Asymmetric Induction of Conduritols via AAA Reactions: Synthesis of the Aminocyclohexitol of Hygromycin A

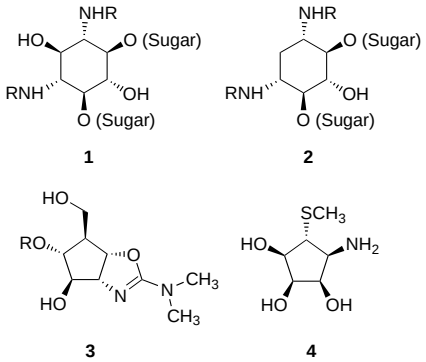
Barry M. Trost,* Joseph Dudash, Jr., and Erik J. Hembre[a]

Abstract: Two synthetic routes towards the construction of the aminocyclohexitol moiety of hygromycin A have been developed based on palladium-catalyzed asymmetric alkylation of conduritol derivatives. A protocol has been established whereby this biologically relevant molecule is formed from benzoquinone. A conduritol A derivative is synthesized in eight steps from benzoquinone and is then subjected to the palladium reaction. From this flexible intermediate, four epimers of the aminocyclitol, including the natural one, can be obtained with complete stereoselectivity. Racemic conduritol B derivatives are available in four steps from benzoquinone, and these are then made enantiomerically pure by a palladium-catalyzed dynamic kinetic resolution. From the chiral conduritol B, the aminocyclitol is available in six steps. Excellent levels of enantio- and diastereoselectivity highlight these strategies.

Keywords: amino alcohols · asymmetric catalysis · asymmetric synthesis · palladium · total synthesis

Introduction

Aminocyclitols represent a continuing and growing class of important compounds for biological function. The aminocyclohexitols represented by streptomycin [containing streptamine moiety (**1**)] and kanamycin [containing 2-deoxy-streptamine moiety (**2**)] are significant antibiotics.[1] Recently, the aminocyclopentitols represented by allosamidin [containing allosamizoline (**3**)][2] and mannostatin (**4**)[3] illustrate the five-membered ring analogues also have promise for biological applications. Developing general synthetic strategies to these families of compounds constitutes an important objective to enable a broader investigation of the utility of such compounds. Previous work in these laboratories developed a general strategy for the asymmetric synthesis of the aminocyclopentitols **3** and **4**[4] which was further improved by our ability to utilize the asymmetric allylic alkylation (AAA) reaction[5] to desymmetrize *meso*-diols with >95% *ee*.[6] In this paper, we develop two general strategies to aminocyclohexitols based upon the utilization of the AAA reaction with achiral or racemic conduritols.



Conduritols, the various diastereomers of cyclohexene tetraols, have been of interest both because of their biological activity and of their utility as building blocks.[7] For the latter to be most useful, these compounds must be accessible asymmetrically. Most approaches rely on the use of chiral pool starting materials (typically sugars) or on resolution of racemic material.[8] In the case of conduritols A and D which are *meso*-compounds, enzymatic desymmetrization has been successful.[9] A fascinating strategy employs the asymmetric microbial dihydroxylation of substituted aromatic rings.[10] An advantage of the AAA reaction is the ability to easily access either enantiomeric series simply by change of ligand. Thus, the range of applications should be significantly enhanced by such ease of defining the absolute configuration.

Hygromycin A (**5**) is a fermentation derived natural product first isolated from *Streptomyces hygroscopicus*[11] in 1953. The mode of action of hygromycin A is peptidyltransferase inhibition and the compound shares the same binding site on the ribosome as chloramphenicol.[12] It has been shown that inhibition occurs specifically by interfering with peptide bond formation, resembling chloramphenicol, and is closely related as **5** inhibits the effects of the latter. It has been

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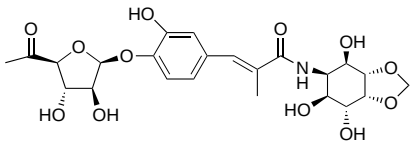


Hygromycin A
5

reported that **5** has a relatively broad spectrum of activity against Gram-positive and Gram-negative bacteria.[11a,b] Recently, **5** has attracted renewed interest due to the discovery of its hemaglutination inactivation activity[13] as well as its high antitreponemal activity,[14] especially as an effective agent for the control of swine dysentery, a mucohemorrhagic disease of economic importance to swine producers. Furthermore the antibiotic also demonstrates efficacy in the treatment of an induced dysentery infection model of swine at a level of 5–20 g per ton feed.[11b]

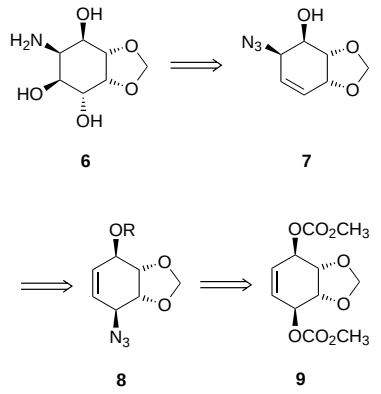
The structural studies of **5**, using a degradation method by Mann[15] and careful spectral analyses by Kakinuma,[16] revealed that it has quite a unique structure among the aminocyclohexitol antibiotic family. The cyclohexitol structure of **5**, assigned as 1L-4,5-*O*-methylene-2-amino-2-deoxy-*neo*-inositol (**6**), is much different from that of common and general cyclitols found in other aminocyclohexitol antibiotics.[1]

In spite of the unique structure and interesting biological activity of **5**, only a few reports have appeared on the synthesis of the structural components of **5**, and only one report of its total synthesis has been described. The total synthesis utilized D-glucose as the starting material for both the furanoside and cyclohexitol moieties of **5**.[17] Overall, twenty steps were necessary for the preparation of the cyclitol moiety, including a separation of a 3:2 mixture of diastereomers at a late stage in the synthesis due to an unselective dihydroxylation. Arjona and co-workers reported an improvement of a similiar dihydroxylation step, achieving a diastereoselectivity of 6:1 in favor of the natural epimer.[8e] We therefore chose the aminocyclohexitol moiety of hygromycin **6** as a target to develop asymmetric syntheses to such a family of compounds.

Results and Discussion

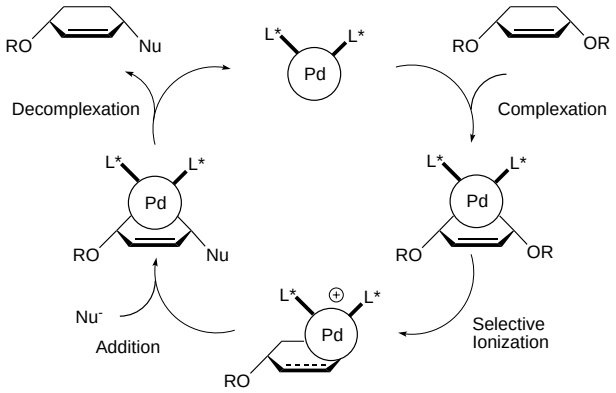
Plan A: Desymmetrization strategy

In our first approach, we envisioned the aminocyclohexitol **6** to be derived from the suitably protected hydroxy azide **7** by *trans*-dihydroxylation of the cyclohexene (Scheme 1). This compound would be obtained from the palladium-catalyzed desymmetrization of the dicarbonate derivative of conduritol A **9** using an azide nucleophile to give **8** followed by [3,3]-sigmatropic rearrangement of the allylic azide.[18, 19] Advantages of this approach include the ability to set the relative stereochemistry of four chiral centers before asymmetry is induced, to obtain either enantiomer from the palladium reaction, to access different regioisomeric aminocyclohexitols, and to access a variety of such compounds by differential functionalization of the double bond.



Scheme 1. Retrosynthetic analysis.

The ability to discriminate between two prochiral centers of a *meso*-compound in an allylic alkylation reaction has been made possible by the use of C_2-symmetric ligands chelated to a palladium(0) source developed in these laboratories.[6] The mechanism for the allylic alkylation of a cyclic substrate is shown in Scheme 2. The enantiodiscriminating step occurs



Scheme 2. Conceptualization of the palladium-catalyzed desymmetrization.

when the catalyst selectively ionizes one of the two possible enantiotopic allylic esters, depending on the chirality of the ligand. The energy difference between the two diastereomeric transition states arising from the steric interactions between the leaving group and the phenyl rings on phosphine accounts for the enantioselectivity.

The conduritol A derivative **10**, previously available to us from our work directed toward the total synthesis of pancratistatin,[18] was a logical choice of precursor to acetal **9** by simple exchange of the acetonide for the methylenedioxy unit. Surprisingly, all attempts to convert the diol **11** to acetal **9** failed in contrast to the facility of acetonide formation. The only identifiable formaldehyde adduct is the diadduct **12** which was obtained only in 18% yield in the presence of Montmorillonite clay (Scheme 3). A more efficient synthesis would install the methylenedioxy unit early, in lieu of the acetonide (see Scheme 4). Thus, the diol **13a** was dihydroxylated to give tetraol **14a** as previously described.[20]

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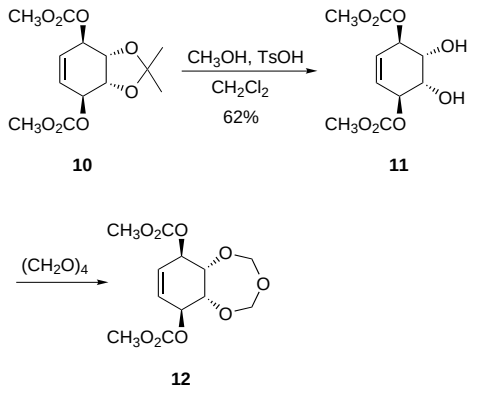
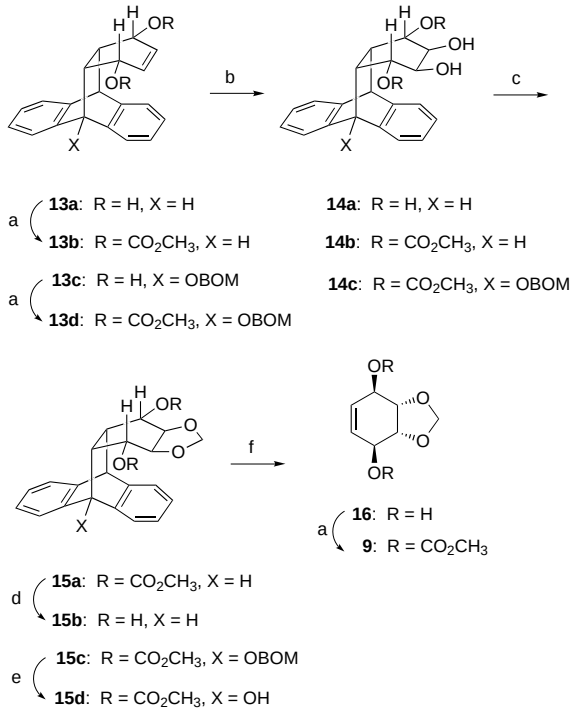


Scheme 3. Formaldehyde adduct side reaction.

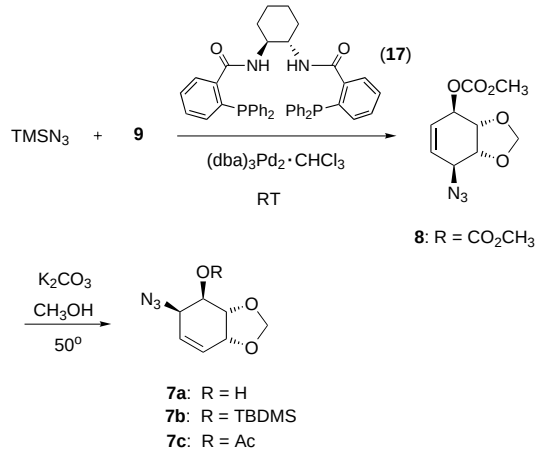


Scheme 4. Synthesis of conduritol A substrate **9**: a) *n*-C_4H_9Li, $ClCO_2$, CH_3, THF, 0 °C. b) OsO_4, NMO, THF, *t*-C_4H_9OH, H_2O or CH_2Cl_2, H_2O, RT. c) $CH_3OCH_2OCH_3$, $TMSOSO_2CF_3$, 2,6-lutidine, 0 °C, RT. d) K_2CO_3, CH_3OH, RT. e) TsOH, CH_3OH, RT. f) FVT, 500 °C.

While chemoselective formation of the acetonide of **14a** occurred nearly quantitatively, formation of the methylenedioxy derivative **15b** simply failed. On the other hand, the differentiated tetraol derivative **14b**, obtained from *cis*-dihydroxylation of **13b** in 69% yield which, in turn derived from diol **13a** in 90% yield, smoothly gave the desired methylenedioxy compound **15a** in 91% yield. Unfortunately, attempted direct thermolysis of **15a** to form **9** failed. However, the diol **15b** readily obtained by simple base hydrolysis in 82% yield smoothly underwent retro-Diels–Alder reaction to produce diol **16** in 73% yield which is converted to the required dicarbonate in 81% yield under standard conditions.

The decomposition of the dicarbonate **15a** under FVT conditions was envisioned to derive from the high temperatures required. If a low temperature retro-Diels–Alder reaction could be performed, the need to remove the carbonate might be avoided. Taking advantage of the known charge accelerated retro-Diels–Alder reaction which may occur even at room temperature,[21] the diol **13c** was converted in completely analogous fashion through **13d**–**14c** (51% for two steps) and **15c** into the desired precursor **15d** (68% for two steps). Oxy-anion accelerated retro-Diels–Alder reaction was thwarted by migration of the carbonate to the bridgehead alcohol under base conditions.

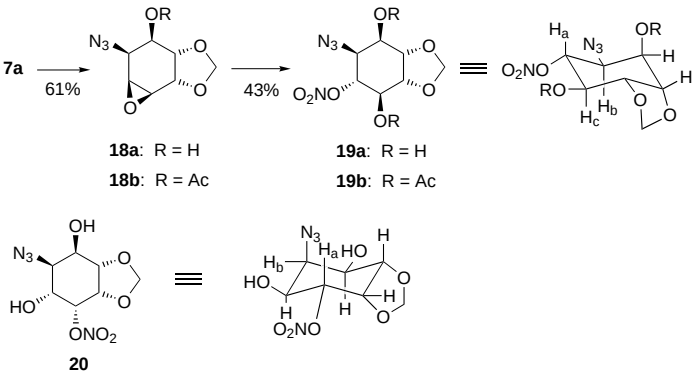
With the requisite substrate **9** in hand, the palladium-catalyzed substitution with azide was pursued as shown in Scheme 5. The initial product **8** was directly hydrolyzed in



Scheme 5. Palladium-catalyzed substitution.

basic methanol at 50 °C to give hydroxy azide **7a** in 70% yield. Using the cyclohexyl ligand **17**, chiral HPLC analysis indicated the *ee* of **7a** to be 93%. Silylation of the alcohol proceeded readily under standard conditions to give silyl ether **7b** in 73% yield.

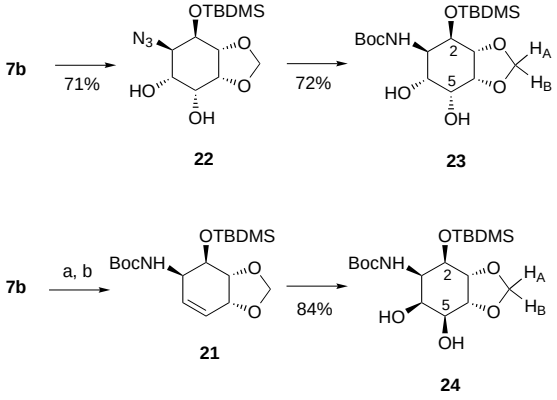
The next stage requires a diastereoselective *trans* dihydroxylation of the double bond. The first strategy envisioned a diastereoselective epoxidation from the β face and a regioselective ring opening being dictated by the electronics of the neighboring substituents. Epoxidation of **7a** with trifluoroperacetic acid[22] proceeded slowly but diastereoselectively to form a single epoxide assigned as β, that is **18a** (Scheme 6).



Scheme 6. Diastereoselective epoxidation of **7a**.

On the other hand, the acetate **7c** failed to react under the same conditions. This observation suggests hydroxy participation in the epoxidation which would direct the stereochemistry to give the depicted product. When the corresponding acetate **18b** was subjected to conditions to open the epoxide, acetate removal occurred first with no further reaction observed. The hydroxy epoxide **19a** proved resistant to ring opening with carboxylate nucleophiles. On the other hand, tetra-*n*-butylammonium nitrate did lead to ring opening in the presence of boron trifluoride/etherate. The proton, H_a, adjacent to the nitrate appeared as a double doublet with $J =$ 9.1 and 8.5 Hz showing coupling to the proton, H_b, adjacent to azide at $\delta = 3.20$. The large vicinal couplings to both adjacent hydrogens also indicate a *trans,trans* relation as in **19** but not **20**. The ^{1}H NMR spectrum of the corresponding acetate **19b** shows H_a ($\delta = 5.37$) as a double doublet with $J = 9.6$ and 9.3 Hz coupled to H_b ($\delta = 3.47$, dd, $J = 9.2$, 3.2 Hz) and H_c ($\delta =$ 5.28, dd, $J = 9.6$, 7.3 Hz) consistent with **19b** but not **20**. Thus, the neighboring oxygen of the methylenedioxy ring rather than the azide group controls the regioselectivity of the ring opening.

An alternative strategy envisions regio- and diastereoselective delivery of oxygen by electrophilic initiated cyclization of the carbamate **21** (available by a Staudinger reduction) but to no avail.[23] Dihydroxylation of azide **7b** using catalytic osmium tetraoxide in moist methylene chloride gave a single diol **22** (Scheme 7). Catalytic hydrogenation in the presence

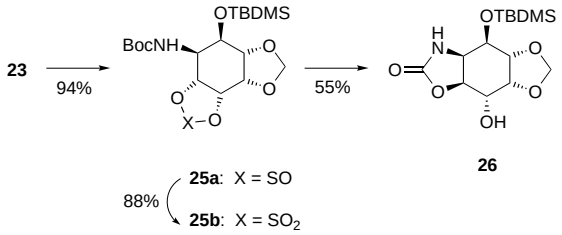


Scheme 7. Reductive amine protection. a) $(CH_3)_3P$, H_2O (96%). b) Boc_2O (84%).

of Boc anhydride gave the carbamate **23** as a single isomer. On the other hand, dihydroxylation of the carbamate **21** also gave a single isomer **24** which was different from that obtained above (see Scheme 7). Previous work suggested a simple method to determine stereochemistry at C-2 and C-5 based upon the chemical shifts of the methylenedioxy protons H_A and H_B. When the groups at C-2 and C-5 are *cis*, the absorptions for H_A and H_B are typically around $\delta = 5.0$ and $\delta = 5.3$ with $\Delta\delta < 0.3$. When the groups are *trans*, the chemical shifts are around $\delta = 4.8$ and $\delta = 5.3$ with $\Delta\delta > 0.4$. In the case of diol **23**, the observed shifts are $\delta = 5.27$ and 4.82 ($\Delta\delta = 0.45$) and for diol **24** the observed shifts are $\delta = 5.19$ and 5.02 ($\Delta\delta =$ 0.17). These shifts are in accord with the assigned structures as depicted. Ultimate conversion of **23** to the aminocyclohexitol of hygromycin confirms this assignment.

The dramatic difference in facial selectivity by choice of nitrogen substituent cannot be understood on the basis of conformational analysis. Steric effects would appear to be dominated by the methylenedioxy group which would favor β attack as observed with **21**. In this sense, the unusual diastereoselectivity derives from the reaction of the azide **7**. In this case, an orbital distortion argument would seem appropriate,[24] that is the azide group would distort the π-system to favor electrophilic attack *anti* to itself as observed. The dramatic difference makes further investigation of this phenomenon highly worthwhile.

The synthesis of the diastereomer of the aminocyclohexitol of hygromycin requires inversion at C-6 of diol **23**. The completion of the synthesis is illustrated in Scheme 8.

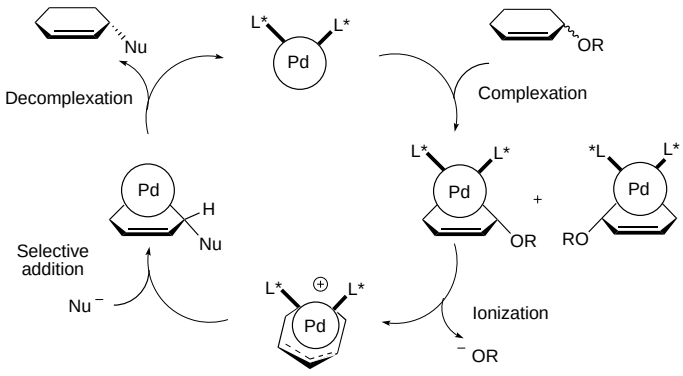


Scheme 8. Cyclization yielding oxazolidinone **26**.

Exposure to thionyl chloride ($(C_2H_5)_3N$, THF, 0 °C) forms the cyclic sulfite **25a** which proved too unreactive to cyclize to the oxazolidinone **26**. On the other hand, standard oxidation ($NaIO_4$, $RuCl_3 \cdot 3H_2O$, H_2O, CH_3CN, CCl_4)[25] gave the cyclic sulfate which did cyclize in THF at 50 °C to give the desired oxazolidinone **26**.

Plan B: Dynamic kinetic asymmetric transformation of conduritol B

A second strategy emanates from a conceptually different process of asymmetric induction as illustrated in Scheme 9. In this process, a racemic substrate is converted to an



Scheme 9. Conceptualization of a dynamic kinetic asymmetric transformation.

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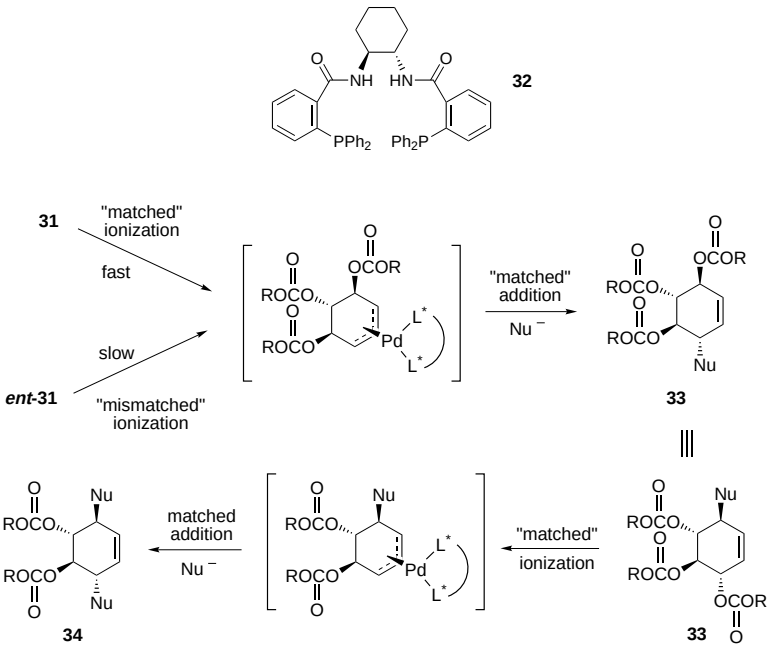
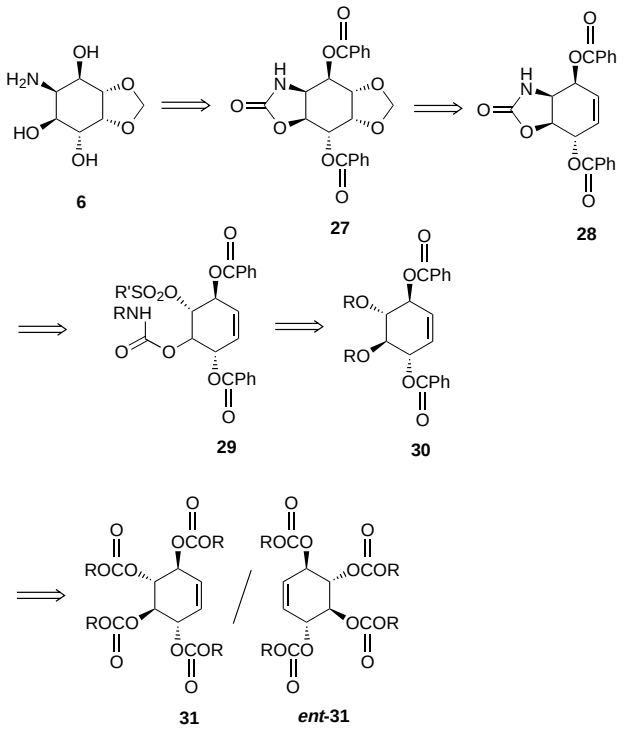
intermediate which is formally a *meso* complex thereby losing the stereochemical identity of the precursor.[5, 26] Asymmetric induction occurs in the nucleophilic addition step. For this process, conduritol B tetraesters **31**/***ent*-31**[27, 28] become the starting materials as depicted in the retrosynthetic analysis of Scheme 10.

This analysis raises the interesting question of the effect of the symmetry of **31**/***ent*-31** on a dynamic kinetic asymmetric transformation (DYKAT) reaction. As depicted in Scheme 11 with a given ligand such as *S*,*S*-isomer **32**, ionization of **31** constitutes an energetically favorable process (i.e., a "matched" event); whereas that of ***ent*-31** is a disfavored one (i.e., a "mismatched" event). Indeed, the energy differences between the matched and mismatched events is sufficient that a nearly perfect kinetic resolution may be achieved. Interestingly, the product of the kinetic resolution, **33**, still possesses an allylic ester with the same orientation with respect to the double bond as that in **31**. Thus, its ionization also constitutes a "matched" event. The result may be a double substitution to form **34**. If a carboxylate nucleophile is employed, the formation of enantiomerically pure tetraester product **34** is equivalent to a deracemization of conduritol B tetracarbonate accompanied by simultaneously differentiation of the allylic esters from the non-allylic esters. Such a process then allows formation of **30** (R = H, Scheme 10) which sets the stage through **29** for formation of the requisite *cis* vicinal aminoalcohol **28** and thus completion of an efficient approach to the aminocyclohexitol.

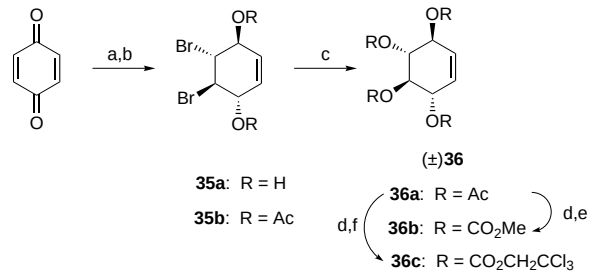


Scheme 11. Deracemization reaction of conduritol B tetracarbonate.



Scheme 10. Retrosynthetic analysis through DYKAT reaction of conduritol B.

Racemic conduritol B tetraacetate (±)-**36** was obtained using a modification (Scheme 12) of the method reported by Guo et al.[26b] Guo et al. had reported that the diacetoxydibromide **35b**, available from *p*-benzoquinone in three steps,

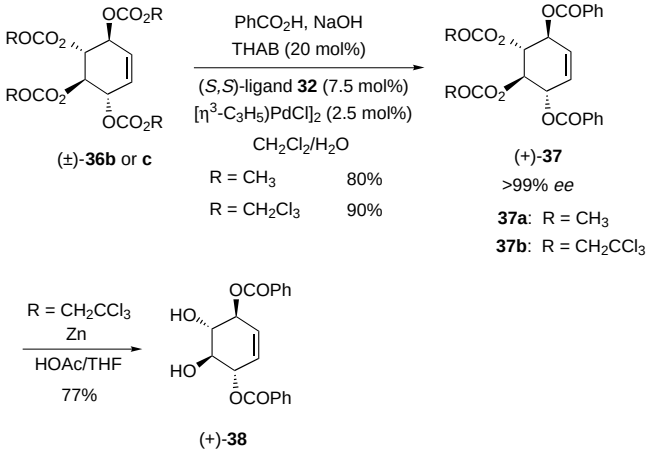


Scheme 12. Synthesis of conduritol B derivative **36** from *p*-benzoquinone: a) Br_2, CH_2Cl_2, 76%. b) $NaBH_4$, H_2O/Et_2O, 82%. c) Ac_2O, K_2CO_3, 0 °C → RT; then HOAc, reflux, 71%. d) $(C_2H_5)_3N$, $MeOH/H_2O$, 100%. e) $ClCO_2CH_3$; pyridine, DMAP, CH_2Cl_2, 93%. f) $ClCO_2CH_2CCl_3$, pyridine, DMAP, CH_2Cl_2, 90%.

could be converted to (±)-**36a** by heating with potassium acetate and acetic anhydride in refluxing acetic acid. We found that **35b** could be generated in situ by adding potassium carbonate to a suspension of the diol-dibromide **35a**[30, 31] in acetic anhydride. Addition of acetic acid to this mixture followed by warming to reflux then led to formation of (±)-**36**. Using this route, (±)-**36** could be prepared in 44% yield over

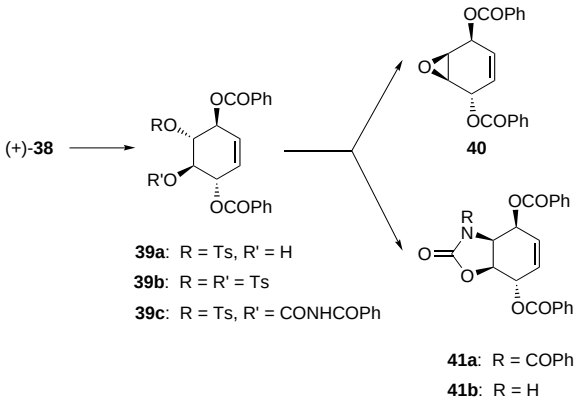
three steps from *p*-benzoquinone in relatively large amounts (>20 g in a single run). A further benefit of this route was that no chromatographic purifications were required since the intermediates and (±)-**36** were readily crystallized solids.

When the racemic tetraacetate (±)-**36a** was submitted to the palladium-catalyzed reaction with carboxylate nucleophiles in the presence of the *R*,*R* isomer of the chiral ligand **32** an excellent kinetic resolution was observed, however, greater than 50% conversion of the starting material was difficult to obtain due to the relative inactivity of the "mismatched" enantiomer of the racemic tetraacetate starting material. By simply converting the tetraacetate to the more reactive tetra(methylcarbonate) derivative **36b** a dynamic kinetic asymmetric transformation was realized using benzoate as the nucleophile, yielding the dibenzoate **37a** in 80% yield and >99% *ee* (see Scheme 13). Selective cleavage of the methyl carbonate groups in the presence of the benzoates to provide the diol **38** proved difficult. Replacing the methyl carbonate groups in **36b** with 2,2,2-trichloroethyl carbonates gave **36c** (see Scheme 12) which also reacted smoothly in the palladium-catalyzed reaction to give the dibenzoate **37** in excellent yield and >99% *ee* (see Scheme 13). The trichloroethyl carbonate groups could now be easily cleaved in the presence of the benzoates by simply treating with zinc metal and acetic acid to give the desired conduritol B 2,3-diol **38** in 77% yield.



Scheme 13. Selective deprotection.

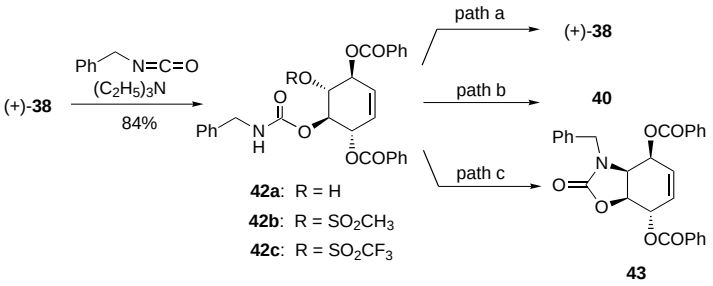
Installation of the amino functionality of **6** envisioned an N-alkylative cyclization of a suitable carbamate. Initial attempts to selectively activate one of the hydroxy groups of **38** by conversion to the mesylate or tosylate met with mixed results. Generally, mixtures of mono- and di-sulfonylation were observed in ratios that varied from experiment to experiment. Under the best conditions (TsCl, DMAP, CH_2Cl_2, 0°C), yields of a monotosylate **39a** were as high as 67% with the bis-tosylate **39b**, a significant by-product (16–20%), see Scheme 14. The crude mixture was treated directly with benzoylisocyanate to give the imide **39c** in a 67% overall yield from diol **38**. Curiously, treatment of the tosylate **39c** with DBU in THF (room temperature to reflux) gave only the epoxide **40** in 68% yield. This product arises by loss of benzoylisocyanate to form an alkoxide which simply cyclizes



Scheme 14. Hydroxy group activation.

to form **40**. Initial success for forming the oxazolidinone was observed with sodium hydride in THF (0°C to reflux). While the expected *N*-benzoyloxazolidin-2-one (**41a**) was not observed, the more satisfactory debenzoylated derivative **41b** was obtained in 34% yield. Use of sodium hexamethyldisilamide proved more satisfactory but the maximum yield > was still only 52%.

A more satisfactory solution was devised when we discovered that treatment of the diol (+)-**38** with benzylisocyanate provided the mono-carbamate **42** in consistently good yield (Scheme 15) with only minor amounts of the dicarbamate and



Scheme 15. Successful oxazolidinone cyclization (path c).

recovered diol. An attempt to cyclize this hydroxy carbamate directly under Mitsunobu conditions (DIAD, PPh_3) only led to cleavage of the carbamate and return of the diol **38** (path a). An attempt at oxazolidinone formation involving cyclizing the mesylate **42b** with sodium hydride led to carbamate elimination and formation of the epoxide **40** (path b).

The key to forming the oxazolidinone was the combination of the use of a more reactive leaving group and a hydroxide free base. Thus, reaction of the mono-carbamate **42a** with triflic anyhdride, followed by treatment of the crude triflate **42c** with potassium bis(trimethylsily)amide at low temperature (−40°C) provided the desired benzyl oxazolidinone **43** in a gratifying 70% yield over the two steps (path c).

The remainder of the aminocylitol synthesis was relatively straightforward as summarized in Scheme 16. Dihydroxylation of **43** with catalytic osmium tetraoxide occurred predominantly from the convex side of the bicyclic alkene (greater than 10:1 diastereoselectivity) to provide the desired diol **44**

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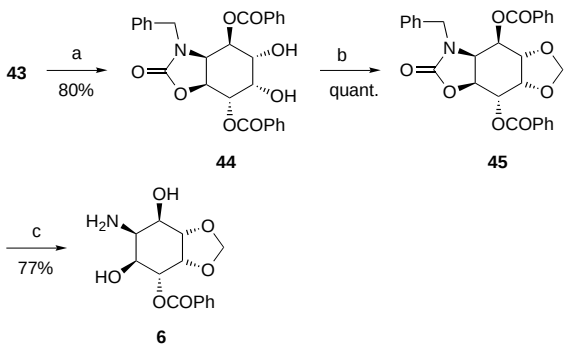

Scheme 16. Final stage of the hygromycin aminocyclitol synthesis: a) OsO_4, NMO, THF, H_2O, RT. b) $CH_3OCH_2OCH_3$, CF_3SO_3TMS, 2,6-lutidine, 0 °C → RT. c) Li, NH_3, THF, −78 to −33 °C then H_2O, −78 °C to reflux.

in 80% yield. Conversion of the diol to the methylene acetal **45** proceeded quantitatively using dimethoxymethane and trimethylsilyl triflate. Final deprotection of the benzyl amine, the benzoate esters, and the oxazolidinone was accomplished in a single step using lithium/ammonia followed by an aqueous quench and warming to reflux. Purification by ion-exchange chromatography (Amberlite IRC-76, H^+ form) provided the desired amino-triol **6** in 77% yield. Comparison of the data for **6** to that of a known sample indicated their identity.

The conduritol B approach to the hygromycin aminocyclitol was performed in 23% overall yield requiring 10 steps from the readily available racemic conduritol B tetraacetate **36a**. The highlight of the synthesis was the dynamic kinetic asymmetric transformation of the racemic tetracarbonate **36c** into the dibenzoate (+)-**37b** in 90% yield and 99% *ee*. A further benefit of this synthesis was the fact that all of the compounds except **43** and **6** were solids that were purified by crystallization.

Conclusion

The AAA reaction constitutes a potentially powerful tool in asymmetric synthesis because of the diverse mechanisms for asymmetric induction. The conduritols illustrate the potential. Conduritol A, a *meso* compound, can be desymmetrized; whereas, conduritol B, a chiral compound that generates an achiral π-allyl complex, can be "deracemized" by a dynamic kinetic asymmetric transformation. Both conduritols, the latter as a racemate, are readily available from *p*-benzoquinone. Thus, great flexibility derives from the resultant relative stereochemistry and the differential functionality for further elaboration. These points are nicely illustrated by the synthesis of the hygromycin aminocyclohexitol.

When starting from the *meso*-conduritol A derivative, the methylene acetal, which is critical for biological activity, is already in place, while the introduction of a nitrogen synthon and asymmetric induction occur in a single operation. Using an azide as a nucleophile allows ready access to two different regioisomeric products taking advantage of a [3.3]-sigmatropic rearrangement of an allylic azide. The utility of this aspect is clearly demonstrated in that one regioisomer led to pancratistatin and the other to the aminocyclohexitols herein. Further, from this latter allylic azide, four different epimers of the aminocyclitol moiety can be accessed with complete stereoselectivity. Such flexibility lends itself to the possibility of synthesizing other analogues for biological evaluation. When beginning with racemic conduritol B, an advantage is the ease of obtaining the substrate since gram quantities are readily available in three steps from *p*-benzoquinone. Upon formation of enantiomerically pure conduritol B in a complex palladium-catalyzed dynamic kinetic resolution, the system can be manipulated in a straightforward, seven-step sequence to give the desired natural product. Both routes circumvent the need for starting from the chiral pool as is typical in most reported aminocyclitol syntheses and, thus, allow for the opportunity to easily obtain either enantiomer of the natural product by simply changing the ligand. These findings should lead to expanding the use of palladium-catalyzed asymmetric alkylation reactions in the synthesis of cyclohexitols and other carbohydrate derivatives.

Experimental Section

General methods: NMR spectra were recorded at room temperature using either a Varian Gemini-300, Gemini-200, or EM-400 instrument. IR spectra were recorded on a Perkin–Elmer FT-IR as neat films on NaCl plates or as KBr pellets for solid products. Mass spectra were recorded by the Mass Spectrometer Facility of the School of Pharmacy, University of California, San Francisco. Optical rotations were measured with a Jasco DIP-360 digital polarimeter. Microanalyses were performed by M-H-W Laboratories, Phoenix AZ. Melting points were not corrected.

Reactions were generally conducted under a positive pressure of dry argon or nitrogen in flame-dried glassware. THF was distilled from sodium/benzophenone. Methylene chloride and acetonitrile were distilled from calcium hydride. Methanol and ethanol were distilled from magnesium methoxide and magnesium ethoxide, respectively. Acetone was distilled from calcium sulfate. Common reagents and materials were purchased from commercial sources and purified by distillation or recrystallization. Anhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. Flash chromatography employed ICN silica gel (Kieselgel 60, 230–400 mesh), analytical TLC was performed with 0.2 mm silica-coated glass plates (E. Merck, DC-Platten Kieselgel 60 F_{254}).

1,4-Bis(methoxycarboxy)-1β,4β,4aβ,9α,9aβ,10α-hexahydro-9,10[1′,2′]-benzenoanthracene (13b): *n*-Butyllithium (1.4 M in hexanes, 64 mmol, 2.2 equiv) was added dropwise to a solution of diol **13a** (8.4 g, 29 mmol, 1 equiv) in THF (530 mL) at 0 °C. The slurry was stirred at 0 °C for 30 min, then at room temperature for 30 min. The mixture was recooled to 0 °C, at which point methyl chloroformate (10.9 g, 116 mmol, 4 equiv) was added dropwise. The reaction was stirred at room temperature for 1 h, diluted with ethyl acetate, washed with saturated ammonium chloride solution and brine, dried ($MgSO_4$) and evaporated in vacuo. The dicarbonate **13b** (10.77 g, 90%) was obtained as a white solid. M.p. 167–169 °C (decomp); IR (neat): $\tilde{\nu}$ = 1749, 1442, 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2H), 7.22–7.19 (m, 2H), 7.11–7.04 (m, 4H), 5.14 (d, J = 5.5 Hz, 2H), 4.84 (s, 2H), 4.43 (s, 2H), 3.89 (s, 6H), 2.86 (d, J = 6.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.4, 143.8, 141.6, 126.4, 126.1, 124.8, 124.3, 123.7, 73.3, 55.0, 44.2, 40.9; HRMS: calcd for $C_{24}H_{22}O_6$ $[M]^+$: 406.1416; found: 406.1397.

1,4-Bis(methoxycarboxy)-2,3-dihydroxy-(1β,2α,3α,4β,4aβ,9α,9aβ,10α)-octahydro-9,10[1′,2′]-benzenoanthracene (14b): NMO (5.4 g, 39.6 mmol, 1.5 equiv) followed by osmium tetroxide (4% solution in water, 0.4 mL, 2.5 mol%) was added to a solution of olefin **13b** (10.77 g, 26.4 mmol, 1 equiv) in THF (100 mL), *tert*-butanol (49 mL), and water (26 mL). The reaction was stirred for 16 h at room temperature. A 15% aqueous sodium bisulfite solution was added and the mixture stirred for 1 h. The reaction was diluted with ethyl acetate and the aqueous layer was washed with ethyl

acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. After column chromatography on silica gel (50% ethyl acetate/pentane) followed by precipitation of the resulting oil with diethyl ether, diol **14b** (7.2 g, 69%) was produced as a white solid. M.p. 160–162 °C; IR (neat): $\tilde{\nu}$ = 3468, 1750, 1443, 1266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37 (dd, J = 5.5, 3.2 Hz, 2H), 7.26 (dd, J = 5.1, 3.5 Hz, 2H), 7.14 (dd, J = 5.5, 3.2 Hz, 2H), 7.08 (dd, J = 5.4, 3.2 Hz, 2H), 4.95–4.90 (m, 2H), 4.52 (s, 2H), 3.88 (s, 6H), 2.95 (app t, J = 5.3 Hz, 2H), 2.87 (d, J = 4.5 Hz, 2H), 2.79 (app t, J = 2.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.7, 143.2, 142.0, 127.4, 126.5, 125.8, 123.7, 79.1, 66.2, 55.4, 43.7, 39.9; HRMS: calcd for $C_{24}H_{24}O_8$ $[M]^+$: 440.1453; found: 440.1471.

1,4-Bis(methoxycarboxy)-2,3-methylenedioxy-(1*β*,2*α*,3*α*,4*β*,4a*β*,9*α*,9a-*β*,10*α*)-octahydro-9,10[1′,2′]-benzenoanthracene (15a): 2,6-Lutidine (3.68 g, 35.5 mmol, 2.3 equiv) followed by trimethylsilyl trifluoromethanesulfonate (13.8 g, 63 mmol, 4.1 equiv) was added dropwise at 0 °C to a solution of diol **14b** (6.7g, 15.41 mmol, 1 equiv) in dimethoxymethane (114 mL). The reaction was stirred at room temperature for 1.5 h, then quenched with saturated $NaHCO_3$. The reaction was diluted with ethyl acetate, the organic layer was washed with 1N sodium hydrogen sulfate and brine, dried ($MgSO_4$), and evaporated in vacuo. Methylene acetal **15a** (6.3 g, 91%) was obtained as a white solid. M.p. 220–221 °C; IR (neat): $\tilde{\nu}$ = 2958, 1751, 1442, 1264, 1166, 1082, 996, 973, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40 (dd, J = 5.4, 3.26 Hz, 2H), 7.26 (dd, J = 5.3, 3.15 Hz, 2H), 7.17 (dd, J = 5.4, 3.2 Hz, 2H), 7.08 (dd, J = 5.4, 3.2 Hz, 2H), 4.99–4.94 (m, 2H), 4.82 (s, 1H), 4.54 (s, 1H), 4.52 (s, 2H), 3.89 (s, 6H), 3.22 (dd, J = 7.2, 1.9 Hz, 2H), 2.85 (app t, J = 2.4 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.2, 143.3, 141.9, 127.1, 126.2, 125.7, 123.6, 92.6, 75.9, 74.5, 55.1, 43.5, 40.5; HRMS: calcd for $C_{25}H_{24}O_8$ $[M]^+$: 452.1471; found: 452.1474.

1,4-Dihydroxy-2,3-methylidene-(1*β*,2*α*,3*α*,4*β*,4a*β*,9*α*,9a*β*,10*α*)-octahydro-9,10[1′,2′]-benzenoanthracene (15b): K_2CO_3 (5.22 g, 37.2 mmol, 2.5 equiv) was added at room temperature to a solution of dicarbonate **15a** (6.75 g, 15 mmol, 1 equiv) in methanol (50 mL) and methylene chloride (50 mL). The reaction mixture was stirred for 4 h, the solid was removed by filtration, and the filtrate was evaporated in vacuo. After column chromatography on silica (60% ethyl acetate/pentane), the diol **15b** (4.1 g, 82%) was obtained as a white solid. M.p. 211–212 °C; IR (KBr): $\tilde{\nu}$ = 3418, 3020, 2918, 2850, 1466, 1164, 1091, 1066, 978, 902, 751 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.32–7.26 (m, 4H), 7.11–7.09 (m, 2H), 7.06–7.02 (m, 2H), 5.31 (d, J = 4.1 Hz, 2H), 4.67 (br s, 3H), 4.36 (s, 1H), 3.73 (br s, 2H), 2.74 (d, J = 7.0 Hz, 2H), 2.36 (br s, 2H); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 145.1, 143.3, 125.9, 125.4, 125.3, 123.2, 91.1, 77.2, 67.8, 43.1, 43.0; elemental analysis calcd (%) for $C_{21}H_{20}O_4$+0.5 H_2O: C 73.02, H 6.13; found: C 73.21, H 6.20.

1,4-Bis(methoxycarboxy)-2,3-methylenedioxy-(1*α*,2*β*,3*β*,4*α*)-cyclohex-5-ene (9): The diol **15b** (605 mg, 0.82 mmol, 1 equiv) was flash vacuum thermolyzed (500 °C, 0.025 mmHg) to yield a mixture of anthracene and the desired diol **16**. After column chromatography on silica gel (50% ethyl acetate/pentane), the diol **16** (208 mg, 73%) was obtained as a white solid. M.p. 111–112 °C; IR (neat): $\tilde{\nu}$ = 3386, 1642, 1377 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 5.67 (s, 2H), 5.07 (s, 1H), 4.86 (s, 2H), 4.83 (s, 1H), 4.10 (d, J = 3.8 Hz, 2H), 3.91 (d, J = 3.0 Hz, 2H); ^{13}C NMR (75.5 MHz, CD_3OD): δ = 132.0, 95.1, 81.2, 70.5.

n-Butyllithium (6.85 mL, 2.5M in hexanes, 2.2 equiv) was added dropwise to a solution of diol **16** (1.22 g, 7.72 mmol, 1 equiv) in THF (33 mL). The slurry was stirred at 0 °C for 10 min, then at room temperature for 20 min. The mixture was recooled to 0 °C and methyl chloroformate (2.93 g, 30.8 mmol, 4 equiv) was added. The reaction was stirred at room temperature for 2 h, then diluted with ethyl acetate. The organic layer was washed twice with water then brine, dried ($MgSO_4$), and evaporated in vacuo. After column chromatography on silica gel (30% ethyl acetate/petroleum ether), biscarbonate **9** (1.71 g, 81%) was obtained as a white solid. M.p. 89–90 °C; IR (neat): $\tilde{\nu}$ = 2960, 2862, 1755, 1447, 1326, 1254, 1086, 1009, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.81 (s, 2H), 5.19 (d, J = 4.1 Hz, 2H), 5.14 (s, 1H), 4.91 (s, 1H), 4.20 (d, J = 4.6 Hz, 2H), 3.82 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.2, 127.8, 94.5, 75.5, 73.9, 55.1; HRMS: calcd for $C_9H_{11}O_6$ $[M - C_2H_3O_2]^+$: 215.0556; found: 215.0548.

(1*R*,3*R*,4*R*,5*R*)-5-Azido-4-hydroxy-3a,4,5,7a-tetrahydrobenzo-[1,3]-dioxole (7a): Dicarbonate **9** (390 mg, 1.4 mmol, 1 equiv) in THF (10 mL) was added to a degassed (Ar) solution of tris(dibenzylideneacetone)dipalladium-(chloroform) (14 mg, 0.014 mmol, 1 mol%) and the *S*,*S*-cyclohexyl ligand **17** (39 mg, 0.059 mmol, 4 mol%) in THF (1.4 mL). After 10 min, freshly distilled trimethylsilyl azide (232 mg, 2.1 mmol, 1.5 equiv) was added and the reaction stirred for 6 h. The unreacted starting material (52 mg, 15%) was separated from the desired product by chromatography on silica gel (15% ethyl acetate/pentane). The resulting product oil was dissolved in methanol (5 mL) and K_2CO_3 (58 mg, 0.42 mmol, 40 mol%) was added. The mixture was heated at 50 °C for 48 h, the solid was collected by filtration, and the filtrate was concentrated in vacuo. After column chromatography on silica gel (30% ethyl acetate/pentane) of the resulting oil, the azido alcohol **7a** (127 mg, 56% two steps; 70% yield based on recovered starting material) was obtained as a clear oil. $[\alpha]_D^{20} = -318.44°$ (c = 2.06, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3447, 2106, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.02 (ddd, J = 10.0, 3.4, 0.9 Hz, 1H), 5.93 (dd, J = 10.0, 4.6 Hz, 1H), 5.04 (s, 1H), 4.92 (s, 1H), 4.55 (dd, J = 6.3, 3.3 Hz, 1H), 4.24 (app t, J = 6.6 Hz, 1H), 4.13 (app t, J = 4.0 Hz, 1H), 4.04 (dd, J = 7.1, 3.8 Hz, 1H), 2.92 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 127.9, 126.9, 94.4, 75.0, 72.2, 69.9, 57.9; HRMS: calcd for $C_7H_9N_3O_3$ $[M]^+$: 182.0565; found: 182.0564. Enantiomeric excess 93% determined by HPLC [Chiralcel AD column, eluting with 96:4 heptane/*i*PrOH, 1 mL min^{-1}: major enantiomer t_R = 25.5 min, minor enantiomer t_R = 28.6 min].

(1*R*,3*R*,4*R*,5*R*)-5-Azido-4-*tert*-butyldimethylsiloxy-3a,4,5,7a-tetrahydro-benzo-[1,3]-dioxole (7b): 2,6-Lutidine (0.21 g, 1.81 mmol, 3.4 equiv) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.28 g, 1.11 mmol, 2.1 equiv) was added to alcohol **7a** (100 mg, 0.54 mmol, 1 equiv) in methylene chloride (0.54 mL) at 0 °C. The reaction was stirred for 1.5 h at room temperature, then diluted with methylene chloride. The organic layer was extracted with 1N sodium hydrogen sulfate, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated in vacuo. After column chromatography on silica gel (15% ethyl acetate/pentane), silyl ether **31** was obtained as a clear oil (116 mg, 73%). $[\alpha]_D^{25} = -135.18°$ (c = 1.19, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 2954, 2858, 2102, 1472, 1256, 1128, 906, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.95–5.87 (m, 2H), 4.97 (s, 1H), 4.92 (s, 1H), 4.55 (dd, J = 5.7, 1.8 Hz, 1H), 4.18 (app t, J = 6.4 Hz, 1H), 4.10 (dd, J = 6.4, 2.0 Hz, 1H), 3.89 (app s, 1H), 0.89 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 127.6, 127.2, 94.2, 75.5, 72.3, 71.6, 58.1, 25.6, 17.9, −4.91, −5.20; elemental analysis calcd (%) for $C_{13}H_{23}N_3Si$: C 52.50, H 7.79, N 14.13; found: C 52.39, H 7.60, N 14.06.

(1*R*,3*R*,4*R*,5*R*,6*R*,7*R*)-4-*tert*-Butyldimethylsiloxy-5-*tert*-butyloxycarbonyl-amino-6,7-dihydroxy-1,3,4,5,6,7-hexahydrobenzo[1,3]dioxole (23): NMO (63 mg, 0.53 mmol, 1.5 equiv) followed by osmium tetroxide (4% solution in water, 0.2 mL, 0.018 mmol, 5 mol%) was added to a solution of olefin **7b** (106 mg, 0.36 mmol, 1 equiv) in methylene chloride (3.6 mL) at room temperature. The reaction was stirred for 16 h, then concentrated in vacuo and chromatographed on silica gel (50% ethyl acetate/pentane) to give the diol **23** (84 mg, 71%) as a clear oil. IR (neat): $\tilde{\nu}$ = 3441, 2106, 1472, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.20 (s, 1H), 4.84 (s, 1H), 4.22–4.18 (m, 2H), 4.13–4.06 (m, 2H), 4.03 (app t, J = 6.8 Hz, 1H), 3.81 (dd, J = 6.4, 2.2 Hz, 1H), 3.21 (br s, 1H), 3.08 (br s, 1H), 0.88 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 95.2, 77.5, 76.3, 70.3, 69.7, 66.8, 64.0, 25.6, 17.9, −4.98, −5.2.

A suspension of palladium on carbon (10%, 7.2 mg) in ethyl acetate (0.7 mL) was stirred under an atmosphere of hydrogen at room temperature for 20 min. A solution of di-*tert*-butyl dicarbonate (65 mg, 0.3 mmol, 1.2 equiv) and azide **22** (83 mg, 0.25 mmol, 1 equiv) in ethyl acetate (0.7 mL) was then added and the reaction stirred for 22 h. The mixture was diluted with ethyl acetate, filtered through celite, and evaporated in vacuo. After column chromatography on silica gel (50% ethyl acetate/pentane), carbamate **23** was obtained as a clear oil (86 mg, 72%). $[\alpha]_D^{20} = 16.65°$ (c = 1.40, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3453, 1712, 1510, 1472, 1391, 1366, 1254, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.27 (s, 1H), 4.89 (br s, 1H), 4.82 (s, 1H), 4.23–4.21 (m, 2H), 4.14–4.13 (m, 1H), 3.97–3.95 (m, 2H), 3.76 (dd, J = 6.4, 2.0 Hz, 1H), 3.23 (br s, 2H), 1.43 (s, 9H), 0.86 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.5, 95.7, 79.9, 77.3, 75.2, 69.7, 68.2, 52.9, 30.6, 28.3, 25.6, 17.8, −4.89, −5.13; elemental analysis calcd (%) for $C_{18}H_{35}NO_7Si$: C 53.31, H 8.70, N 3.45; found: C 53.53, H 8.72, N 3.48.

Oxazolidinone 26: Triethylamine (71 mg, 0.7 mmol, 4 equiv) followed by thionyl chloride (23 mg, 0.19 mmol, 1.1 equiv) was added at 0 °C to a solution of diol **23** (71 mg, 0.18 mmol, 1 equiv) in THF (1.7 mL). The reaction was stirred at 0 °C for 1 h, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo. The cyclic sulfite **25a** (71 mg, 90%) was obtained as a

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clear oil and used without purification. Data was reported for a 1:1 mixture (by ^{1}H NMR) of diastereomers at sulfur. IR (neat): $\tilde{\nu}$ = 3375, 2930, 2858, 1710, 1505, 1471, 1391, 1366, 1257, 1169, 1015 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.37 (br s, 1H), 5.29 (s, 1H), 5.26–5.22 (m, 2H), 4.95 (dd, J = 7.6, 3.2 Hz, 1H), 4.79 (s, 2H), 4.71 (app s, 2H), 4.51–4.48 (m, 1H), 4.43 (dd, J = 6.9, 3.2 Hz, 2H), 4.32 (dd, J = 6.9, 2.9 Hz, 2H), 4.13–4.04 (m, 3H), 3.91 (app s, 1H), 1.44 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H).

Ruthenium trichloride (0.5 mg, 0.0024 mmol, 2 mol%) and sodium periodate (32 mg, 0.15 mmol, 1.2 equiv) was added at room temperature in one portion to a solution of cyclic sulfite **25a** (55 mg, 0.12 mmol, 1 equiv) in acetonitrile (1.4 mL) and CCl_4 (0.55 mL). Water (0.71 mL) was then added and the reaction was stirred for 1.5 h. The mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered through a silica plug, and evaporated in vacuo. The cyclic sulfate **25b** (49 mg, 88%) was obtained as a clear oil and used without further purification. IR (neat): $\tilde{\nu}$ = 3381, 1711, 1519, 1471, 1393, 1367, 1212, 1165, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.39 (br s, 1H), 5.29 (s, 1H), 5.20 (dd, J = 7.3, 3.4 Hz, 1H), 4.82–4.76 (m, 2H), 4.46 (dd, J = 6.8, 2.9 Hz, 2H), 4.14 (dd, J = 7.3, 2.0 Hz, 1H), 3.92 (app s, 1H), 1.42 (s, 9H), 0.82 (s, 9H), 0.08 (s, 6H).

A solution of cyclic sulfate **25b** (22 mg, 0.04 mmol, 1 equiv) was heated in THF (0.4 mL) at 50 °C for 6 h. The solution was cooled to 0 °C and treated with 20% aq. sulfuric acid solution. After stirring for 4.5 h, the mixture was diluted with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo. After column chromatography on silica (50% ethyl acetate/pentane), the oxazolidinone **26** (7 mg, 55%) was obtained as a white solid. M.p. 180–182 °C; $[\alpha]_D^{20}$ = −15.38° (c = 0.59, CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu}$ = 3573, 3458, 1769, 1471, 1232, 1086 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.18 (s, 1H), 5.09 (s, 1H), 4.85 (dd, J = 9.3, 5.4 Hz, 1H), 4.69 (s, 1H), 4.43 (app t, J = 4.9, 2.9 Hz, 1H), 4.30 (dd, J = 7.8, 2.9 Hz, 1H), 4.14–4.09 (m, 2H), 4.05 (dd, J = 4.9, 3.4 Hz, 1H), 2.53 (br s, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8, 94.59, 74.46, 69.51, 67.79, 53.12, 25.63, 17.8, −4.72, −4.98; HRMS: calcd for $C_{14}H_{26}NO_6Si$ $[M+H]^+$: 332.1529; found: 332.1525.

(+)-(1*S*,2*R*,3*R*,4*S*)-1,4-Dibenzoyloxy-2,3-di[(2,2,2-trichloroethoxy)carbonyl]oxy-5-cyclohexene (37): Racemic conduritol B tetracarbonate **36c** (424 mg, 0.50 mmol), tetrahexylammonium bromide (43 mg, 0.10 mmol), benzoic acid (214 mg, 1.75 mmol), $[\eta^3$-$(C_3H_5)PdCl]_2$ (4.6 mg, 0.0125 mmol, 2.5 mol%), and the ligand (*S*,*S*)-**32** (25.8 mg, 0.0375 mmol, 7.5 mol%) were thoroughly degassed. The flask was evacuated and purged with Ar (3×). Freshly distilled methylene chloride (1.5 mL) was added, followed by 1N sodium hydroxide solution (1.5 mL) that had been previously degassed by sparging with argon. The biphasic mixture was stirred vigorously at room temperature under an atmosphere of Ar (balloon). After 18 h, the layers were separated and the aqueous layer was extracted with methylene chloride (2×2 mL). The combined organic layers were dried ($MgSO_4$), diluted with an equal volume of diethyl ether and filtered through a plug of silica gel (≈10 g). The filtrate was concentrated to give a colorless oil that was treated with methanol (5 mL); the flask was placed in a refrigerator. After 1 h, the solid was filtered and rinsed with cold methanol. The filtrate was concentrated and this procedure repeated two more times to provide dibenzoate **37b** as a crystalline white solid (317 mg, 90%). R_f = 0.47 (4:1 hexanes/EtOAc); m.p. 141–143 °C; $[\alpha]_D^{23}$ = +177.1° (c = 1.22, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 1771 (s), 1724 (s), 1248 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.03 (d, J = 7.1 Hz, 4H), 7.59 (t, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 4H), 5.96 (m, 4H), 5.59 (dd, J = 5.3, 2.6 Hz, 2H), 4.81 (d, J = 12.0 Hz, 2H), 4.66 (d, J = 11.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.5, 153.5, 133.7, 129.9, 128.8, 128.5, 127.3, 94.1, 76.8, 75.6, 72.1; elemental analysis calcd (%) for $C_{26}H_{20}Cl_6O_{10}$: C 44.29, H 2.86; found: C 43.39, H 3.04. Enantiomeric excess 99% determined by HPLC [Chiralcel AD column, eluting with 90:10 heptane/*i*PrOH, 1 mL min^{-1}: (+)-enantiomer t_R = 13.5 min, (−)-enantiomer t_R = 29.1 min].

(+)-(1*S*,2*R*,3*R*,4*S*)-1,4-Dibenzoyloxy-5-cyclohexene-2,3-diol (38): Freshly acid washed zinc dust (1.36 g, 20.8 mmol) was suspended in THF/acetic acid (14 mL) and the mixture was cooled to 0 °C. The dicarbonate **37b** (2.45 g, 3.47 mmol) was added in four batches. After the addition was complete the solution was warmed to room temperature. After 2 h, the mixture was diluted with ethyl acetate (100 mL) and washed with water (2×50 mL) and then sat. K_2CO_3 until the organic layer was no longer acidic. The organic layer was then washed with brine, dried (Na_2SO_4) and concentrated. Crystallization from ethyl acetate/petroleum ether ≈1:5 provided diol **38** (0.95 g, 77%) in three batches. R_f = 0.40 (1:1 hexanes/EtOAc); m.p. 153 °C; $[\alpha]_D^{23}$ = +206.8° (c = 2.11, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3384 (br m), 1716 (s), 1265 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.08 (d, J = 8.0 Hz, 4H), 7.61 (t, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 4H), 5.84 (s, 2H), 5.70 (dd, J = 5.4, 2.4 Hz, 2H), 4.05 (dd, J = 5.6, 2.2 Hz, 2H), 3.39 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.9, 133.4, 129.9, 129.5, 128.5, 127.8, 74.9, 74.0; elemental analysis calcd (%) for $C_{20}H_{18}O_6$: C 67.79, H 5.12; found: C 67.70, H 5.30.

Oxazolidinone of (+)-(1*S*,2*R*,3*R*,4*S*)-1,4-dibenzoyloxy-2-(*N*-benzyl)carbamyl-5-cyclohexene-3-ol (43): Triethylamine (0.560 mL, 407 mg, 4.02 mmol) and benzylisocyanate (0.248 mL, 268 mg, 2.01 mmol) were added to a solution of the diol **38** (475 mg, 1.34 mmol) in methylene chloride (7 mL) and the resulting mixture was stirred at room temperature. After 2.5 h, water (1 mL) was added. The solution was diluted with ethyl acetate (30 mL) and washed with 1M HCl (2×15 mL), sat. $NaHCO_3$ (15 mL) and brine (10 mL). The organic phase was then dried (Na_2SO_4) and concentrated. Precipitation from ethyl acetate with petroleum ether provided the mono-carbamate **42a** as an amorphous white solid (509 mg, 78%). The mother liquor was concentrated and the residue was purified by flash chromatography (3:1 to 1:1 petroleum ether/EtOAc gradient) to provide the dicarbamate (50 mg, 6%) [R_f = 0.40 (2:1 hexanes/EtOAc)], followed by **42a** [43 mg, combined yield: 552 mg, 84%] followed by diol **38** (50 mg, 10%). Data for **42a**: R_f = 0.23 (2:1 hexanes/EtOAc); m.p. 150–152 °C; $[\alpha]_D^{23}$ = +202.8° (c = 0.91, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3335 (br m), 1724 (s), 1690 (s), 1551 (m), 1264 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.07 (m, 4H), 7.58 (m, 2H), 7.44 (m, 4H), 7.13 (m, 5H), 5.68 (m, 4H), 5.40 (dd, J = 11.0, 8.5 Hz, 1H), 5.20 (t, J = 5.6 Hz, 1H), 4.36 (dd, J = 15.2, 6.4 Hz, 1H), 4.27 (dd, J = 5.9, 15.3 Hz, 1H), 4.13 (m, 1H), 3.23 (d, J = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.7, 166.1, 156.5, 137.9, 133.4, 129.9, 129.4, 128.6, 128.5, 128.4, 127.8, 127.4, 127.2, 75.5, 75.0, 72.9, 72.2, 45.0.

Pyridine (33 μL, 32 mg, 0.410 mmol) was added to a solution of the alcohol **42a** (100 mg, 0.205 mmol) in methylene chloride (1 mL) and the solution was cooled to −50 °C. Triflic anhydride (52 mL, 87 mg, 0.308 mmol) was added in dropwise fashion and the resulting mixture was stirred at −50 °C for 10 min, then warmed to 0 °C over 20 min and quenched by adding one drop of water. The mixture was diluted with diethyl ether (3 mL), $MgSO_4$ (≈100 mg) was added, and the mixture was filtered through a plug of SiO_2, rinsing with diethyl ether (5 mL). The filtrate was concentrated to provide the crude triflate as a yellow foam that was used without further purification (134 mg, 100%). R_f = 0.61 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.08 (t, J = 7.1 Hz, 4H), 7.62 (t, J = 7.3 Hz, 2H), 7.47 (t, J = 7.6 Hz, 4H), 7.12 (m, 5H), 6.09 (d, J = 6.6 Hz, 1H), 5.91 (m, 3H), 5.73 (dd, J = 11.0, 8.3 Hz, 1H), 5.37 (dd, J = 11.0, 8.3 Hz, 1H), 5.23 (t, J = 5.4 Hz, 1H), 4.40 (dd, J = 6.3, 15.1 Hz, 4.25 (dd, J = 4.9, 14.9 Hz, 1H).

The crude triflate was dissolved in THF (4 mL), the resulting solution was cooled to −40 °C, and potassium bis(trimethylsilyl)amide (0.51 mL, 0.5M in toluene, 0.256 mmol) was added in dropwise fashion. After 15 min, 15% aqueous $NaHCO_3$ solution (5 mL) was added. The mixture was extracted with diethyl ether (2×10 mL), the organic layers were washed with sat. $NaHCO_3$ (5 mL), and brine (5 mL), then dried ($MgSO_4$), and concentrated to give a brown oil. Chromatography (2:1 to 1:1 petroleum ether/ether) provided the oxazolidinone **43** as a white foam (68 mg, 70%). R_f = 0.37 (2:1 hexanes/EtOAc); $[\alpha]_D^{23}$ = +235.9° (c = 0.79, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1760 (s), 1723 (s), 1269 (s), 1107 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.04 (d, J = 7.6 Hz, 2H), 8.00 (d, J = 7.3 Hz, 2H), 7.60 (m, 2H), 7.47 (m, 4H), 6.32 (ddd, J = 9.5, 5.9, 2.2 Hz, 1H), 6.13 (dd, J = 9.8, 2.2 Hz, 1H), 5.96 (m, 1H), 5.56 (dd, J = 5.6, 3.7 Hz, 1H), 5.00 (dd, J = 9.5, 4.6 Hz, 1H), 4.87 (d, J = 15.1 Hz, 1H), 4.07 (d, J = 15.1 Hz, 1H), 3.97 (dd, J = 9.3, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.5, 165.4, 157.5, 135.2, 133.8, 133.7, 133.6, 130.1, 129.8, 129.7, 129.2, 128.8, 128.5, 128.5, 128.2, 128.1, 127.3, 74.6, 71.0, 63.4, 54.2, 46.8; HRMS (EI): calcd for $C_{27}H_{23}NO_4$ $[M-CO_2]^+$: 425.1627; found: 425.1625.

Oxazolidinone of (+)-(1*S*,2*R*,3*R*,4*S*,5*R*,6*R*)-2-amino-2-deoxy-*neo*-inositol (44): NMO (70 mg, 0.60 mmol) and osmium tetraoxide (38 μL, 4% in H_2O, 0.006 mmol) were added to a solution of the alkene **43** (145 mg, 0.30 mmol) in THF/water (10:1, 1.5 mL) and the resulting solution was stirred at room temperature. After 4 h, 15% aq. $NaHCO_3$ was added (2 mL) and the mixture was stirred for 30 min. The mixture was then extracted with methylene chloride (5×5 mL), the combined organic layers were washed with brine (5 mL), then dried (Na_2SO_4), and concentrated to give a white solid. Recrystallization from methanol provided the purified diol **44** (121 mg, 80%) in three crops. R_f = 0.31 (1:1 hexanes/EtOAc); m.p. 224 °C;

$[\alpha]_D^{23} = +85.0^\circ$ ($c = 0.95$, THF); IR (neat): $\tilde{\nu} = 3422$ (br m), 1761 (s), 1725 (s), 1268 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.08$ (d, $J = 7.3$ Hz, 2H), 7.99 (d, $J = 7.6$ Hz, 2H), 7.60 (m, 2H), 7.47 (m, 4H), 7.25 (m, 5H), 5.56 (dd, $J = 6.8$, 1.5 Hz, 1H), 5.23 (br s, 1H), 5.07 (t, $J = 7.6$ Hz, 1H), 4.70 (d, $J = 15.1$ Hz, 1H), 4.43 (dd, $J = 5.1$, 1.5 Hz, 1H), 4.30 (dd, $J = 8.3$, 3.4 Hz, 1H), 4.17 (dd, $J = 5.1$, 1.5 Hz, 1H), 4.06 (d, $J = 15.4$ Hz, 1H), 2.68 (br s, 2H); ^{13}C NMR ([D$_6$]acetone, 75 MHz): $\delta = 166.1$, 165.6, 158.6, 137.4, 134.4, 134.3, 130.5, 129.53, 129.47, 129.44, 128.5, 128.4, 74.89, 74.85, 72.3, 69.6, 68.6, 54.8, 47.2; elemental analysis calcd (%) for $C_{28}H_{25}NO_8$: C 66.78, H 5.01, N 2.78; found: C 66.74, H 5.03, N 2.86.

Oxazolidinone of (1*R*,2*R*,3*R*,4*S*,5*R*,6*R*)-2-amino-2-deoxy-4,5-methylene-*neo*-inositol (45): Trimethylsilyl triflate (94 μL, 115 mg, 0.51 mmol) was added to a cooled (0 °C) suspension of the diol **44** (64 mg, 0.127 mmol) and 2,6-lutidine (37 μL, 34 mg, 0.32 mmol) in dimethoxymethane (0.65 mL). The resulting solution was allowed to warm to room temperature. After 12 h, the mixture was diluted with diethyl ether (10 mL), washed with sat. $NaHCO_3$ (5 mL), 15% sodium bisulfate (2 × 5 mL), sat. $NaHCO_3$ again (5 mL), and brine (5 mL), then dried ($MgSO_4$) and concentrated to give acetal **45** (70 mg, 100%) as a white foam that was used without further purification. $R_f = 0.32$ (2:1 hexanes/EtOAc); $[\alpha]_D^{23} = +56.2^\circ$ ($c = 0.55$, $CHCl_3$); IR (neat): $\tilde{\nu} = 1762$ (s), 1726 (s), 1262 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.10$ (d, $J = 7.7$ Hz, 2H), 8.00 (d, $J = 7.7$ Hz, 2H), 7.61 (m, 2H), 7.48 (m, 4H), 7.29 (m, 5H), 5.96 (dd, $J = 7.6$, 2.2 Hz, 1H), 5.40 (t, $J = 2.5$ Hz, 1H), 5.13 (s, 1H), 5.08 (dd, $J = 9.0$, 7.8 Hz, 1H), 4.71 (d, $J = 15.1$ Hz, 1H), 4.64 (s, 1H), 4.56 (dd, $J = 7.3$, 1.7 Hz, 1H), 4.50 (dd, $J = 7.3$, 2.2 Hz, 1H), 4.21 (dd, $J = 9.0$, 2.9 Hz, 1H), 4.07 (d, $J = 15.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 165.7$, 164.8, 157.1, 135.3, 134.0, 133.6, 129.9, 129.0, 128.9, 128.5, 128.3, 128.2, 128.1, 95.4, 74.0, 73.0, 71.6, 65.8, 52.8, 46.4; HRMS calcd for $C_{29}H_{25}NO_8$ $[M]^+$: 515.1580; found: 515.1563.

(1*S*,2*R*,3*R*,4*S*,5*R*,6*R*)-2-Amino-2-deoxy-4,5-methylene-*neo*-inositol (6): Freshly cut Li metal (11.5 mg, 1.63 mmol, three pieces) was added to a cooled (−78 °C) solution of the oxazolidinone **45** (42 mg, 0.082 mmol) in THF/NH_3 (1:2, 1.5 mL). The flask was removed from the cold bath and allowed to warm to −33 °C. Blue streaks started to form from the metal and after ≈5 min. the solution turned completely blue. After another 5 min, the solution was recooled to −78 °C and the reaction was quenched by carefully adding water (0.5 mL). TLC analysis showed disappearance of the starting material and formation of a new lower spot corresponding to the debenzylated diol-oxazolidinone. $R_f = 0.30$ (10:1 EtOAc/MeOH); IR (neat): $\tilde{\nu} = 3347$ (br s), 1739 (s) cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): $\delta = 5.12$ (s, 1H), 4.71 (dd, $J = 6.9$, 9.0 Hz, 1H), 4.66 (s, 1H), 4.47 (d, $J = 6.9$ Hz, 1H), 4.23 (br s, 2H), 4.06 (dd, $J = 2.9$, 9.0 Hz, 1H), 3.78 (br s, 1H).

The mixture was warmed to room temperature and the ammonia was allowed to evaporate. The mixture was then heated in a 90 °C oil bath. After 1 h, no oxazolidinone was observed by TLC. The solution was cooled to room temperature and applied directly to an ion-exchange column (Amberlite IRC-76, H^+ form, ≈5 mL wet) that was eluted with water and then 5% ammonium hydroxide to give the amino cyclitol **6** as an amorphous solid (12 mg, 77%). $R_f = 0.37$ (10:10:1 CH_2Cl_2/MeOH/NH_4OH); $[\alpha]_D^{22} = -28.9^\circ$ ($c = 0.85$, H_2O) [lit. $[\alpha]_D^{22} = -33^\circ$ ($c = 1.97$, H_2O),[11] $[\alpha]_D^{21} = -36^\circ$ ($c = 0.49$, H_2O)[16]]; IR (neat): $\tilde{\nu} = 3347$ (br s), 2884 (w), 1098 (s) cm^{-1}; ^1H NMR (D_2O, with acetone as an internal standard at $\delta = 2.08$, 300 MHz): $\delta = 5.07$ (s, 1H), 4.83 (s, 1H), 4.17 (dd, $J = 7.8$, 5.1 Hz, 1H), 4.03 (m, 2H), 3.74 (dd, $J = 9.8$, 3.7 Hz, 1H), 3.61 (dd, $J = 7.8$, 3.4 Hz, 1H), 3.26 (t, $J = 3.4$ Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz): $\delta = 95.7$, 79.4, 78.7, 71.9, 71.7, 70.3, 56.1. These data were consistent with literature values.

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