Synthesis of L-Daunosamine Derivatives on the Basis of the Asymmetric Dihydroxylation of 3-((*E*)-1-Propenyl)-4,5-dihydroisoxazole

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Methyl L-*N*,*O*-diacetyldaunosaminide was prepared from 3-nitro-4,5-dihydroisoxazole in 8.5% overall yield. A key step in the synthesis involved the AD reaction of (*E*)-3-(1-propenyl)-4,5-dihydroisoxazole (**2b**), affording the corresponding diol in 76% yield (92% ee). A second key step involved reductive cleavage of the dihydroisoxazole **4a** and subsequent *N*-acetylation to afford separable diastereomeric γ-(acetylamino)alcohols **7a** and **8a** in 62% yield (72:28, **7a**/**8a**). Swern oxidation of **7a** and subsequent methanolysis followed by acetylation provided methyl L-*N*,*O*-diacetyldaunosaminide as an anomeric mixture. The AD reactions of chiral alkenyl dihydroisoxazole **16** with $(DHQ)_2$−PHAL and $(DHQD)_2$−PHAL afforded diastereomeric diol products, isolated as the acetates **18** and **19** (98:2 and 5:95 ratios, respectively, depending on the chiral auxiliary).

Introduction

Several syntheses of aminosugar derivatives employing 4,5-dihydroisoxazoles (DHIs) as intermediates have been reported.[1,2] The DHI ring typically serves as a latent γ-amino alcohol synthon in these syntheses. The key transformation, reductive cleavage of the DHI ring, affords the corresponding γ-amino alcohols with a demonstrated diastereofacialselectivity at the C,N-double bond. Substituents at any of three sites, the C-4 ring atom, C-5 ring atom, and the C-3 side chain (α- and β-positions), can control access of the reducing agent to the DHI C,N-double bond. Thus, the main advantage of a DHI intermediate is that it can be stereoselectively converted to the desired γ-amino alcohol.

The synthesis of 3-(1-alkenyl)-substituted DHIs is relatively straightforward, and we have previously shown[3] that the Sharpless AD reaction[4] can be applied to these compounds to afford DHI α,β-diols. However, we had not previously applied phthalazine-derived chiral auxiliaries to enantioselective DHI α,β-diol synthesis. Here, we describe the enantioselective total synthesis of L-daunosamine derivatives on the basis of the AD reaction of (*E*)-3-(1-propenyl)-4,5-dihydroisoxazole (**2b**) and subsequent reductive cleavage of the DHI ring. We also report experimental procedures for double asymmetric synthesis using chiral alkenyl DHI **16** in the AD reaction. The reactions of **16** were used to initially confirm that 3-alkenyl DHIs undergo AD reaction according to the Sharpless model.

Results and Discussion

The synthesis of 3-(1-propynyl)-4,5-dihydroisoxazole (**1**) from 3-nitro-4,5-dihydroisoxazole and its conversion to the *Z*- and *E*-isomers of 3-(1-propenyl)-4,5-dihydroisoxazole (**2a,b**) have previously been reported.[1b] Lindlar reduction of alkynyl DHI **1** afforded either predominantly (*Z*)-alkene **2a** or (*E*)-alkene **2b** depending on the conditions used (Scheme 1). Using 5% by weight of catalyst afforded crude alkene that was largely the *Z*-isomer (**2a**/**2b**, 90:10). Using 50% by weight of the Lindlar catalyst afforded a 50:50 mixture of the (*E*)-alkene **2b** and the overreduction product 3-(1-propyl)-4,5-dihydroisoxazole. Here, we report an improved procedure for obtaining **2b**. The crude alkene, largely *Z*-isomer (**2a**/**2b**, 90:10), was prepared as previously described and was isomerized to **2b**, isolated in 79% overall yield and containing none of the *Z*-isomer. The *cis* → *trans* isomerization was conducted using catalytic iodine under sun lamp irradiation: the (*E*)-alkene was obtained nearly pure [contaminated by 2% of 3-(1-propyl)-4,5-dihydroisoxazole] after flash chromatography. Fifty-gram quantities of **2b** were readily preparable by the method, and the small amount of overreduction product did not interfere with the subsequent AD reaction.

The AD reaction of alkene **2b** was carried out using AD mix-α and the conditions recommended by Sharpless[4] but with one substantive variation: benzenesulfonamide was used rather than the recommended methanesulfonamide. This change was made because chromatographic separation of methanesulfonamide from diol **3** was inefficient. However, we were able to easily separate the less polar benzenesulfonamide from **3**. In this way, the diol **3** was obtained in 76% isolated yield and with $[\alpha]_D$ +23.7°.

Conversion of diol **3** to diastereomeric benzylidene acetals **4a,b** was carried out in 92% yield, and these were separated by flash chromatography. The major acetal **4a**, obtained in 57% isolated yield, proved to be crystal-

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(1) (a) Wade, P. A.; D'Ambrosio, S. G.; Price, D. T. *J. Org. Chem.* **1995**, *60*, 6302. (b) Wade, P. A.; Rao, J. A.; Bereznak, J. F.; Yuan, C.-K. *Tetrahedron Lett.* **1989**, *30*, 5969. (c) See also: Wade, P. A.; Shah, S. S.; Govindarajan, L. *J. Org. Chem.* **1994**, *59*, 7199.

(2) For pertinent reviews, see: (a) Jäger, V.; Müller, I.; Leibold, T.; Hein, M.; Schwartz, M.; Fengler, M.; Jaraskova, L.; Pätzel, M.; LeRoy, P.-Y. *J. Chem. Soc. Belg.* **1994**, *103*, 491. (b) Hassner, A.; Murthy, K. S. K.; Maurya, R.; Dehaen, W.; Friedman, O. *Lect. Heterocycl. Chem.* **1994**, 687. (c) Torssell, K. B. G. In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988. (d) Curran, D. P. *Adv. Cycloadd.* **1988**, *1*, 129. (e) Kozikowski, A. P.; Chen, Y.-Y. *Tetrahedron* **1984**, *40*, 2345.

(3) (a) Wade, P. A.; Cole, D. T.; D'Ambrosio, S. G. *Tetrahedron Lett.* **1994**, *35*, 53. (b) For an account of our first attempts to perform AD reactions on alkene **2b**, see ref 1b.

(4) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483 and references cited therein.

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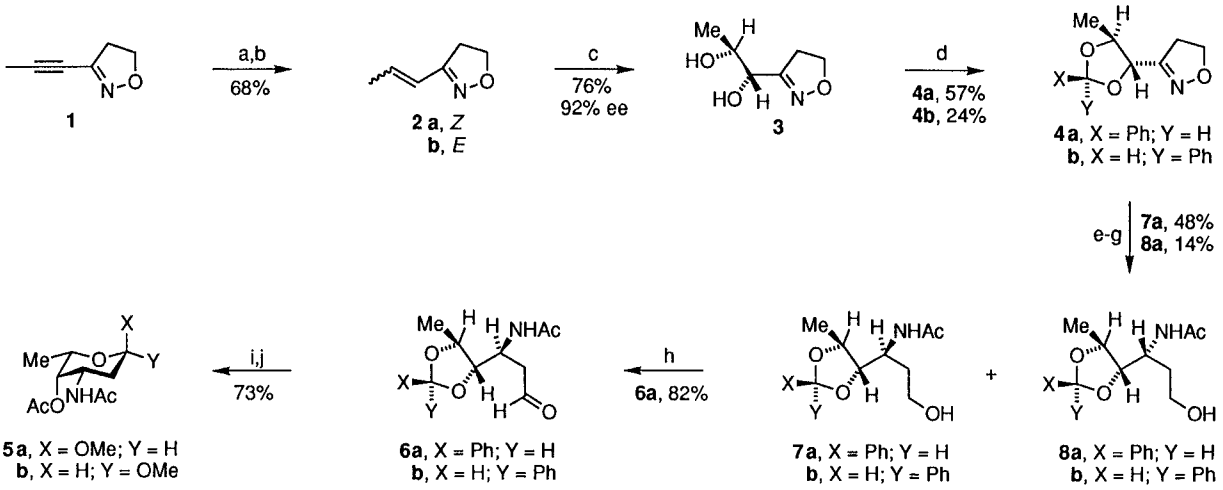
Scheme 1[a]



[a] Reagents: (a) H_2, Lindlar cat., quinoline, C_6H_6; (b) cat. I_2, *hν*, C_6H_6; (c) AD mix-α, $PhSO_2NH_2$, *t*-BuOH/H_2O; (d) PhCH=O, $ZnCl_2$; (e) $LiBH_4$, Et_2O, 35 °C; (f) $HOCH_2CH_2NH_2$, C_6H_6; (g) Ac_2O, $NaHCO_3$, aqueous MeOH; (h) Swern; (i) 0.1 N HCl in MeOH; (j) Ac_2O, pyridine.

line, and its repetitive recrystallization resulted in material of increased rotation: $[\alpha]_D$ rose from +30° to +32.0°. Assignment of stereochemistry to the two product acetals was not straightforward. Benzylidene acetals with a single substituent at the 4-position or with *cis*-4,5 substituents are easily assigned on the basis of ^{1}H-NMR spectra: the isomer having the more upfield signal attributable to the dioxolane 2-proton has the phenyl group *cis* to the substituents.[5] However, for 4,5-*trans*-substituents, it is unclear which of the two groups will be *cis* to the phenyl group. An X-ray structure determination was necessary to make the assignment: the methyl group proved to be *cis* to the phenyl group in the major isomer, acetal **4a**.[22] Hydrolysis of a portion of this material back to diol **3** gave material $[\alpha]_D$ +25.7°. These results, in conjunction with rotation data for the L-daunosamine derivative obtained at the end of the synthesis, confirmed that **4a** was now optically pure, or very nearly so, allowing us to establish that the AD reaction had occurred with 92% ee.

Reductive cleavage[1a] of acetal **4a** using lithium borohydride afforded a nonseparable diastereomeric mixture of γ-amino alcohols that were *N*-acetylated and separated as the acetamide derivatives **7a** and **8a**. In this way, a 48% yield of **7a** and a 14% yield of **8a** were obtained, and the diastereomer ratio of the original reductive cleavage products was established as 72:28. No variability was noted here as a function of the lithium borohydride reagent whether freshly prepared or of commercial origin.[6] It was, however, noted that a lengthy reaction time with ethanolamine[7] was necessary for complete removal of boron from the initially produced complex.

Diastereoselectivity for the reductive cleavage was presumably controlled by groups on the side chain attached at the 3-position of the DHI ring. The X-ray structure determination established the preferred conformation of **4a** present in the crystal lattice. This preferred conformation placed the α-H-atom *syn* to the N-atom of the ring and placed the side chain β-C- and

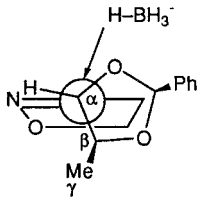
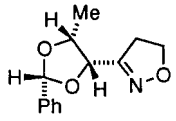


Figure 1. Preferred direction of hydride attack.

γ-C-atoms under the C,N double bond (Figure 1). Assuming reaction through a similar conformation, hydride was then introduced from the top, next to the α-O-atom. This is counter to predictions based on the anti-periplanar effect[8] but is similar to our previous observation[1b] for attack on the racemic DHI acetal **9** leading to acosamine derivatives. For DHI acetal **9**, the γ-C-atom (methyl group) shields the bottom of the C,N-double bond.



9 (one enantiomer)

Models do not show similar shielding in **4a**, however. We attribute facial selectivity in **4a** as arising predominantly from the steric influence of groups attached to the α-C-atom. The X-ray data show a crystal-state conformational preference where the $O_\alpha-C_\alpha-C_3-N_2$ dihedral angle is −125.6 (±0.2)° and the $C_\beta-C_\alpha-C_3-N_2$ dihedral angle is 117.2 (±0.3)°. The α-H-atom is located 3(±2)° above the C,N double bond. Assuming the Bürgi-Dunitz[9] approach trajectory of 107°, the top face of the C,N-double bond is more open in this conformation. If the reacting conformation in solution is similar, attack should be preferable between the O-atom and α-H-atom, affording the major observed product **7a**. It is also quite possible

(5) Assigned by analogy to 2-phenyl-4,5-*cis*-dimethyl-1,3-dioxalane diastereomers: Willy, W. E.; Binsch, G.; Eliel, E. E. *J. Am. Chem. Soc.*, **1970**, *92*, 5394. Eliel, E. L.; Ko, K.-Y. *Tetrahedron Lett.* **1983**, *24*, 3547.

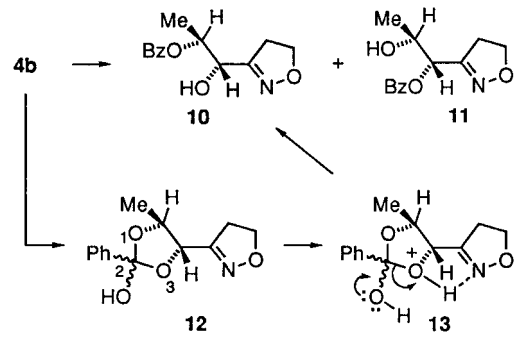
(6) Reductive cleavage of 3-[2-(1,3-dithianyl)]-4-(benzyloxy)-4,5-dihydroisoxazole using $LiBH_4$ showed variability of from 70:30 to 95:5 in the product diastereomer ratio: ref 1a.

(7) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197.

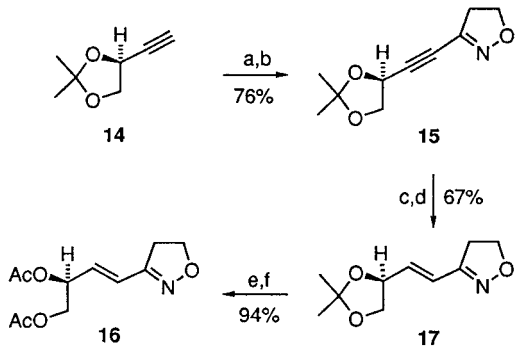
(8) Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Houk, K. N.; Schohe, R.; Jäger, V.; Fronczek, F. R. *J. Am. Chem. Soc.*, **1984**, *106*, 3880. Attack anti-periplanar to the α-C,O-bond would be inconsistent with the observed major product: Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788 and references cited therein.

(9) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956.

Scheme 2



Scheme 3[a]



[a] Reagents: (a) BuLi, THF, −78 °C; (b) 3-nitro-4,5-dihydroisoxazole, 0−5 °C; (c) H_2, Lindlar cat., quinoline; (d) cat. I_2, *hν*, C_6H_6; (e) pyridinium tosylate, MeOH; (f) Ac_2O, pyridine.

that lithium borohydride coordinates with **4a** at any of the four heteroatoms. Coordination of lithium at the α-O-atom might be responsible for directing hydride attack from the top face to afford **7a** preferentially.

The DHI acetal **4b**, the minor benzylidene diastereomer in which phenyl is *trans* to methyl, could also be reductively cleaved with lithium borohydride: here, too, two products, **7b** and **8b**, were obtained in a ratio of 77:23, respectively, slightly higher diastereoselectivity than for the major diastereomer. The diols were *N*-acetylated, and the resulting acetamide mixture was separated, affording **7b** in 52% yield and **8b** in 12% yield. However, the acetal **4b** proved to be a noncrystallizable oil so that we were unable to increase optical purity as done by recrystallization of the major diastereomer **4a** prior to reductive cleavage. Hydrolysis of acetal **4b** provided diol **3** in 81% yield. This portion of **3** could then presumably have been reacetalized to improve the efficiency of the synthesis, although in actual practice this was not carried out.

Partial autoxidation[10] of acetal **4b** was noted for a sample left standing for 2 weeks (Scheme 2). Two inseparable isomeric esters, **10** and **11**, were obtained in 9% yield (37% conversion; 85:15 **10**/**11**). It is thought that autoxidation at C-2 of the dioxolane ring occurred, affording a hydroperoxide that was reduced to hydroxy acetal **12**. Acid-catalyzed cleavage of **12** then afforded the esters **10** and **11**. The preference for ester **10** might arise from intramolecular hydrogen bonding in its direct precursor, oxonium ion **13**: protonation at O-3 of **12** to afford **13** might be favored over protonation at O-1 to afford the isomeric oxonium ion.

The synthesis of methyl *N*,*O*-diacetyldaunosaminide (two anomers: **5a,b**) was then completed by sequential Swern oxidation, methanolysis, and acetylation. Swern oxidation of **7a** under the standard conditions afforded aldehyde **6a** in 82% yield. The benzylidene protecting group was removed by acid-catalyzed methanolysis, affording the methyl pyranoside. The free hydroxyl group of the methyl pyranoside was acetylated, and an 82:18 anomeric mixture of **5a,b** was obtained in 73% overall yield. Flash chromatography as recommended by Jurczak et al.[11] was applied to the anomeric mixture, and pure α-anomer **5a** was obtained. It is noteworthy that the observed optical rotation ($[\alpha]_D$ −210.2°) was somewhat higher than rotations reported in the literature.[11,12] Indeed, it appears that previous so-called pure samples of **5a** were contaminated with small amounts of the β-anomer **5b**. The presence of **5b** can be easily discerned: the ^{1}H NMR spectrum in deuteriochloroform exhibits a signal at δ 3.48 attributable to the C-1 methoxy protons and occurring downfield from the corresponding signal of **5a** (δ 3.35). The anomer separation procedure was not suitable for large quantities of material, and we were unable to obtain pure **5b**,[13] a compound that previously had been synthesized free of **5a**.

The acetamide **7b**, a benzylidene diastereomer of **7a**, was also converted to an anomeric mixture of methyl *N*,*O*-diacetyldaunosaminide. Swern oxidation of **7b** afforded aldehyde **6b** in 85% yield. Acid-catalyzed methanolysis of **6b** afforded deacetalization and ensuing cyclization to the methyl pyranoside. This was acetylated to afford an 83:17 anomeric mixture of **5a,b** in 75% overall yield but in lower optical purity (91%) than the anomeric mixture obtained from acetamide **7a**.

In a preliminary communication,[3a] we reported the AD reaction of chiral 3-alkenyl DHI **16**, establishing that alkenes of this type follow the Sharpless model. The alkenyl DHI **16** was available via a three-step synthesis using 3-nitro-4,5-dihydroisoxazole and the known[14] optically active alkyne **14** as starting materials (Scheme 3). First, alkyne **14** was converted to the corresponding lithium acetylide using excess butyllithium. The acetylide was allowed to react with excess 3-nitro-4,5-dihydroisoxazole, affording the alkynyl DHI **15**, obtained in 76% yield. Lindlar reduction of alkynyl DHI **15** followed by iodine-catalyzed photochemical *cis* → *trans* isomerization afforded alkenyl DHI **17** in 67% overall yield for the two steps. Removal of the acetonide using pyridinium tosylate[15] followed by acetylation afforded alkenyl DHI **16** in 94% yield from **17**.

Using optically active alkenyl DHI **16** as a substrate for the AD reaction constitutes a double asymmetric synthesis.[16] One can envision a matched pair and a mismatched pair of stereoisomers. The $(DHQD)_2$−PHAL[4] chiral system recommended by Sharpless et al. would be expected to promote *anti*-addition: application to **16** then should constitute the matched pair, affording

(10) Autoxidation of acetals: (a) Suzuki, M.; Inai, T.; Matsushima, R. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1585. (b) Kuramshin, E. M.; Kulak, L. G.; Nazarov, M. N.; Zlotsky, S. S. *J. Prakt. Chem.* **1989**, *331*, 591.

(11) Jurczak, J.; Kozak, J.; Golebiowski, A.; *Tetrahedron* **1992**, *48*, 4231.

(12) Arcamone, F.; Cassinelli, G.; Francesschi, G.; Mondelli, R.; Orezzi, P.; Penco, S. *Gazz. Chim. Ital.* **1970**, *100*, 949. Arcamone, F.; Cassinelli, G.; Francesschi, G.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5335.

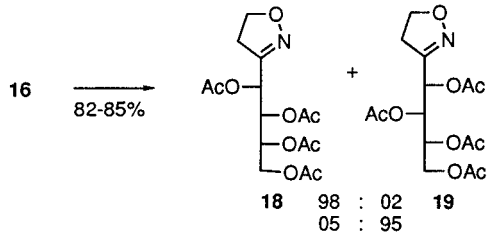
(13) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227.

(14) Taylor, E. C.; Ray, P. S.; Darwish, I. S.; Johnson, J. L.; Rajagopalan, K. V. *J. Am. Chem. Soc.* **1989**, *111*, 7664.

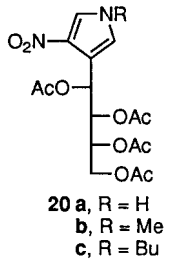
(15) Sterzycki, R. *Synthesis* **1979**, 724.

(16) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int., Ed. Engl.* **1985**, *24*, 1.

tetraacetate **18** as the major product after acetylation. This proved to be the case but necessitated an essential modification of the recommended catalytic conditions. Attempts to use AD mixes were unsuccessful owing to insufficient potassium osmate. It was necessary to use 0.08 mol equiv (40 times the recommended amount) of potassium osmate for efficient dihydroxylation of **18**. After acetylation of the crude diols, the diastereomeric tetraacetates **18** and **19** were obtained as a 98:2 mixture, respectively, in 82% overall yield.



The configuration assigned to **18** is based on its ^{1}H NMR spectrum. In particular, the coupling constant $J_{\beta,\gamma}$ = 8.2 Hz is consistent with the *anti*-introduction of acetate to the β-C-atom. The glucose-derived pyrroles **20a**−**c** exhibited similar coupling constants: $J_{\beta,\gamma}$ = 8.6−8.8 Hz.[17] In contrast, tetraacetate **19** exhibited $J_{\beta,\gamma}$ = 4.5



Hz. It is assumed that the conformations of **18** and **20a**−**c** are similar, presumably a regular zig-zag arrangement.

The preceding results are for the matched pair of stereoisomers and might be anticipated. Application of the (DHQ)$_2$−PHAL chiral auxilliary to the AD reaction of **16**, however, presented a mismatched pair where the stereochemical outcome was not initially predictable. The AD reaction of **16** using (DHQ)$_2$−PHAL afforded, after acetylation of the initially produced diols the diastereomeric tetraacetates **18** and **19** as a 5:95 mixture, respectively, in 85% overall yield. Thus, the chiral auxilliary strongly controlled the diastereoselectivity in this mismatched pair.

It is noteworthy that alkenyl DHI **2b** required only the recommended amount of potassium osmate for efficient AD reaction, whereas alkenyl DHI **16** required 40 times as much as the recommended amount of potassium osmate for smooth reaction. Alkenyl DHI **17** also exhibited a high potassium osmate requirement for AD reaction as previously noted. At the time preliminary results on **16** were published, it was suggested[18] that the high potassium osmate requirement might be due to Os chelation at the DHI ring N-atom resulting in a low catalyst turnover rate. However, the more recent results with **2b** are not in agreement with this explanation. It now seems that several factors must be involved with the abnormally high potassium osmate requirements of **16** and **17**. Dihydroxylation of alkenes is an electrophilic reaction: low dihydroxylation rates for alkenes possessing an electronegative atom (*i.e.*, O- or N-) at the allylic site have been noted in some cases although not in others.[4,19,20] We therefore suggest that the high potassium osmate requirement of **16** and **17** is due in part to the presence of an allylic O-atom. The adjacent C,N-double bond would also retard an electrophilic process at the C,C-double bond for all of the alkenyl DHIs. The C,C-double bond of **16** and **17** is less accessible than the C,C-double bond of alkenyl DHI **2b**, probably contributing to the lower rate. Finally, although Os chelation at the DHI ring N-atom cannot be solely responsible for the high potassium osmate requirement, it may be partially responsible in combination with the other factors.

Experimental Section

General Methods. Reactions were routinely run under argon. Workup involved separation of the organic layer, drying over anhydrous Na_2SO_4, filtering, and concentration at reduced pressure. ^{1}H NMR spectra and ^{13}C NMR spectra were determined in $CDCl_3$ (TMS internal standard) on a Bruker WM-250 instrument unless otherwise noted. 3-Nitro-4,5-dihydroisoxazole was prepared in 53% yield from 1-bromo-3-chloropropane by the published procedure.[21] Sunlamp irradiation was conducted using a 250-W GE bulb placed 2 ft from the Pyrex reaction vessel. Analytical HPLC was conducted using a Rainin Microsorb silica column. The AD mix-α was used as purchased (Aldrich). Other routine procedures have been previously published.[1a]

Preparation of 3-(1-Propynyl)-4,5-dihydroisoxazole (1). Propyne was condensed (30 mL, 21.2 g, 0.53 mol) in a precalibrated reaction flask cooled by dry ice. A solution of butyllithium (120 mL, 2.5 M in hexanes; 0.3 mol of BuLi) was cautiously added over 1 min to the flask, directly followed over 2−3 min by THF (880 mL). The cold reaction mixture was stirred for 30 min and then allowed to warm to −25 °C. 3-Nitro-4,5-dihydroisoxazole (30.5 g, 0.27 mol) was added dropwise, maintaining the reaction temperature below 0 °C. The reaction mixture was stirred for 2 h at 0 to −5 °C, treated with water (18 mL), concentrated, diluted with CH_2Cl_2 (750 mL), and washed with water (three 150-mL portions). Further workup and distillation of the crude product afforded 24.8 g (86% yield) of pure **1**: bp 50−55 °C (0.1 mmHg); IR (film) 2234 cm^{-1}; ^{1}H NMR δ 4.40 (t, 2H, J = 10.3 Hz), 3.02 (t, 2H, J = 10.3 Hz), 2.05 (s, 3H); ^{13}C NMR δ 142.8, 94.2, 68.8, 68.7, 37.6, 3.5; LRMS (EI) m/e 109 (M^+). Anal. Calcd for C_6H_7NO: C, 66.04; H, 6.47. Found: C, 65.91; H 6.58.

Preparation of (*E*)-3-(1-Propenyl)-4,5-dihydroisoxazole (2). A solution of alkyne **1** (3.04 g, 28 mmol) and quinoline (215 mg, 0.8 mmol) in benzene (70 mL) was transferred to a Parr hydrogenator flask containing a pre-equilibrated (10 min) mixture of benzene (70 mL) and Lindlar catalyst (107 mg) under hydrogen. The flask contents were subjected to vigorous shaking under hydrogen (16 psi) for 30 min and were then filtered, concentrated, and diluted with CH_2Cl_2 (100 mL). The resulting solution was sequentially washed with 5% aqueous HCl (75 mL), 5% aqueous $NaHCO_3$ (75 mL), and water (75 mL). Further workup afforded 2.71 g of crude alkene (*Z*/*E*, 90:10) contaminated with a small amount (*ca.* 1−2% by ^{1}H NMR) of 3-propyl-4,5-dihydroisox-

(17) Gómez-Sánchez, A.; Hidalgo, F.-J.; Chiara, J.-L. *Carbohydr. Res.* **1987**, *167*, 55.

(18) See ref 3a, footnote 10.

(19) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. (c) See also: Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.

(20) For example: Morikawa, K.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 5575.

(21) Wade, P. A. *J. Org. Chem.* **1978**, *43*, 2020.

(22) The author has deposited atomic coordinates for **4a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

azole. A solution of the crude alkene (2.71 g, 25 mmol) and I_2 (273 mg, 1 mmol) in benzene (90 mL) was stirred and irradiated with a sunlamp for 3 h. The resulting solution was concentrated, diluted with CH_2Cl_2 (150 mL), and washed with 10% aqueous sodium thiosulfate (70 mL). The aqueous layer was extracted with CH_2Cl_2 (two 50-mL portions) and the combined organic layers were worked up to give an oil that was distilled at reduced pressure to give 2.45 g (79% yield) of **2** contaminated with a trace (*ca.* 1−2% by ^{1}H NMR) of 3-propyl-4,5-dihydroisoxazole: bp 38−39 °C (0.1 mmHg): IR (film) 1650, 1622 cm^{-1}; ^{1}H NMR δ 6.43 (d, 1H, J = 15.9 Hz), 6.01 (dq, 1H, J = 6.7, 15.8 Hz), 4.34 (t, 2H, J = 10.0 Hz), 3.05 (t, 2H, J = 10.0 Hz), 1.90 (dd, 3H, J = 1.6, 6.7 Hz); ^{13}C NMR δ 157.0, 134.4, 120.9, 68.3, 33.7, 18.0; HRMS (EI) calcd for C_6H_9NO (M^+) 111.0684, found 111.0684.

AD Reaction of Alkene 2. A mixture of AD mix-α (59.6 g), *t*-BuOH (225 mL), and water (225 mL) was stirred for 10 min, and benzenesulfonamide (6.89 g, 43.9 mmol) was added. After 5 min, alkene **2** (4.27 g, 38 mmol) was added, and the resulting mixture was stirred for 26 h at rt. Anhydrous Na_2SO_3 (64 g) was added and stirring continued for 1 h followed by removal of volatiles at reduced pressure. Methanol (100 mL) and acetone (400 mL) were added to the residue, and the resulting slurry was stirred for 1 h. The slurry was filtered through silica gel and the filtrate concentrated to give 13.5 g of crude product. The crude product was purified by flash chromatography (acetone/hexanes, 50:50), affording 64 mg of 3-propyl-4,5-dihydroisoxazole (90% pure by ^{1}H NMR) as the most mobile product: ^{1}H NMR δ 4.27 (t, 2H, J = 10.0 Hz), 2.93 (t, 2H, J = 10.0 Hz), 2.36 (t, 2H, J = 7.5 Hz), 1.63 (sx, 2H, J = 7.5 Hz), 0.97 (t, 3H, J = 7.4 Hz); ^{13}C NMR δ 158.5, 67.6, 37.1, 29.2, 19.5, 13.3. HRMS (EI) calcd for $C_6H_{11}NO$ (M^+) 113.0840, found 113.0840.

Further elution afforded benzenesulfonamide followed by 4.55 g of diol **3** as the least mobile fraction. The diol was Kugelrohr distilled to furnish 4.18 g (76% yield) of **3** (pure by ^{1}H NMR) as a syrup: bp 110−125 °C (0.04 mmHg); $[\alpha]^{23}_D$ +23.7° (*c* 2.93, $CHCl_3$); IR (film) 3378 cm^{-1}; ^{1}H NMR δ 4.35 (t, 2H, J = 10.0 Hz), 4.26 (d, 1H, J = 4.5 Hz), 3.95−4.1 (m, 1H), 2.9−3.2 (m, 2H), 2.78 (br var s, 2H), 1.28 (d, 3H, J = 6.4 Hz); ^{13}C NMR δ 160.0, 71.8, 68.5, 68.4, 34.7, 18.7; HRMS (FAB, NaBr) calcd for $C_6H_{11}NO_3Na$ ($M + Na^+$) 168.0637, found 168.0633.

Preparation of 4,5-Dihydro-3-(5-methyl-2-phenyl-1,3-dioxolan-4-yl)isoxazole (4a,b). A mixture of diol **3** (5.60 g, 39 mol), $ZnCl_2$ (5.0 g, 36 mmol), and PhCHO (27 mL, 266 mmol) was stirred for 18 h. Aqueous 40% $NaHSO_3$ (75 mL) was added and the mixture stirred for 15 min. Volatiles were removed at reduced pressure, and the residue was treated with CH_2Cl_2 (100 mL). The resulting slurry was stirred vigorously for 1 h and was filtered. The filtrate was concentrated to give 9.59 g of crude acetal as a mixture of two diastereomers. Flash chromatography (hexanes/EtOAc, 93:7) afforded PhCHO as the most mobile product followed by partially separated acetal diastereomers. Repetitive chromatography of mixed fractions afforded pure **4a** and pure **4b**. The more mobile isomer (2.18 g, 24% yield; pure by ^{1}H NMR) was **4b**, isolated as an oil: $[\alpha]^{26}_D$ −15.3° (*c* 1.86, $CHCl_3$); ^{1}H NMR δ 7.35−7.55 (m, 5H), 6.07 (s, 1H), 4.63 (d, 1H, J = 6.6 Hz), 4.25−4.45 (m, 3H), 2.85−3.2 (m, 2H), 1.45 (d, 3H, J = 6.2 Hz); ^{13}C NMR δ 156.8, 137.4, 129.2, 128.2, 126.2, 103.1, 78.5, 75.1, 68.6, 33.9, 17.5; HRMS (FAB) calcd for $C_{13}H_{16}NO_3$ ($M + H^+$) 234.1130, found 234.1129.

The less mobile isomer (5.09 g, 57% yield) was **4a**, isolated as a solid. Recrystallization from CH_2Cl_2/hexanes afforded 3.56 g of **4a**: $[\alpha]^{26}_D$ +30.0° (*c* 1.16, $CHCl_3$). An analytical sample was obtained after two more recrystallizations: mp 82.5−83 °C; $[\alpha]^{26}_D$ +32.0° (*c* 1.41, $CHCl_3$); ^{1}H NMR δ 7.35−7.55 (m, 5H), 5.94 (s, 1H), 4.53 (d, 1H, J = 7.7 Hz), 4.40 (t, J = 9.8 Hz) on 4.3−4.45 (m) [3H total], 3.13 (m, 2H), 1.50 (d, 3H, J = 6.0 Hz); ^{13}C NMR δ 157.0, 137.2, 129.5, 128.4, 126.6, 104.2, 77.8, 76.6, 68.7, 34.8, 17.2; HRMS (FAB) calcd for $C_{13}H_{16}NO_3$ ($M + H^+$) 234.1130, found 234.1129. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.81; H, 6.38; N, 5.92.

The above procedure was repeated, but the crude product was directly recrystallized from CH_2Cl_2/hexanes without chromatography to give 2.68 g (30% yield) of **4a**.

Regeneration of Diol 3 from 4a and 4b. A mixture of thrice-recrystallized acetal **4a** (71 mg, 0.3 mmol), water (1 mL), and acetic acid (4 mL) was stirred for 46 h at rt, and then volatiles were removed under reduced pressure to give 48.7 mg of crude product. The crude product was purified by preparative TLC (EtOAc) to give 38 mg (87% yield) of diol **3**: $[\alpha]^{23}_D$ +25.7° (*c* 0.71, $CHCl_3$).

Similar treatment of the oil **4b** (71 mg, 0.3 mmol) gave 36 mg (81% yield) of diol **3**: $[\alpha]^{26}_D$ +21.7° (*c* 1.12, $CHCl_3$).

Reductive Cleavage of DHI 4a. A solution of **4a** (1.04 g, 4.48 mmol) in diethyl ether (100 mL) was added to $LiBH_4$ (36 mL of a 2 M THF solution, 72 mmol of $LiBH_4$), and the resulting solution was refluxed for 3 d. More $LiBH_4$ (10 mL, 20 mmol of $LiBH_4$) was added, and the solution was refluxed for another 3 d. The reaction solution was concentrated at reduced pressure, and CH_2Cl_2 (100 mL) was added. The resulting solution was cooled to 0−5 °C, and aqueous 10% NaH_2PO_4 (adjusted to pH 7.0 with NaOH, 200 mL) was cautiously added (foaming!). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (two 100-mL portions). The combined organic layers were washed with 10% brine (two 100-mL portions). Workup afforded 1.34 g of crude boron-containing product, which was taken up in benzene (100 mL). Ethanolamine (2 g) was added, and the resulting mixture was stirred vigorously for 5 d. Concentration afforded a residue that was dissolved in CH_2Cl_2 (80 mL), the resulting solution being washed with 10% brine (three 30-mL portions). Further workup gave 1.19 g of boron-free crude product that was purified by flash chromatography (CH_2Cl_2/MeOH from 97:3 to 90:10). An inseparable mixture of diastereomeric γ-amino alcohols (0.77 g, 75:25 ratio by ^{1}H NMR) was obtained. The γ-amino alcohol mixture was dissolved in MeOH/water (70:30, 18 mL), and the solution was cooled (0−5 °C). Acetic anhydride (0.6 mL, 6.32 mmol) and $NaHCO_3$ (110 mg, 1.32 mmol) were added, and the resulting cold solution was stirred for 3 h. Volatiles were removed at reduced pressure, and acetone (10 mL) was added to the residue. The resulting mixture was filtered, and the filtrate was concentrated to give 1.15 g of crude product (**7a/8a**, 78:22 by ^{1}H NMR). Repetitive preparative TLC (CH_2Cl_2/MeOH, 95:5) furnished 0.60 g (48% yield) of amide **7a** as the less mobile product (pure by ^{1}H NMR). The analytical sample was recrystallized from CH_2Cl_2/hexanes: mp 124−126 °C; $[\alpha]^{23}_D$ −30.1° (*c* 1.06, $CHCl_3$); IR (film) 3284, 1649 cm^{-1}; ^{1}H NMR δ 7.35−7.5 (m, 5H), 5.96 (br d, 1H, J = 8.8 Hz), 5.88 (s, 1H), 4.15−4.35 (m, 2H), 3.82 (dd, 1H, J = 4.6, 7.7 Hz), 3.7−3.8 (m, 1H), 3.55−3.7 (m, 1H), 2.41 (br s, 1H), 2.05 (s) on 1.95−2.1 (m) [4H total], 1.6−1.75 (m, 1H), 1.44 (d, 3H, J = 6.0 Hz); ^{13}C NMR δ 171.2, 137.5, 129.5, 128.4, 126.6, 103.7, 84.2, 76.4, 58.4, 47.8, 32.9, 23.1, 18.3; HRMS (FAB) calcd for $C_{15}H_{22}NO_4$ ($M + H^+$) 280.1549, found 280.1548.

Also obtained was 167 mg (14% yield) of amide **8a** as the more mobile chromatography fraction (pure by ^{1}H NMR). An analytical sample was recrystallized from CH_2Cl_2/hexanes: mp 163−165 °C; $[\alpha]^{23}_D$ +45.5° (*c* 1.45, $CHCl_3$); IR (film) 3293, 1649 cm^{-1}; ^{1}H NMR δ 7.35−7.35 (m, 5H), 6.06 (br d, 1H, J = 9.1 Hz), 5.94 (s, 1H), 4.2−4.3 (m, 1H), 3.95−4.05 (m, 1H), 3.66 (d, J = 8.1 Hz) on 3.65−3.8 (m) [2H total], 3.45−3.6 (m, 1H), 3.34 (br s, 1H), 2.10 (s, 3H), 1.75−1.95 (m, 1H), 1.6−1.75 (m, 1H), 1.40 (d, 3H, J = 6.0 Hz); ^{13}C NMR δ 171.6, 138.0, 129.5, 128.5, 126.4, 104.1, 84.3, 75.9, 58.1, 45.2, 37.1, 23.2, 16.9; HRMS (FAB) calcd for $C_{15}H_{22}NO_4$ ($M + H^+$) 280.1549, found 280.1546.

Preparation of Aldehyde 6a. DMSO (0.14 mL, 2.0 mmol) was added over 5 min to cold (−60 °C) oxalyl chloride [0.4 mL of a 2 M CH_2Cl_2 solution; 0.81 mmol $(COCl)_2$], and the resulting solution was stirred for 5 min. A solution of **7a** (192 mg, 0.69 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 9 min. Triethylamine (0.5 mL, 3.7 mmol) was added over 2 min, and the reaction solution was stirred for 90 min at ambient temperature. Aqueous 10% brine (5 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (two 15-mL portions), and the combined organic layers were worked up to afford 177 mg of crude solid product.

Recrystallization from CH_2Cl_2/hexanes gave 156 mg (82% yield; pure by ^1H NMR) of **6a**: mp 124−126 °C; $[\alpha]^{23}_D$ +16.2° (*c* 1.73, $CHCl_3$); IR (film) 3286, 1723, 1656 cm^{-1}; ^1H NMR δ 9.76 (d, 1H, J = 2.0 Hz), 7.35−7.5 (m, 5H), 6.38 (br d, 1H, J = 9.3 Hz), 5.84 (s, 1H), 4.45−4.6 (m, 1H), 4.05−4.2 (m, 1H), 3.81 (t, 1H, J = 7.5 Hz), 2.93 (ddd, 1H, J = 2.0, 5.8, 17.7 Hz Hz), 2.83 (dd, 1H, J = 4.6, 17.7 Hz), 1.99 (s, 3H), 1.42 (d, 3H, J = 6.0 Hz); ^{13}C NMR δ 201.1, 169.8, 137.1, 129.5, 128.4, 126.6, 103.1, 82.7, 77.5, 46.8, 44.6, 23.2, 18.7; HRMS (FAB) calcd for $C_{15}H_{20}NO_4$ (M + H^+) 278.1392, found 278.1395.

Preparation of 5a,b from 6a. A solution of aldehyde **6a** (134 mg, 0.48 mmol) in 0.1 N methanolic HCl was stirred for 12 h at rt and was then concentrated at reduced pressure. Acetic anhydride (3 mL) was added to the residue followed by pyridine (0.2 mL), and the resultant was stirred for 3.5 h and then concentrated. The residue was purified by preparative TLC (CH_2Cl_2/MeOH, 90:10) to give 86 mg (73% yield) of **5** as an anomeric mixture (**5a/5b**, 82:18 by ^1H NMR): $[\alpha]^{23}_D$ −160.7° (*c* 0.92, $CHCl_3$). Repetitive flash chromatography (hexanes/EtOAc/MeOH, 59:40:01) furnished the major anomer **5a**: mp 187−188 °C; $[\alpha]^{23}_D$ −210.2° (*c* 1.18, $CHCl_3$); IR (film) 3316, 1738, 1651 cm^{-1}; ^1H NMR δ 5.34 (br d, 1H, J = 7.5 Hz), 5.09 (d, 1H, J = 2.6 Hz), 4.81 (br s, 1H), 4.5−4.65 (m, 1H), 4.05 (q, 1H, J = 6.5 Hz), 3.35 (s, 3H), 2.19 (s, 3H), 1.94 (s, 3H), 1.7−1.9 (m, 2H), 1.11 (d, 3H, J = 6.5 Hz); ^{13}C NMR δ 170.9, 169.7, 97.9, 71.3, 64.9, 54.8, 43.9, 30.5, 23.2, 20.9, 16.8; HRMS (FAB) calcd for $C_{11}H_{20}NO_5$ (M + H^+) 246.1341, found 246.1332.

Also obtained from the flash chromatography was a fraction consisting of a **5a,b** mixture: **5a/5b** 17:83. The ^1H NMR spectrum of **5a** was subtracted, and the remaining signals matched the reported spectrum[13] of pure **5b**.

Formation of Benzoates 10 and 11 from DHI Acetal 4b. A 651 mg sample of **4b** was stored for several weeks neat in a stoppered flask. The partially air-oxidized sample was then purified by preparative TLC (hexanes/EtOAc, 65:35) to furnish 488 mg of **4b** as a more mobile fraction and 64 mg of an 85:15 mixture (^1H NMR) of **10** and **11** as a less mobile fraction. Attempts at separating the mixture of **10** and **11** by preparative TLC or crystallization failed: $[\alpha]^{24}_D$ +28.3° (*c* 1.95, $CHCl_3$); IR (neat) 3458, 1716 cm^{-1}; ^1H NMR δ 8.0−8.1 (m, 2H), 7.5−7.65 (m, 1H), 7.4−7.5 (m, 2H), 5.76 (d, 1H of **11**, J = 4.1 Hz), 5.35−5.40 (m, 1H), 4.65 (d, 1H of **10**, J = 4.9 Hz), 4.3−4.45 (m, 2H), 2.8−3.2 (m, 2H), 1.65 (br s, 1H), 1.45 (d, 3H of **10**, J = 6.5 Hz), 1.33 (d, 3H of **11**, J = 6.5 Hz); ^{13}C NMR δ 166.0, 165.6*, 158.7, 133.5*, 133.2, 129.8*, 129.6, 128.4, 72.8*, 71.7, 70.6, 68.9, 68.5*, 67.8*, 35.9*, 34.6, 18.7*, 16.0 (*low intensity signals attributed to **11**); HRMS (FAB) calcd for $C_{13}H_{15}NO_4$ (M + H^+) 250.1079, found 250.1081.

Reductive Cleavage of DHI 4b. A solution of **4b** (1.04 g, 4.46 mmol) in diethyl ether (100 mL) was added to $LiBH_4$ (36 mL of a 2 M THF solution, 72 mmol of $LiBH_4$), and the resulting solution was refluxed for 12 d. More $LiBH_4$ (two 15-mL portions, 60 mmol of $LiBH_4$) was added after the third day and eighth day to replenish spent reducing agent. Repetition of the procedure described for preparation of **4a** gave 1.4 g of crude boron-containing product. This was taken up in benzene (100 mL), and ethanolamine (2 g) was added. The resulting mixture was stirred vigorously for 8 d and was worked up as described for **4a** to give 0.93 g of boron-free crude product. Flash chromatographic purification as described for **4a** afforded 0.83 g of diastereomeric γ-amino alcohols (75:25 ratio) as an oil. Acetylation followed by repetitive preparative TLC furnished 241 mg (51% yield) of amide **7b** as the less mobile product (pure by ^1H NMR). The analytical sample was recrystallized from CH_2Cl_2/hexanes: mp 88−89 °C; $[\alpha]^{23}_D$ −39.8° (*c* 4.5, $CHCl_3$); IR (film) 3300, 1650 cm^{-1}; ^1H NMR δ 7.35−7.5 (m, 5H), 6.37 (br d, 1H, J = 9.0 Hz), 5.92 (s, 1H), 4.2−4.35 (m, 2H), 3.85−3.89 (dd, 1H, J = 4.5, 5.7 Hz), 3.5−3.75 (m, 2H), 1.97 (s) on 1.85−2.05 (m) [4H total], 1.45−1.65 (m, 1H), 1.36 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.2, 137.1, 129.3, 128.3, 126.4, 102.3, 84.9, 74.6, 58.3, 47.8, 32.2, 22.8, 18.7; HRMS (FAB) calcd for $C_{15}H_{22}NO_4$ (M + H^+) 280.1549, found 280.1550.

Also obtained from the more mobile chromatography fraction was 56 mg (12% yield; pure by ^1H NMR) of amide **8b** as an oil: $[\alpha]^{21}_D$ +43.1° (*c* 1.46, $CHCl_3$); IR (film) 3290, 1654 cm^{-1}; ^1H NMR δ 7.35−7.55 (m, 5H), 6.03 (s, 1H), 5.71 (br d, 1H, J = 8.4 Hz), 4.15−4.3 (m, 1H), 4.05 (quint, 1H, J = 6.3 Hz), 3.81 (d, 1H, J = 6.9 Hz), 3.65−3.75 (m, 1H), 3.4−3.55 (m, 1H), 2.55 (br s, 1H), 1.86 (s) on 1.8−2.0 (m) [4H total], 1.65−1.8 (m, 1H), 1.40 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.6, 138.0, 129.4, 128.7, 125.9, 102.4, 85.6, 74.7, 58.1, 45.3, 36.9, 22.9, 18.0; HRMS (FAB) calcd for $C_{15}H_{22}NO_4$ (M + H^+) 280.1549, found 280.1548.

Preparation of Aldehyde 6b. The procedure employed for preparation of **6a** was repeated on **7b** (85 mg, 0.3 mmol) to afford 72 mg (85% yield; pure by ^1H NMR) of **6b**: mp 124−126 °C; $[\alpha]^{26}_D$ +15.0° (*c* 1.0, $CHCl_3$); IR (film) 3278, 1717, 1644 cm^{-1}; ^1H NMR δ 9.73 (s, 1H), 7.35−7.5 (m, 5H), 6.18 (br d, 1H, J = 9.3 Hz), 5.92 (s, 1H), 4.45−4.6 (m, 1H), 4.20 (quint, 1H, J = 6.2 Hz), 3.92 (t, 1H, J = 6.2 Hz), 2.93 (ddd, 1H, J = 1, 6.2, 17.8 Hz), 2.73 (dd, 1H, J = 4.3, 17.8 Hz), 1.98 (s, 3H), 1.38 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 201.1, 169.8, 137.1, 129.4, 128.4, 126.4, 102.5, 83.7, 75.7, 47.0, 43.9, 23.2, 18.9; HRMS (FAB) calcd for $C_{15}H_{20}NO_4$ (M + H^+) 278.1392, found 278.1385.

Preparation of 5a,b from 6b. The procedure employed for **6a** was repeated using **6b** (68 mg, 0.24 mmol) to furnish 45 mg (75% yield) of **5** as an anomeric mixture (**5a/5b**, 83:17 by ^1H NMR): $[\alpha]^{23}_D$ −146.6° (*c* 1.02, $CHCl_3$).

Preparation of Alkynyl DHI 15. Butyllithium (1.2 mL of a 2 M pentane solution; 2.4 mmol) was added dropwise over 15 min to a cold (dry ice) solution of alkyne **14**[13] (194 mg, 1.53 mmol) in THF (1 mL). The resulting solution was allowed to warm to room temperature, and a solution of 3-nitro-4,5-dihydroisoxazole (267 mg, 2.31 mmol) in THF (1 mL) was added dropwise over 15 min. Water (2 mL) was added, and organic products were extracted with CH_2Cl_2 (four 15-mL portions). The combined extracts were worked up, and the resulting residue was purified by preparative TLC (CH_2Cl_2/MeOH, 95:5) to afford 227 mg (76% yield) of pure **15** as an oil: $[\alpha]^{23}_D$ +39.4° (*c* 1.7, MeOH); IR (film) 2233 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.84 (t, 1H, J = 6.2 Hz), 4.39 (t, 2H, J = 10.4 Hz), 4.17 (dd, 1H, J = 6.5, 8.2 Hz), 3.96 (dd, 1H, J = 6.0, 8.2 Hz), 3.02 (t, 2H, J = 10.4 Hz), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 142.3, 110.5, 94.6, 74.6, 69.7, 69.3, 65.4, 37.7, 25.9, 25.6; LRMS (EI) *m/e* 195 (M^+). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.51; H, 6.73; N, 7.18. Found: C, 61.29; H, 6.49; N, 7.08.

Preparation of Alkenyl DHI 17. A solution of alkyne **15** (0.61 g, 3.1 mmol) and quinoline (215 mg, 0.83 mmol) in benzene (205 mL) was transferred to a Parr hydrogenator flask containing a mixture of benzene (20 mL) and Lindlar catalyst (60 mg) that had been preequilibrated (10 min) under hydrogen. The flask contents were subjected to vigorous shaking under hydrogen (20 psi) for 3 h and were then filtered, concentrated, and diluted with CH_2Cl_2 (100 mL). The resulting solution was worked up as described for **2b**, affording 0.54 g of crude alkene (*Z*/*E*, 90:10). An analytical sample (pure by ^1H NMR) of the *Z*-alkene was obtained by preparative TLC (hexanes/EtOAc, 60:40): $[\alpha]^{23}_D$ +66.1° (*c* 0.95, MeOH); ^1H NMR δ 6.13 (d, 1H, J = 11.8 Hz), 5.97 (dd, 1H, J = 7.8, 11.8 Hz), 5.11 (q, 1H, J = 7.0 Hz), 4.38 (t, 1H, J = 9.8 Hz), 4.25 (dd, 1H, J = 6.5, 8.1 Hz), 3.63 (dd, 1H, J = 7.1, 8.1 Hz), 2.95−3.2 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 154.4, 137.2, 119.1, 109.6, 73.2, 69.4, 69.0, 37.2, 26.6, 25.5; HRMS (FAB) calcd for $C_{10}H_{26}NO_4$ (M + H^+) 198.1130, found 198.1123.

The crude (*Z*)-alkene (0.54 g, 2.76 mmol) and iodine (76 mg, 0.3 mmol) were dissolved in benzene (45 mL), and the solution was stirred and irradiated with a sunlamp for 3 h. The resulting solution was worked up as described for **2b**. Preparative TLC (hexanes/EtOAc 60:40) on the resulting residue provided 0.43 g (70% yield based on **14**; pure by ^1H NMR) of (*E*)-alkenyl DHI **15**: $[\alpha]^{23}_D$ +37.1° (*c* 1.3, MeOH); IR (film) 1650 $cm^{-1;}$ ^1H NMR δ 6.70 (d, 1H, J = 15.9 Hz), 5.93 (dd, 1H, J = 7.0, 15.9 Hz), 4.66 (q, 1H, J = 7.2 Hz), 4.40 (t, 2H, J = 10.1 Hz), 4.18 (dd, 1H, J = 6.3, 8.2 Hz), 3.66, (dd, 1H, J = 7.4, 8.2 Hz), 3.08 (t, 2H, J = 10.1 Hz), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR δ 156.4, 135.3, 121.9, 109.6, 75.8, 69.0, 68.9, 33.0, 26.5, 25.6. HRMS (FAB) calcd for $C_{10}H_{26}NO_4$ (M + H^+) 198.1130, found 198.1132.

Preparation of Alkenyl DHI 16. A solution containing **17** (170 mg, 0.86 mmol) and pyridinium *p*-toluenesulfonate

(265 mg, 1.05 mmol) in MeOH (29 mL) was refluxed for 2 d. To the cooled solution were added $NaHCO_3$ (1 g) and Na_2SO_4 (2 g). The resulting mixture was filtered and concentrated, toluene being added with further concentration to entrain residual pyridine. The residue was treated with Ac_2O (0.6 mL), DMAP (1 crystal), pyridine (0.7 mL), and CH_2Cl_2 (1.5 mL). The resulting solution was stirred for 3 h and brine (5 mL) was added. The organic product was extracted into EtOAc (six 30-mL portions), and the combined extracts were worked up. Preparative TLC (acetone/ether 08:92) on the resulting residue afforded 162 mg (78% yield; pure by ^{1}H NMR) of **16** as an oil: $[\alpha]^{23}_D$ +36.6° (*c* 1.1, $CHCl_3$); IR (film) 1736, 1651 cm^{-1}; ^{1}H NMR δ 6.68 (d, 1H, J = 16.1 Hz), 5.92 (dd, 1H, J = 5.9, 16.1 Hz), 5.6−5.7 (m, 1H), 4.40 (t, 2H, J = 10.2 Hz), 4.31 (dd, 1H, J = 3.9, 11.8 Hz), 4.14, (dd, 1H, J = 6.5, 11.8 Hz), 3.07 (t, 2H, J = 10.2 Hz), 2.13 (s, 3H), 2.08 (s, 3H); ^{13}C NMR δ 170.3, 169.6, 156.3, 131.6, 122.8, 70.7, 69.3, 64.2, 33.6, 21.0, 20.8; HRMS (FAB) calcd for $C_{11}H_{16}NO_5$ (M + H$^+$) 242.1028, found 242.1027.

AD Reaction of Alkenyl DHI 16 Using (DHQD)$_2$−PHAL. A mixture consisting of (DHQD)$_2$−PHAL (37 mg, 0.045 mmol), methanesulfonamide (10.5 mg, 0.11 mmol), $K_3Fe(CN)_6$ (80 mg, 0.24 mmol), K_2CO_3 (39 mg, 0.28 mmol), K_2OsO_4·2H_2O (3.8 mg, 0.01 mmol), water (0.6 mL), and *t*-BuOH (0.6 mL) was stirred for 10 min at rt. To the mixture was added a solution of **16** (16.9 mg, 0.07 mmol) in *t*-BuOH (0.6 mL). Stirring was continued for 21 h, and anhydrous Na_2SO_3 (1 g) was added with additional stirring for 1 h. The mixture was concentrated in vacuo, and the solids were triturated for 30 min (MeOH/acetone 20:80; 200 mL). The resulting slurry was filtered through silica gel (1 g), and the filtrate was concentrated. Traces of water were removed by azeotropic distillation with two portions of absolute EtOH followed by drying *in vacuo*. The resulting crude diol was then taken up in CH_2Cl_2 (1 mL) and the solution cooled (0−5 °C). Pyridine (0.1 mL), Ac_2O (0.1 mL), and DMAP (1 crystal) were added, and stirring at 0−5 °C was continued for 2 h. Saturated aqueous brine (5 mL) was then added, and the mixture was extracted with EtOAc (six 30-mL portions). The combined organic layers were worked up, and the crude product was purified by preparative TLC (diethyl ether) to afford 21 mg (82% yield) of tetraacetates **18** and **19** [98:2 mole ratio, respectively, by analytical HPLC (hexanes/*i*-PrOH 90:10)]: $[\alpha]^{23}_D$ −9.0° (*c* 1.1, $CHCl_3$); IR (film) 1738 cm^{-1}; ^{1}H NMR δ 5.78 (d, 1H, J = 3.4 Hz), 5.51 (dd, 1H, J = 3.4, 8.2 Hz), 5.2−5.3 (m, 1H), 4.1−4.5 (m, 4H), 2.9−3.1 (m, 2H), 2.14 (s, 3H), 2.12 (s 3H), 2.09 (s) and 2.08 (s) [6H total];^{13}C NMR δ 170.5, 169.7, 169.6, 154.7, 69.0, 68.6, 68.3, 67.0, 61.6, 35.3, 20.7, 20.6, 20.6, 20.5; HRMS (FAB) calcd for $C_{15}H_{22}NO_9$ (M + H$^+$) 360.1295, found 360.1296.

AD Reaction of Alkenyl DHI 16 Using (DHQ)$_2$−PHAL. A mixture of (DHQ)$_2$−PHAL (65 mg, 0.08 mmol), methanesulfonamide (17 mg, 0.18 mmol), $K_3Fe(CN)_6$ (143 mg, 0.43 mmol), K_2CO_3 (67 mg, 0.48 mmol), K_2OsO_4·2H_2O (4 mg, 0.01 mmol), water (0.6 mL), and *t*-BuOH (0.6 mL) was stirred for 10 min at rt. A solution of the (*E*)-alkene **16** (31 mg, 0.13 mmol) in *t*-BuOH (0.6 mL) was added, and the procedure used for the preceding (DHQD)$_2$−PHAL reaction was repeated. Preparative TLC (diethyl ether) of the crude product furnished 38.6 mg (85% yield) of mainly tetraacetate **19** [**18/19** 5:95 by analytical HPLC (hexanes/*i*-PrOH, 90:10)]: $[\alpha]^{23}_D$ +40.0° (*c* 1.4, $CHCl_3$); IR (film) 1740 cm^{-1}; ^{1}H NMR δ 5.76 (d, 1H, J = 6.4 Hz), 5.56 (dd, 1H, J = 4.5, 6.4 Hz), 5.25−5.35 (m, 1H), 4.3−4.45 (m, 3H), 4.03 (dd, 1H, J = 6.1, 11.9 Hz), 2.9−3.1 (m, 2H), 2.13 (s), 2.12 (s), 2.11 (s) [9H total], 2.06 (s, 3H); ^{13}C NMR δ 170.4, 169.9, 169.7, 169.5, 154.2, 69.5, 69.0, 68.9, 67.4, 61.7, 35.3, 20.7, 20.6; HRMS (FAB, NaBr) calcd for $C_{15}H_{21}NO_9Na$ (M + Na$^+$) 382.1114, found 382.1115.

Supporting Information Available: An ORTEP drawing of **4a** and ^{1}H NMR spectra of all new products (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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