by X-ray crystallography to have the undesired configuration. Thus the methyl group was delivered from the *re*-face of the carbonyl probably through the chelation mode **19** to form the initial methylated product **16**. Further experimentation with other methylating agents did not produce a useful yield of material having the required stereochemistry. Therefore the decision was made to carry **16** through to an 5′-*epi*-nogalamycin model as a test for the functional group interconversions required for an eventual natural product synthesis.

Ultimately, the $C_{1'}$ primary hydroxyl is to become an aldehyde as a precursor for the complex glycosidation to form the bicyclic E–F system. Application of reported methods of selective oxidation of primary alcohols in the presence of secondary alcohols to our system failed.[42-49] Therefore the oxidation was carried out after a stepwise protection–deprotection sequence. The primary alcohol was selectively protected as TBDMS ether **20** and the secondary alcohol was protected as acetate **21**. Then the silyl ether was removed with tetrabutylammonium fluoride to give alcohol **22** and the primary alcohol (produced in 62% overall yield) was oxidized to the aldehyde via Swern oxidation[50] (Scheme V).

As the aldehyde formed, the hydroxy at $C_{5'}$ was expected to add to the carbonyl to produce the desired lactol. Precedent in the carbohydrate literature suggested that some lactone would form if overoxidation occurred.[51] The product characterized was the (methylthio)methyl glycoside **23** obtained in 55% yield, rather than the expected lactol or lactone. (Methylthio)methyl ethers of alcohols are known byproducts in the Swern process.[52] The deallylation of (methylthio)methyl glycoside **23** with $(PPh_3)_3RhCl$[53] did not take place, affording only recovered starting material. We assumed that the presence of the sulfur in the glycoside poisoned the catalyst. Other allyl deprotection methods[54-58] also gave unsatisfactory results. Eventually, a useful cleavage of the bis-allyl ether to alcohol **24** was accomplished by palladium-catalyzed tributyltin hydride reduction in 78% yield.[59,60]

Naphthol **24** was easily oxidized to naphthoquinone, using Salcomine and oxygen.[25] The final step of our synthesis required a reduction of the naphthoquinone **25** to naphthohydroquinone and construction of the E ring by acid-catalyzed cyclization.[61] Several such experiments with $Na_2S_2O_3$ as reductant yielded no characterizable fully cyclized material. We assumed that the formation of E ring in our system **26**, epimeric to the natural series **27**, was energetically unfavorable because formation of the bicyclic framework would force all the functional groups of the resulting F ring to be axial.

In conclusion, our studies show that the main framework containing key features of the CDEF rings of nogalamycin

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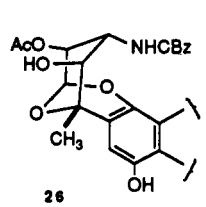

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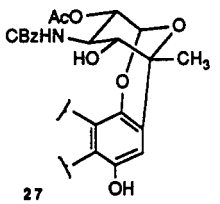


27

can be efficiently prepared by using two convergent steps, i.e. nitrile oxide dipolar and Bradsher cycloaddition reactions. The pressure-assisted version of the Bradsher reaction, using 5-nitroisoquinoline as soluble base, promises to be an important development for this versatile method.

Experimental Section

The high-resolution mass spectra were obtained by the Mass Spectrometric Biotechnology Resource, The Rockefeller University, New York, NY. High pressure experiments were performed with a LECO TEM-Press pressure generator (Model PG-100 HPC). Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) with use of 2,4-dinitrophenylhydrazine spray, potassium permanganate spray, ninhydrin spray, phosphomolybdic acid, and/or short- and longwave ultraviolet light to visualize the spots. Preparative TLC plates were prepared by using Kieselgel 60 PF_{254} (E. Merck). Chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merck), and all separations using the chromatotron were done under nitrogen atmosphere. Chemicals used were purchased from Aldrich Chemical Co.

1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol. A mixture of D-mannitol (9.00 g, 49.45 mmol), cyclohexanone (15.50 mL, 149.55 mmol), triethyl orthoformate (8.31 mL, 50 mmol), BF_3·Et_3O (0.50 mL, 4.06 mmol) and dry DMSO (20 mL) was stirred for 10 h at rt. The mixture was then poured into 50 mL of 10% ice-cooled $NaHCO_3$ solution and was extracted with ether (25 mL × 3) and worked up. Most of the excess cyclohexanone was removed in vacuo. After addition of hexane to the concentrate, 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol crystallized as a white solid. The crystals were filtered, washed with hexane, and dried in vacuo. The product was used for further reaction without any purification. (5.01 g, 56% yield): mp 104–105 °C (lit.[31] mp 105–106 °C); ^1H NMR ($CDCl_3$) δ 4.18–4.11 (m, 4 H, H-1, H-2), 4.00 (AB q, J = 5, 8 Hz, 2 H, H-1), 3.75 (t, J = 7 Hz, 2 H, H-3), 2.98 (d, J = 7 Hz, 2 H, OH), 1.41–1.61 (br m, 20 H, cyhx).

(2*S*)-2,3-*O*-Cyclohexylidene-D-glyceraldoxime. To a solution of 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol (5.04 g, 14.74 mmol) in 50 mL of ether was added a solution of $NaIO_4$ (3.64 g, 17 mmol) and Bu_4NF (0.07 g, 0.27 mmol) in 30 mL of water, and the mixture was stirred for 4 h at rt. The reaction mixture was poured into aqueous hydroxylamine hydrochloride (2.35 g, 33.81 mmol in 50 mL of water) and $NaHCO_3$ (3.52 g, 41.89 mmol) and was stirred for 4 h. The glyceraldoxime was extracted with CH_2Cl_2 (50 mL × 3), and the organic layers were worked up. The oily crude glyceraldoxime was obtained as a mixture of cis and trans isomers and was sufficiently pure for further reactions (4.6 g, 89% yield): ^1H NMR ($CDCl_3$) δ 9.19 (br s, 1 H, OH), 8.9 (s, 1 H, OH), 7.44 (d, J = 7 Hz, 1 H, NCH), 6.99 (d, J = 4 Hz, 1 H, NCH), 5.15 (dq, J = 4, 7 Hz, 1 H, H-2), 4.67 (q, J = 7 Hz, 1 H, H-2′), 4.38 (dd, J = 7, 8 Hz, 1 H, H-3′), 4.20 (ABX, J = 6, 9 Hz, 1 H, H-3′), 3.91 (ABX, J = 6, 9 Hz, 1 H, H-4), 3.84 (ABX, J = 7, 9 Hz, 1 H, H-4′), 1.77-1.45 (br m, 20 H, cyhx, cyhx′); ^{13}C NMR ($CDCl_3$) δ 153.0, 149.9, 110.9, 110.4, 72.8, 70.3, 67.5, 67.0, 36.2, 35.7, 35.0, 34.8, 25.0, 23.9, 23.8; HRMS m/z (rel intensity) 186.1 (12), 185.1 (36), 156.1 (18), 142.0 (100), 124.00 (8), 99 (15), 97 (8), 88 (10), 81 (12), 73 (15), 70 (32); MS calcd for $C_9H_{15}NO_3^+$ 185.1052, found 185.1036 (−1.6 mmu).

(3a*R*,6a*R*)-3-[(2*S*)-1,2-(Cyclohexylidenedioxy)eth-2-yl]-3a,6a-dihydrofuro[2,3-*d*]isoxazole (7) and the 3a*S*,6a*S* Epimer (7′). A solution of (2*S*)-2,3-*O*-cyclohexylidene-*D*-glyceraldoxime (3.89 g, 21.02 mmol in 10 mL of $CHCl_3$) was added to a suspension of NCS (2.79 g, 20.9 mmol) in 10 mL of dry $CHCl_3$ and pyridine (0.1 mL) at rt. The completion of chlorination was observed by the disappearance of suspended NCS (about 30 min). This reaction mixture was added to a refluxing solution of Et_3N (3.06 mL, 21.97 mmol) in 350 mL of furan over 18 h by using a syringe pump. Then the mixture was refluxed for another 10 h. Most of the furan was removed by distillation. The concentrate was poured into water (50 mL), extracted with EtOAc (50 mL × 3), and worked up. The concentrate was purified by column chromatography (silica gel, 10% EtOAc/petroleum ether) to provide 3.06 g of the diastereomeric mixture of products (61% yield). Approximately 15% of furoxan was also isolated: bp 120–122 °C (0.4 mm); ^1H NMR ($CDCl_3$) δ 6.63 (m, 2 H, H-5, H-5′), 6.00 (d, J = 9 Hz, 1 H, H-3a), 5.96 (d, J = 9 Hz, 1 H, H-3a′), 5.92–5.88 (m, 2 H, H-6a, H-6a′), 5.39–5.35 (m, 2 H, H-6, H-6′), 5.13 (t, J = 7 Hz, 1 H, H-5 dioxo), 4.96 (t, J = 6 Hz, 1 H, H-5′ dioxo), 4.33–4.30 (m, 2 H, H-4 dioxo), 4.22–4.12 (m, 2 H, H-4′ dioxo), 1.81–1.46 (br m, 20 H, cyhx, cyhx′); ^{13}C NMR ($CDCl_3$) δ 154.8, 149.9, 111.1, 110.9, 101.1, 89.0, 88.7, 88.1, 87.8, 87.3, 70.5, 69.9, 66.7, 66.6, 35.6, 34.8, 25.0, 23.8; HRMS calcd for $C_{13}H_{17}NO_4^+$ 251.1158, found 251.1100 (−5.8 mmu).

3-[(4*R*,5*R*)-3-[(2*S*)-1,2-(Cyclohexylidenedioxy)eth-2-yl]-4-hydroxy-4,5-dihydroisoxazolin-5-yl]-1-naphthaldehyde (6) and the 4*S*,5*S* Epimer (6′). *N*-(2,4-Dinitrophenyl)isoquinolinium chloride salt 8 (1.74 g, 5.23 mmol), 5-nitroisoquinoline (1.35 g, 7.75 mmol), and furoisoxazolines 7 and 7′ (1.30 g, 5.18 mmol) were dissolved in 5 mL of dry MeOH. The solution was transferred to a 10-mL plastic syringe and subjected to 6 kbar pressure for 3 d. The precipitated 5-nitroisoquinolium chloride salt was filtered and washed with CH_2Cl_2. The filtrate, which contained cycloadduct, was concentrated and dried in vacuo. The concentrate was dissolved in 50 mL of THF and 3 mL of water and magnetically stirred with Amberlyst 15 (wet) ion-exchange resin (2.10 g) for 10 h. The mixture was filtered, and most of the THF was removed on a rotary evaporator. The concentrate was then diluted with water (50 mL) and extracted with EtOAc (30 mL × 3) and worked up. The residue was dissolved in THF (4 mL) and was added to a solution of 50 mL of 5% K_2CO_3 in 80% aqueous MeOH. The reaction mixture was warmed at 45 °C in a water bath for 2 min, poured into 25 mL of ice water, and then extracted with EtOAc (50 mL). The aqueous layer was saturated with NaCl and extracted with EtOAc (50 mL × 2). Workup of the combined organic layers afforded the product naphthaldehyde which was purified by radial chromatography (silica gel, 0.3% MeOH/CH_2Cl_2, 1.18 g, 60% yield). Though the two diastereoisomers were not cleanly separable, small samples of pure isomers were obtained by partial separation for analysis purposes: IR ($CHCl_3$) 1690 cm^{-1}; isomer A ^1H NMR ($CDCl_3$) δ 10.41 (s, 1 H, CHO), 9.22 (d, J = 8 Hz, 1 H, H-8 Np), 8.14 (s, 1 H, H-4 Np), 8.01 (d, J = 1 Hz, 1 H, H-2 Np), 7.98 (d, J = 8 Hz, 1 H, H-5 Np), 7.71 (ddd, J = 1, 7, 8 Hz, 1 H, H-6 Np), 7.61 (ddd, J = 1, 7, 8 Hz, 1 H, H-7 Np), 5.61 (d, J = 7 Hz, 1 H, H-5 isoxo), 5.34 (dd, J = 4, 7 Hz, 1 H, H-4 isoxo), 5.15 (t, J = 6 Hz, 1 H, H-5 dioxo), 4.3 (d, J = 6 Hz, 2 H, H-4 dioxo), 2.52 (d, J = 4 Hz, 1 H, OH), 1.74–1.41 (br m, 10 H, cyhx); isomer B δ 10.35 (s, 1 H, CHO), 9.17 (d, J = 8 Hz, 1 H, H-8 Np), 8.12 (s, 1 H, H-4, Np), 8.01 (d, J = 1 Hz, 1 H, H-2 Np), 7.90 (d, J = 8 Hz, 1 H, H-5 Np), 7.68 (ddd, J = 1, 7, 8 Hz, 1 H, H-6 Np), 7.58 (ddd, J = 1, 7, 8 Hz, 1 H, H-7 Np), 5.54 (d, J = 7 Hz, 1 H, H-5 isoxo), 5.28 (d, J = 7 Hz, 1 H, H-4 isoxo), 5.17 (t, J = 6 Hz, 1 H, H-5 dioxo), 4.34 (dd, J = 6, 8, Hz, 1 H, H-4 dioxo), 4.20 (dd, J = 6, 8 Hz, 1 H, H-4 dioxo), 3.02 (br s, 1 H, OH), 1.75–1.39 (br m, 10 H, cyhx); ^{13}C NMR ($CDCl_3$) mixture of two isomers δ 193.6, 193.4, 159.3, 159.1, 152.8, 146.3, 136.5, 136.3, 134.5, 133.5, 131.2, 130.3, 129.5, 128.7, 127.4, 124.8, 124.7, 111.47, 111.3, 86.1, 85.9, 71.0, 70.4, 67.2, 67.0, 35.9, 35.8, 34.6, 25.0, 24.0, 23.8; HRMS calcd for $C_{22}H_{23}NO_5$ 381.1576, found 381.1814 (+23.8 mmu).

3-[(4*R*,5*R*)-3-[(2*S*)-1,2-(Cyclohexylidenedioxy)eth-2-yl]-4-hydroxy-4,5-dihydroisoxazolin-5-yl]naphthol (12) and the 4*S*,5*S* Epimer (12′). To a stirred solution of naphthaldehydes 6 and 6′ (2.16 g, 5.66 mmol) in anhyd CH_2Cl_2 (60 mL) was added *m*-CPBA (1.95 g, 11.31 mmol) which was allowed to react at rt under N_2 for 24 h. A 10% aqueous sodium sulfite solution (25 mL) was added to destroy the excess *m*-CPBA. The aqueous layer was extracted with CH_2Cl_2 (25 mL × 3) and worked up. The formate obtained was dissolved in anhyd CH_2Cl_2 (60 mL) and was stirred with 10 g of neutral alumina (activity 1) for 24 h. The mixture was filtered and the alumina was stirred with CH_2Cl_2–MeOH (1:1) (30 mL × 3, 15 min each) and filtered. The filtrates were concentrated under reduced pressure. One isomer of naphthol was separated by crystallization with CH_2Cl_2 from the

above concentrate. The more soluble isomer was purified by radial chromatography (silica gel, 0–10% MeOH/CH_2Cl_2; 1.78 g, 85% total yield). *4R,5R* isomer (**12**): mp 220 °C; ^{1}H NMR (CD_3COCD_3) δ 8.22 (m, 1 H, H-8 Np), 7.81 (m, 1 H, H-5 Np), 7.51–7.43 (m, 3 H, H-4, H-6, H-7 Np), 6.99 (d, *J* = 1 Hz, 1 H, H-2 Np), 5.35 (d, *J* = 7 Hz, 1 H, H-5 isoxo), 5.24 (d, *J* = 7 Hz, 1 H, H-4 isoxo), 5.05 (t, *J* = 7 Hz, 1 H, H-5 dioxo), 4.32–4.19 (m, 2 H, 2 H-4 dioxo), 3.01 (br s, 2 H, 2-OH), 1.75–1.39 (m, 10 H, cyhx); ^{13}C NMR (CD_3COCD_3) δ 127.4, 126.2, 124.6, 121.9, 118.4, 108.6, 87.1, 75.6, 71.3, 66.5, 35.5, 34.9, 24.9, 23.7, 23.6. HRMS calcd for $C_{21}H_{23}NO_5^+$ 369.1576, found 369.1500 (–7.6 mmu). *4S,5S* isomer (**12′**): mp 146–147 °C; ^{1}H NMR (CD_3COCD_3) δ 8.21 (m, 1 H, H-8 Np), 7.81 (m, 1 H, H-5 Np), 7.49–7.43 (m, 3 H, H-4, H-6, H-7 Np), 6.98 (d, *J* = 1 Hz, 1 H, H-2 Np), 5.36 (d, *J* = 7 Hz, 1 H, H-5 isoxo), 5.25 (d, *J* = 7 Hz, 1 H, H-4 isoxo), 5.03 (t, *J* = 6 Hz, 1 H, H-5 dioxo), 4.35 (dd, *J* = 6, 8 Hz, 1 H, H-4 dioxo), 4.25 (dd, *J* = 6, 8 Hz, 1 H, H-4 dioxo), 3.01 (br s, 1 H, OH), 1.64–1.40 (m, 10 H, cyhx); ^{13}C NMR ($CDCl_3$) δ 127.4, 126.2, 124.6, 121.9, 118.4, 108.3, 86.6, 76.7, 70.0, 66.1, 35.9, 34.9, 24.9, 23.7, 23.6.

1-(Allyloxy)-3-[(4*R*,5*R*)-4-(allyloxy)-3-[(2*S*)-1,2-(cyclohexylidenedioxy)eth-2-yl]-4,5-dihydroisoxazolin-5-yl]naphthalene (13). A mixture of naphthol **12** (1.78 g, 4.84 mmol), allyl bromide (4.17 g, 48.3 mmol), and 40% potassium fluoride–alumina (7.01 g, ca. 48 mmol of KF) in 25 mL of CH_3CN was magnetically stirred at room temperature for 24 h. The solid material was filtered and washed with CH_2Cl_2, and the filtrate was concentrated. Purification of the concentrate by radial chromatography yielded 1.73 g of **13** as a colorless oil (silica gel, 0–4% MeOH/CH_2Cl_2, 80% yield): ^{1}H NMR ($CDCl_3$) δ 8.32 (m, 1 H, H-8 Np), 7.82 (m, 1 H, H-5 Np), 7.54–7.48 (m, 3 H, H-4, H-6, H-7 Np), 6.93 (s, 1 H, H-2 Np), 6.23–6.13 (m, 1 H, $NpOCH_2CH$=CH_2), 5.52 (dd, *J* = 1, 17 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.46–5.36 (m, 1 H, OCH_2CH=CH_2), 5.34 (dd, *J* = 1, 11 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.31 (d, *J* = 7 Hz, 1 H, H-5 isoxo), 5.13 (t, *J* = 7 Hz, 1 H, H-5 dioxo), 4.97–4.85 (m, 3 H, OCH_2CH=CH_2, H-4 isoxo), 4.75 (d, *J* = 5 Hz, 2 H, $NpOCH_2CH$=CH_2), 4.27 (d, *J* = 7 Hz, 2 H, 2H-4 dioxo), 3.55 (dd, *J* = 6, 12 Hz, 1 H, OCH_2CH=CH_2), 3.35 (dd, *J* = 6, 12 Hz, 1 H, OCH_2CH=CH_2), 1.80–1.43 (m, 10 H, cyhx); ^{13}C NMR ($CDCl_3$) δ 158.0, 154.5, 133.9, 133.5, 133.2, 130.4, 127.6, 126.8, 126.0, 125.8, 122.2, 120.7, 117.8, 117.5, 110.8, 105.4, 86.7, 82.6, 72.3, 71.2, 69.0, 67.1, 38.1, 34.8, 25.2, 24.0, 23.8; HRMS calcd for $(C_{27}H_{31}NO_5 - H)^-$ 448.2124, found 448.2060 (–6.4 mmu).

1-(Allyloxy)-3-[(1*R*,2*R*,3*S*,4*S*)-2-(allyloxy)-3-[*N*-(benzyloxycarbonyl)amino]-4,5-(cyclohexylidenedioxy)-1-hydroxypent-1-yl]naphthalene (14). To LAH (2 mL of 1 M solution in ether, 2 mmol) in ether at 0 °C was added a solution of **13** (0.35 g, 0.78 mmol) in 0.5 mL of dry ether. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with 2 equiv of water (as 20% NaOH solution) with CH_2Cl_2, and the mixture was stirred for 2 h at rt. The Al_2O_3 precipitate was filtered and washed thoroughly with CH_2Cl_2. The filtrate was concentrated in vacuo. The concentrate was dissolved in ether (5 mL) and poured into Na_2CO_3 solution (0.21 g, 2 mmol, 6 mL). The mixture was cooled to 5 °C, and benzyl chloroformate (0.12 mL, 0.84 mmol) was added slowly. The mixture was stirred for 3 h. Then the aqueous layer was extracted with EtOAc (10 mL × 3) and worked up. The oily product **14** was purified by radial chromatography (silica gel, 0–5% EtOAc/CH_2Cl_2, 81% yield): IR ($CHCl_3$) 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.32 (m, 1 H, H-8 Np), 7.82 (m, 1 H, H-5 Np), 7.53–7.46 (m, 3 H, H-4, H-6, H-7 Np), 7.38–7.27 (m, 5 H, Ph), 6.92 (s, 1 H, H-2 Np), 6.24–6.15 (m, 1 H, $NpOCH_2CH$=CH_2), 5.91–5.84 (m, 1 H, OCH_2CH=CH_2), 5.58 (d, *J* = 17 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.38 (d, *J* = 1 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.28 (d, *J* = 17 Hz, 1 H, OCH_2CH=CH_2), 5.24 (d, *J* = 12 Hz, 1 H, H-1), 5.20 (d, *J* = 11 Hz, 1 H, OCH_2CH=CH_2), 5.05 (AB q, *J* = 10 Hz, 2 H, $PhCH_2$), 4.87 (d, *J* = 5 Hz, 1 H), 4.71 (br s, 2 H, $NpOCH_2CH$=CH_2), 4.34 (t, *J* = 6 Hz, 1 H), 4.20–3.96 (m, 4 H), 3.76–3.73 (m, 1 H), 3.68 (m, 2 H), 1.65–1.44 (m, 10 H, cyhx); ^{13}C NMR ($CDCl_3$) δ 156.4, 154.5, 138.7, 136.5, 134.5, 134.3, 133.4, 128.5, 128.1, 127.9, 127.7, 126.7, 125.6, 125.3, 122.1, 118.9, 117.6, 117.3, 110.2, 104.2, 83.6, 75.0, 73.7, 73.5, 69.0, 66.9, 66.2, 51.0, 35.9, 34.7, 25.2, 24.0, 23.9.

1-(Allyloxy)-3-[(2*R*,3*S*,4*S*)-2-(allyloxy)-3-[*N*-(benzyloxycarbonyl)amino]-4,5-(cyclohexylidenedioxy)-1-oxopent-1-yl]naphthalene (15). Activated MnO_2 (1.33 g, 15.33 mmol) was added to a solution of alcohol **14** (0.76 g, 1.36 mmol) in 10 mL of dry $CHCl_3$ and was stirred at reflux for 5 h. The mixture was cooled to rt and was filtered through a Celite pad. The Celite was washed with $CHCl_3$. The total filtrate was evaporated to dryness under reduced pressure. The oily ketone was purified by radial chromatography (silica gel, 0–2% MeOH/CH_2Cl_2, 0.74 g, 90% yield): IR ($CHCl_3$) 1715, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.34 (d, *J* = 8 Hz, 1 H, H-8 Np), 8.24 (s, 1 H, H-4 Np), 7.88 (d, *J* = 8 Hz, 1 H, H-5 Np), 7.64–7.53 (m, 2 H, H-6, H-7 Np), 7.41 (s, 1 H, H-2 Np), 7.33–7.31 (m, 5 H, Ph), 6.28–6.15 (m, 1 H, $NpOCH_2CH$=CH_2), 6.02–5.90 (m, 1 H, OCH_2CH=CH_2), 5.58 (d, *J* = 17 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.38–5.18 (m, 4 H, $NpOCH_2CH$=CH_2, OCH_2CH=CH_2, H-2), 5.05 (s, 2 H, $PhCH_2$), 4.80 (d, *J* = 5 Hz, 2 H, $NpOCH_2CH$=CH_2), 4.45–4.38 (m, 2 H), 4.25–4.19 (m, 1 H, OCH_2CH=CH_2), 4.06–3.94 (m, 3 H, H-5, OCH_2CH=CH_2), 1.68–1.41 (m, 10 H, cyhx); ^{13}C NMR ($CDCl_3$) δ 197.6, 156.2, 154.8, 136.3, 134.0, 133.5, 133.2, 132.9, 129.4, 128.7, 128.5, 128.3, 128.11, 128.09, 127.4, 123.9, 122.4, 118.3, 117.8, 110.2, 102.5, 78.9, 74.0, 71.4, 69.1, 67.0, 65.5, 53.6, 36.1, 34.2, 25.2, 24.1, 23.7; HRMS calcd for $(M - H)^-$ $[(C_{35}H_{39}NO_7 - H)^-]$ 584.2648, found 584.2478 (–17.0 mmu).

(2*S*,3*R*,4*S*,5*S*)-3-(Allyloxy)-4-[*N*-(benzyloxycarbonyl)amino]-5,6-(cyclohexylidenedioxy)-2-[1-(allyloxy)naphth-3-yl]-2-hexanol (16). A solution of ketone **15** (0.69 g, 1.19 mmol in 5 mL of anhyd ether) was slowly added to MeMgBr (4 mL, 3 M solution in ether) in 4 mL of ether at –30 °C. Stirring was continued for 30 min at –30 °C, 30 min at 0 °C, and 1 h at rt. After addition of 5 mL of 25% NH_4Cl, the aqueous layer was extracted with ether (20 mL × 3) and worked up. The concentrate so obtained was purified by radial chromatography (silica gel, 0–2% MeOH/CH_2Cl_2, 0.63 g, 88% yield): IR ($CHCl_3$) 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.29 (m, 1 H, H-8 Np), 7.81 (m, 1 H, H-5 Np), 7.56 (s, 1 H, H-4 Np), 7.52–7.40 (m, 2 H, H-6, H-7 Np), 7.39–7.25 (m, 5 H, Ph), 7.03 (s, 1 H, H-2 Np), 6.24–6.15 (m, 1 H, $NpOCH_2CH$=CH_2), 5.91–5.81 (m, 1 H, OCH_2CH=CH_2), 5.58 (dd, *J* = 1, 17 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.39 (d, *J* = 11 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.27 (d, *J* = 17 Hz, 1 H, OCH_2CH=CH_2), 5.20 (d, *J* = 11 Hz, 1 H, OCH_2CH=CH_2), 5.12 (d, *J* = 9 Hz, 1 H, H-3), 5.07 (AB q, *J* = 12 Hz, 2 H, $PhCH_2$), 4.90 (AB q, *J* = 12 Hz, 2 H, $PhCH_2$), 4.76 (d, *J* = 5 Hz, 2 H, $NpOCH_2CH$=CH_2), 4.27–4.04 (m, 3 H, OCH_2CH=CH_2), 3.92–3.84 (m, 2 H), 3.76 (s, 2 H), 3.64 (t, *J* = 8 Hz, 1 H), 1.71 (s, 3 H, CH_3), 1.68–1.34 (m, 10 H, cyhx); ^{13}C NMR ($CDCl_3$) δ 156.6, 154.2, 143.6, 136.4, 134.6, 134.1, 133.4, 128.5, 128.0, 127.8, 126.7, 125.2, 124.8, 122.0, 121.9, 117.4, 117.3, 116.6, 116.5, 110.6, 110.1, 103.5, 84.6, 76.5, 73.8, 69.0, 66.9, 66.0, 50.2, 36.0, 34.6, 26.2, 25.1, 24.0, 23.9; HRMS calcd for $(M - H)^-$ $[(C_{36}H_{43}NO_7 - H)^-]$ 600.2961, found 600.2963 (+0.2 mmu).

(2*S*,3*R*,4*S*,5*S*)-3-(Allyloxy)-4-[*N*-(benzyloxycarbonyl)amino]-5,6-dihydroxy-2-[1-(allyloxy)naphth-3-yl]-2-hexanol (17). To a solution of 2-alcohol **16** (0.83 g, 1.38 mmol) and propane-1,3-dithiol (0.17 mL, 1.61 mmol) in CH_2Cl_2 (2 mL) at –78 °C was added BF_3·Et_2O (0.20 mL, 1.65 mmol) dropwise, and the mixture was magnetically stirred for 2 h. Stirring was continued for an additional 2 h at –40 °C and 1 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and quenched with water (2 mL) and 5% $NaHCO_3$ solution (2 mL). The solution was then extracted with CH_2Cl_2 (10 mL × 3) and worked up. The product was purified by radial chromatography (silica gel, 0–10% MeOH/CH_2Cl_2, 0.65 g, 90% yield): IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.29 (m, 1 H, H-8 Np), 7.80 (m, 1 H, H-5 Np), 7.48–7.41 (m, 3 H, H-4, H-6, H-7 Np), 7.33–7.12 (m, 5 H, Ph), 6.92 (s, 1 H, H-2 Np), 6.24–6.09 (m, 1 H, $NpOCH_2CH$=CH_2), 5.92–5.83 (m, 1 H, OCH_2CH=CH_2), 5.50 (dd, *J* = 1, 17 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.31 (dd, *J* = 1, 11 Hz, 1 H, $NpOCH_2CH$=CH_2), 5.22 (dd, *J* = 1, 17 Hz, 1 H, OCH_2CH=CH_2), 5.21 (d, *J* = 10 Hz, 1 H, OCH_2CH=CH_2), 5.00 (d, 1 H, H-3), 4.94 (AB q, *J* = 12 Hz, 2 H, $PhCH_2$), 4.66 (AB q, *J* = 12 Hz, 1 H, $PhCH_2$), 4.73 (d, *J* = 5 Hz, 2 H, $NpOCH_2CH$=CH_2), 4.20 (dd, *J* = 6, 12 Hz, 1 H, OCH_2CH=CH_2), 4.01–3.88 (m, 4 H, OCH_2CH=CH_2, H-3, H-4, NH), 3.54–3.37 (m, 5 H, H-6, 3-OH), 1.70 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 156.9, 154.3, 142.4, 136.0, 134.3, 134.1, 133.3, 128.4, 128.2, 128.0, 127.9, 126.8, 125.3, 124.9, 122.0, 117.7, 117.4, 116.3, 116.28, 103.2, 103.1, 83.9, 76.7, 73.7, 71.3, 69.0, 66.9, 63.7, 51.4, 27.3; HRMS calcd for $(M - H)^-$ $[(C_{30}H_{35}NO_7 - H)^-]$ 520.2335, found 520.2305 (–3.0 mmu).

(2S,3R,4S,5S)-3-(Allyloxy)-4-[N-(benzyloxycarbonyl)-amino]-6-[(tert-butyldimethylsilyl)oxy]-5-hydroxy-2-[1-(allyloxy)naphth-3-yl]-2-hexanol (20). A solution of TBDMSOTf (0.02 mL, 0.17 mmol) was added dropwise to a solution of alcohol **17** (0.08 g, 0.15 mmol) and DBU (0.03 mL, 0.20 mmol) in 3 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 40 min and then diluted with 5 mL of CH_2Cl_2 and washed with water (5 mL × 3) and worked up. The product was purified by preparative TLC on silica gel (4% MeOH/CH_2Cl_2, 0.07 g, 75% yield): IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29 (m, 1 H, H-8 Np), 7.82 (m, 1 H, H-5 Np), 7.56 (s, 1 H, H-4 Np), 7.50–7.44 (m, 2 H, H-6, H-7 Np), 7.43–7.28 (m, 3 H, Ph), 7.14–7.13 (m, 2 H, Ph), 6.94 (s, 1 H, H-2 Np), 6.28–6.15 (m, 1 H, NpOCH$_2$C*H*=CH$_2$), 6.08–5.94 (m, 1 H, OCH$_2$C*H*=CH$_2$), 5.55 (dd, *J* = 1, 17 Hz, 1 H, NpOCH$_2$CH=C*H*$_2$), 5.38 (dd, *J* = 1, 10 Hz, 1 H, NpOCh$_2$CH=C*H*$_2$), 5.35 (dd, *J* = 1, 17 Hz, 1 H, OCH$_2$CH=C*H*$_2$), 5.24 (d, *J* = 10 Hz, 1 H, OCH$_2$CH=C*H*$_2$), 5.01 (d, *J* = 12 Hz, 1 H, PhCH$_2$), 4.84 (d, *J* = 9 Hz, 1 H, H-3), 4.77 (d, *J* = 5 Hz, 2H, NpOC*H*$_2$CH=CH$_2$), 4.68 (d, *J* = 12 Hz, 1 H, PhCH$_2$), 4.33 (dd, *J* = 6, 12 Hz, 1 H, OC*H*$_2$CH=CH$_2$), 4.15 (dd, *J* = 7, 12 Hz, 1 H, OC*H*$_2$CH=CH$_2$), 4.04–3.96 (m, 3 H, H-5, OH), 3.78 (m, 1 H, H-4), 3.61 (br s, 1 H, NH), 3.48–3.42 (m, 1 H, H-6), 3.32 (AB q, *J* = 6, 10 Hz, 1 H, H-6), 1.74 (s, 3 H, CH$_3$), 0.84 (s, 9 H, *t*-Bu), 0.00 (s, 3 H, SiCH$_3$), –0.01 (s, 3 H, SiCH$_3$); ^{13}C NMR ($CDCl_3$) δ 156.4, 154.1, 142.7, 134.4, 134.1, 133.2, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 126.7, 125.1, 124.7, 121.9, 117.6, 117.4, 115.9, 102.8, 83.3, 76.6, 73.2, 70.1, 68.8, 66.6, 63.7, 50.6, 28.2, 25.7, 18.1, –5.6, –5.7.

(2S,3R,4S,5S)-5-Acetoxy-3-(allyloxy)-4-[N-(benzyloxycarbonyl)amino]-6-[(tert-butyldimethylsilyl)oxy]-2-[1-(allyloxy)naphth-3-yl]-2-hexanol (21). Acetic anhydride (0.04 mL, 0.38 mmol) was added to a solution of alcohol **20** (0.08 g, 0.16 mmol), pyridine (0.07 mL, 0.82 mmol), and DMAP (0.002 g) in 2 mL of CH_2Cl_2. After stirring for 2 h at rt, the reaction was diluted with 2 mL of CH_2Cl_2 and was washed with water (3 mL × 2) and worked up. The product was purified by preparative TLC (silica gel, 3% MeOH/CH_2Cl_2, 0.07 g, 85% yield): IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29–8.26 (m, 1 H, H-8 Np), 7.82–7.79 (m, 1 H, H-5 Np), 7.56 (s, 1 H, H-4 Np), 7.50–7.45 (m, 2 H, H-6, H-7 Np), 7.43–7.25 (m, 5 H, Ph), 7.01 (s, 1 H, H-2 Np), 6.27–6.23 (m, 1 H, NpOCH$_2$C*H*=CH$_2$), 5.90–5.82 (m, 1 H, OCH$_2$C*H*=CH$_2$), 5.54 (d, *J* = 17 Hz, 1 H, NpOCH$_2$CH=C*H*$_2$), 5.34 (d, *J* = 11 Hz, 1 H, NpOCH$_2$CH=C*H*$_2$), 5.26 (dd, *J* = 1, 18 Hz, 1 H, OCH$_2$CH=C*H*$_2$), 5.19 (dd, *J* = 1, 11 Hz, 1 H, OCH$_2$CH=C*H*$_2$), 5.12 (d, *J* = 8 Hz, 1 H, H-3), 5.10 (d, *J* = 12 Hz, 1 H, PhCH$_2$), 4.90 (d, *J* = 12 Hz, 1 H, PhCH$_2$), 4.84–4.70 (m, 3 H, H-5, NpOC*H*$_2$CH=CH$_2$), 4.17–4.12 (m, 1 H, H-4), 4.03–3.94 (m, 2 H, OC*H*$_2$CH=CH$_2$), 3.70 (d, *J* = 2 Hz, 1 H, NH), 3.50–3.38 (m, 2 H, H-6), 3.23 (s, 1 H, OH), 2.00 (s, 3 H, OAc), 1.69 (s, 3 H, CH$_3$), 0.75 (s, 9 H, *t*-Bu), –0.09 (s, 6 H, SiCH$_3$); ^{13}C NMR ($CDCl_3$) δ 170.3, 156.6, 154.3, 142.7, 134.3, 134.1, 134.0, 133.5, 128.5, 128.3, 128.2, 127.9, 126.6, 125.2, 124.9, 122.0, 117.6, 117.3, 117.3, 117.1, 117.0, 103.5, 84.1, 76.8, 75.5, 74.3, 74.2, 70.1, 69.0, 62.2, 50.5, 26.4, 25.7, 25.6, 21.0, 20.9, –5.7, –5.8; HRMS calcd for $(M - H)^-$ [($C_{38}H_{51}NO_9Si - H)^-$] ion 676.3306, found 676.3284 (–2.2 mmu).

(2S,3R,4S,5S)-5-Acetoxy-3-(allyloxy)-4-[N-(benzyloxycarbonyl)amino]-6-hydroxy-2-[1-(allyloxy)naphth-3-yl]-2-hexanol (22). Silyl ether **21** (0.04 g, 0.06 mmol) was dissolved in 1 mL of THF, and Bu_4NF (0.2 mL, 0.2 mmol in 1 M THF) was added. The mixture was stirred for 1 h at rt and was concentrated under reduced pressure. The concetrate was purified by preparative TLC to obtain the desired product (silica gel, 50% EtOAc/petroleum ether, 0.03 g, 84% yield); IR ($CHCl_3$) 1730, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30–8.25 (m, 1 H, H-8 Np), 7.82–7.77 (m, 1 H, H-5 Np), 7.52–7.46 (m, 3 H, H-4, H-6, H-7 Np), 7.34–7.28 (m, 4 H, Ph), 7.09 (m, 1 H, Ph), 6.88 (s, 1 H, H-2 Np), 6.24–6.10 (m, 1 H, NpOCH$_2$C*H*=CH$_2$), 6.01–5.92 (m, 1 H, OCH$_2$C*H*=CH$_2$), 5.55 (dd, *J* = 1, 17 Hz, 1 H), NpOCH$_2$CH=C*H*$_2$), 5.34 (dd, *J* = 1, 10 Hz, 1 H, NpOCH$_2$CH=C*H*$_2$), 5.36–5.30 (m, 2 H, OCH$_2$CH=C*H*$_2$, H-3), 5.25 (d, *J* = 11 Hz, 1 H, OCH$_2$CH=C*H*$_2$), 4.96 (d, *J* = 12 Hz, 1 H, PhCH$_2$), 4.79–4.74 (m, 3 H, H-4, NpOC*H*$_2$CH=CH$_2$), 4.64 (d, *J* = 12 Hz, 1 H, PhCH$_2$), 4.28–3.82 (m, 8 H, OC*H*$_2$CH=CH$_2$, H-5, H-6, NH, OH), 1.96 (s, 3 H, OAc), 1.72 (s, 3 H, CH$_3$); ^{13}C NMR ($CDCl_3$) δ 171.0, 156.3, 154.3, 141.9, 134.1, 133.2, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 126.9, 125.3, 124.8, 122.0, 117.9, 117.5, 117.4, 115.8, 102.6, 83.0, 76.9, 73.6, 68.9, 67.8, 66.8, 65.8, 52.1, 28.6, 20.7; HRMS calcd for $(M + H)^+$ [($C_{32}H_{37}NO_8 + H)^+$] ion 564.2597, found 564.2535 (–6.2 mmu).

(2S,3R,4S,5S,6R)-5-Acetoxy-3-(allyloxy)-4-[N-(benzyloxycarbonyl)amino]-2-methyl-6-[(methylthio)methoxy]-2-[1-(allyloxy)naphth-3-yl]tetrahydropyran (23) and the 2S,3R,4S,5S,6S Epimer. DMSO (0.13 mL, 1.78 mmol) was dissolved in CH_2Cl_2, and the solution was cooled to –70 °C. Trifluoroacetic acid (0.25 mL, 1.78 mmol) was added into the above solution dropwise. A white precipitate of trifluoroacetate salt formed after 10 min. A solution of alcohol **22** (0.05 g, 0.09 mmol) in 1 mL of CH_2Cl_2 was added dropwise, and the solution was stirred at –70 to –60 °C for 3 h. The reaction was quenched with Et_3N (0.3 mL) at –60 °C, and the mixture was allowed to warm to 0 °C (ca. 1 h). DMSO and Et_3N were removed under reduced pressure, and the concentrate was dissolved in CH_2Cl_2 and washed with water. After usual workup, the product was purified by preparative TLC (silica gel, 35% EtOAc/petroleum ether, 0.03 g, 55% yield): IR ($CHCl_3$) 1735, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (m, 1 H, H-8 Np), 7.80 (m, 1 H, H-5 Np), 7.52–7.48 (m, 2 H, H-6, H-7 Np), 7.39–7.30 (m, 6 H, H-4, Ph), 7.01 (s, 1 H, H-2 Np), 6.26–6.14 (m, 1 H, NpOCH$_2$C*H*=CH$_2$), 5.61 (d, *J* = 9 Hz, 1 H, H-3), 5.56 (dd, *J* = 1, 17 Hz, 1 H, NpOCH$_2$CH=C*H*$_2$), 5.51–5.39 (m, 1 H, OCH$_2$C*H*=CH$_2$), 5.56 (dd, *J* = 1, 11 Hz, 1 H, NpOCH$_2$CH=C*H*$_2$), 5.06 (d, *J* = 12 Hz, 1 H, PhCH$_2$), 4.97–4.88 (m, 6 H, H-4, H-5, H-6, PhCH$_2$, OCH$_2$CH=C*H*$_2$), 4.87–4.75 (m, 2 H, NpOC*H*$_2$CH=CH$_2$), 4.42 (d, *J* = 10 Hz, 1 H, OCH$_2$S), 4.30 (d, *J* = 10 Hz, 1 H, OCH$_2$S), 4.16 (d, *J* = 1 Hz, 1 H, NH), 3.68 (AB q, *J* = 6, 12 Hz, 1 H, OC*H*$_2$CH=CH$_2$), 3.42 (AB q, *J* = 6, 12 Hz, 1 H, OC*H*$_2$CH=CH$_2$), 2.26 (s, 3 H, SCH$_3$), 2.19 (s, 3 H, OAc), 1.74 (s, 3 H, CH$_3$); ^{13}C NMR ($CDCl_3$) δ 183.4, 156.1, 139.5, 134.0, 133.8, 133.3, 128.5, 128.4, 128.3, 128.1, 127.8, 126.8, 125.7, 125.3, 122.0, 119.7, 117.8, 117.5, 104.0, 82.1, 74.1, 69.0, 67.8, 67.2, 67.08, 57.3, 20.5, 18.1, 15.0; HRMS calcd for $(M - H)^-$ [($C_{34}H_{39}NO_8S - H)^-$] ion 620.2318, found 620.2317 (–0.1 mmu).

(2S,3R,4S,5S,6R)-5-Acetoxy-4-[N-(benzyloxycarbonyl)amino]-3-hydroxy-2-methyl-6-[(methylthio)methoxy]-2-(1-hydroxynaphth-3-yl)tetrahydropyran (24) and the 2S,3R,4S,5S,6S Epimer. Anhyd $ZnCl_2$ (0.03 g, 0.24 mmol, dried at 110 °C (0.5 mm) for 5 h) was added to the solution of allyl ether **23** (0.04 g, 0.09 mmol) in dry THF (2 mL), and the suspension was stirred at rt for 15 min. Tetrakis(triphenylphosphine)palladium (0.02 g, 0.02 mmol) was added, and stirring was continued for 10 min. Tributyltin hydride (0.10 g, 0.36 mmol) was added to the above suspension slowly. After being stirred for 30 min, the reaction mixture was diluted with 5 mL of EtOAc and 1 mL of water. The mixture was acidified with 5% HCl solution, and the product was extracted with EtOAc (10 mL × 3) and worked up. The concentrate was dissolved in acetonitrile–hexane (5 mL–10 mL), and the solution was stirred for 15 min. The acetonitrile layer, which contained the product, was collected and concentrated under reduced pressure. The product was purified by preparative TLC (silica gel, 45% EtOAc/petroleum ether, 0.04 g, 78% yield); IR ($CHCl_3$) 1745, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.90 (s, 1 H, OH-Np), 8.35 (m, 1 H, H-8 Np), 7.79 (m, 2 H, H-4, H-5 Np), 7.55–7.52 (m, 2 H, H-6, H-7 Np), 7.44–7.38 (m, 5 H, Ph), 7.29 (s, 1 H, H-2 Np), 5.82 (br s, 1 H, NH), 5.22 (s, 2 H, OCH$_2$S), 4.55 (d, *J* = 11 Hz, 1 H, PhCH$_2$), 4.53 (m, 1 H, H-4), 4.44–4.36 (m, 2 H, H-5, PhCH$_2$), 4.18 (d, *J* = 11 Hz, 1 H, H-6), 4.00 (t, *J* = 11 Hz, 1 H, H-3), 2.74 (d, *J* = 12 Hz, 1 H, OH), 1.91 (s, 3 H, SCH$_3$), 1.89 (s, 3 H, OAc), 1.78 (s, 3 H, CH$_3$); ^{13}C NMR ($CDCl_3$) δ 169.7, 160.5, 154.4, 135.4, 133.0, 133.2, 128.7, 128.4, 127.44, 127.4, 126.1, 122.7, 118.3, 114.3, 77.2, 73.0, 68.3, 67.5, 65.0, 59.3, 29.7, 27.9, 20.6, 14.5.

(2S,3R,4S,5S,6R)-5-Acetoxy-4-[N-(benzyloxycarbonyl)amino]-3-hydroxy-2-methyl-6-[(methylthio)methoxy]-2-(1,4-dioxonaphth-3-yl)tetrahydropyran (25). Naphthol **24** (0.02 g, 0.04 mmol) was dissolved in dry THF (3 mL) containing salcomine (0.01 g, 0.02 mmol), and O_2 gas was bubbled into the solution for 1 h at rt. The mixture was diluted with EtOAc (0.5 mL), and salcomine was removed by passing the solution through a short column of Florisil with EtOAc. The filtrate was concentrated, and the product was purified by preparative TLC (silica gel, 45% EtOAc/petroleum ether, 0.02 g, 73% yield): IR ($CHCl_3$) 1735, 1720, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13–8.08 (m, 2 H, H-5, H-8 Np), 7.81–7.76 (m, 2 H, H-6, H-7 Np), 7.41–7.33 (m, 5 H, Ph),

7.26 (s, 1 H, H-3 Np), 5.33 (br s, 1 H, NH), 5.20 (s, 2 H, OCH_2S), 5.08 (d, J = 12 Hz, 1 H, $PhCH_2$), 4.98 (d, J = 12 Hz, 1 H, $PhCH_2$), 4.74 (d, J = 12 Hz, 1 H, H-5), 4.54 (d, J = 12 Hz, 1 H, H-6), 4.38 (dd, J = 8, 12 Hz, 1 H, H-4), 3.70 (t, J = 12 Hz, 1 H, H-3), 3.04 (d, J = 12 Hz, 1 H, OH), 2.22 (s, 3 H, SCH_3), 1.97 (s, 3 H, OAc), 1.88 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 183.9, 169.7, 144.2, 141.7, 136.1, 134.5, 134.1, 132.3, 131.9, 128.6, 128.2, 128.1, 127.0, 126.6, 74.8, 72.4, 70.9, 67.5, 65.3, 57.2, 20.8, 20.2, 14.9.

Acknowledgment. This paper was written at the Centro Meccanismi Reazoni Organiche, Universita di Padova, and the Department of Chemistry, Harvard University, during the sabbatical leave of R.W.F., and we are grateful for the generous hospitality of both institutions.

Registry No. 1, 1404-15-5; 6, 137742-87-1; 6′, 137742-86-0; 7, 137820-56-5; 7′, 137742-85-9; 8, 33107-14-1; (*E*)-10, 137742-84-8; (*Z*)-10, 137742-83-7; 12, 137742-88-2; 12′, 137893-09-5; 13, 137742-89-3; 14, 137742-90-6; 15, 137768-16-2; 16, 137742-91-7; 17, 137742-92-8; 20, 137768-17-3; 21, 137742-93-9; 22, 137742-94-0; α-23, 137742-96-2; β-23, 137742-95-1; α-24, 137742-98-4; β-24, 137742-97-3; α-25, 137742-99-5; 1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol, 76779-67-4; D-mannitol, 69-65-8; furan, 110-00-9.

Supplementary Material Available: IR and MS data for all compounds in the Experimental Section and the data for the X-ray crystallograpic structure determinations of structures 12 and 17 (14 pages). Ordering information is given on any current masthead page.

Stereocontrolled Total Synthesis of Leukotriene B_4

M. Avignon-Tropis, J. M. Berjeaud, and J. R. Pougny

Centre de Recherche de Biochimie et Génétique Cellulaires, CNRS 118, Route de Narbonne, 31062 Toulouse, France

I. Fréchard-Ortuno, D. Guillerm, and G. Linstrumelle*

Laboratoire de Chimie Associé au CNRS, Ecole Normale Supérieure, 24 rue Lhomond, 75231 Paris Cédex 05, France

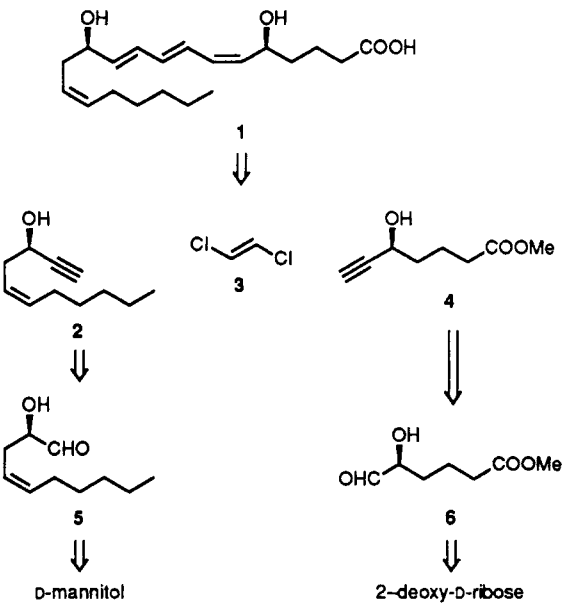
Received January 23, 1991 (Revised Manuscript Received August 8, 1991)

A stereocontrolled synthesis of leukotriene B_4 (1) is accomplished by assembly of the chiral synthons 2 and 4, prepared from D-mannitol and 2-deoxy-D-ribose, with (*E*)-dichloroethylene.

There is a great deal of current interest in hydroxylated eicosatetraenoic acids produced from arachidonic acid by the lipoxygenase pathway.[1] Leukotriene B_4 (LTB_4) has received attention due to its potent chemotactic properties toward macrophages and neutrophiles and its potential role in inflammation.[2] Due to the biological importance and the difficulty in isolating LTB_4 in quantity from biological material, several groups have developed strategies for synthesis of this compound[3] in which the coupling of two chiral building blocks by a Wittig reaction has frequently been employed. However, this coupling is usually not entirely stereoselective, and isolation of LTB_4 by HPLC is required.

Our approach to the synthesis of LTB_4 is based on the following retrosynthetic scheme:

The disconnection of C_7–C_8 and C_9–C_{10} leads to two chiral fragments C_1–C_7 and C_{10}–C_{20} and a single *E* olefin C_8–C_9. It has been shown[4] that the triene system having



a defined geometry can be efficiently generated by the palladium-catalyzed sequential substitution of dichloroethylenes *E* and *Z*. Thus, the sequential coupling of acetylenic alcohols 2 and 4 with (*E*)-dichloroethylene 3 and selective reduction of the triple bonds would give the desired molecule.

Results and Discussion

The α-hydroxy aldehyde 5 was prepared from D-mannitol according to Depezay.[3j] Compound 5 was then

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0022-3263/92/1957-0651$03.00/0