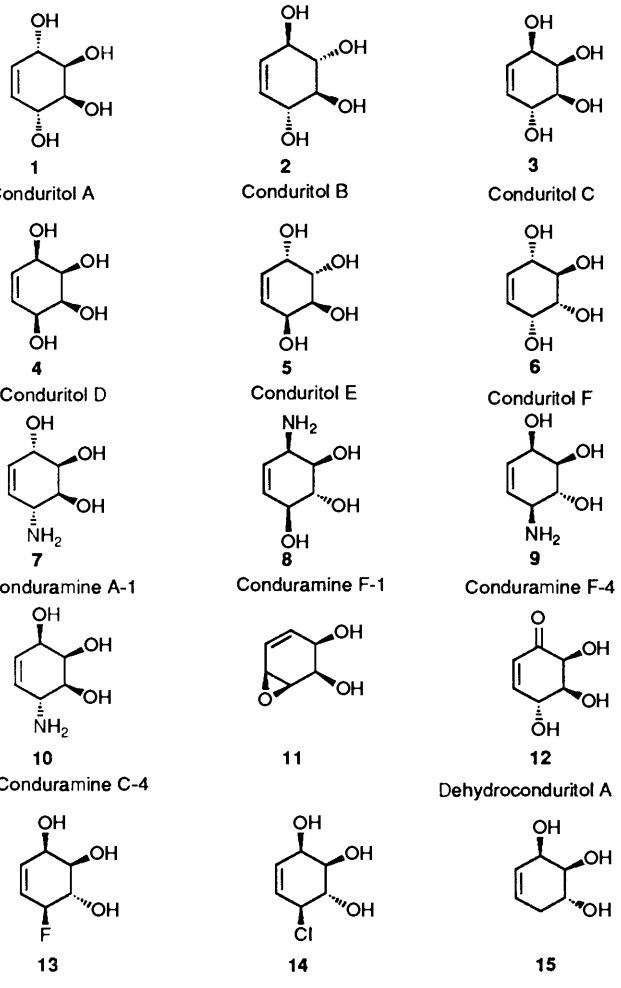
Biocatalysis as the Strategy of Choice in the Exhaustive Enantiomerically Controlled Synthesis of Conduritols†

Tomas Hudlicky,*‡ Hector Luna, Horacio F. Olivo, Catherine Andersen,§ Thomas Nugent§ and John D. Price
Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061

An approach to several conduritols, both naturally occurring and unnatural derivatives, is described. The key strategy of this potentially exhaustive approach relies on the bio-oxidation of chloro- or bromobenzene to their corresponding *cis*-diols. Subsequent synthetic manipulations enjoy extensive use of symmetry considerations in the introduction of functionalities. Complete stereo- and enantio-control is achieved in the preparation of conduritols E **5** and F **6**, aminoconduritols A-1 **7** and F-4 **9**, fluorodeoxyconduritol F **13**, chlorodeoxyconduritol F **14**, and deoxyconduritol E **15**. A detailed discussion of the stereoelectronic parameters that control opening of epoxy alkenes of type **33** or **37** is advanced. Full experimental details are provided for all compounds.

Conduritols are cyclohex-5-ene-1,2,3,4-tetraols of which there are ten possible isomers (two *meso* forms and four DL-pairs). Structures **1**-**15** are representative of natural as well as



unnatural members of this class. There is considerable interest in the stereocontrolled synthesis of these compounds as they have proved to be useful intermediates for the preparation of cyclitols.[1] Additionally, these compounds and their derivatives such as conduritol epoxides, for example **11**, and aminoconduritols act as inhibitors of D-glycosidases.[2] An excellent review on the preparation of conduritols and related compounds has recently appeared.[3]

Unfortunately, the great majority of syntheses of conduritols result in racemic mixtures because of the unavailability of optically pure starting materials. Exceptions include preparations of (−)-conduritol B and (+)-conduritol F (both from the inositol quebrachitol)[4] and most recently syntheses of (−)-conduritol C,[5a,b] (−)-conduritol B,[6] and (+)-conduritol F[6] by the 'naked sugar' approach of Vogel. *cis*-Diols derived from benzene, toluene and chloro- and bromo-benzene have also gained popularity in the context of synthesis of polyhydroxylated cyclohexanes. The approaches of Ley,[7] Carless,[8] Roberts,[9] as well as our own[10] have resulted in the preparation of conduritols, pinitols and other cyclitols. Herein we report a concise and enantiomerically controlled approach to conduritols A (**1**), (−)-C **3**, (+)-E **5** and (−)-F **6**, conduramines A-1 **7**, and F-4 **9**, and the unnatural halogenated or saturated derivatives **13**, **14** and **15** from optically pure arene-derived *cis*-diols. These synthons are generated from chloro- or bromobenzene by biocatalytic means, using a mutant strain of *Pseudomonas putida* (*Pp* 39D) developed by Gibson.[11] The key to a general and exhaustive approach to these compounds lies in the precise planning of placement of successive functionalities by using either the hindering or directing effect of the biocatalytically generated diol unit.

Results and Discussion

Following the original work by Gibson,[11] which provided a practical means of transforming aromatic compounds into diols on a preparative scale, several different classes of natural products have been attained from *cis*-diols in our laboratory, Scheme 1. Even though the exact structure of toluene dioxygenase, the acting enzyme in the aromatic oxidation, is unknown, it has been expressed on *E. coli* for improved efficiency.[12] Thus the transformation of arenes into chiral *cis*-diols has become operationally useful to the point of widespread utility in synthesis.[13,14] Some of the arene *cis*-diols,

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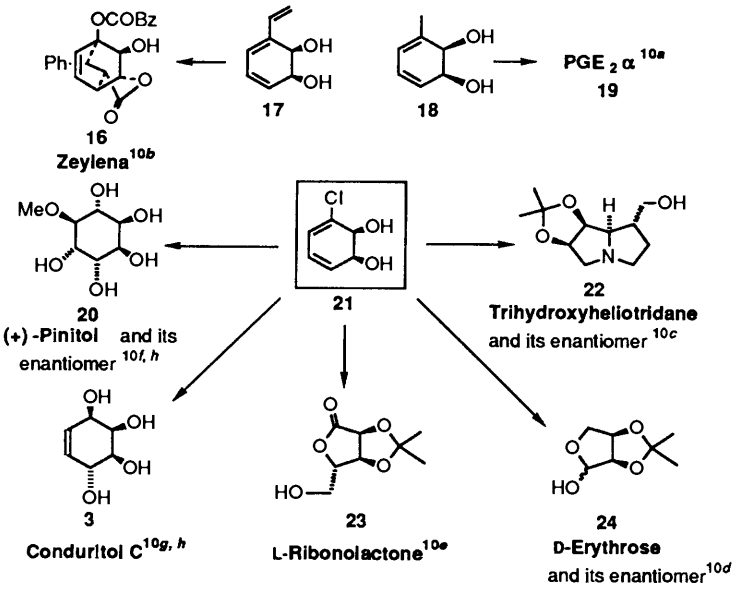
§ Undergraduate research participant, 1990–1991.



Scheme 1 Recent synthetic accomplishments using arene *cis*-diols

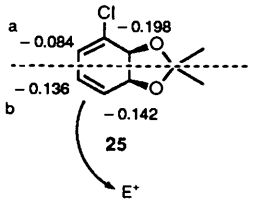
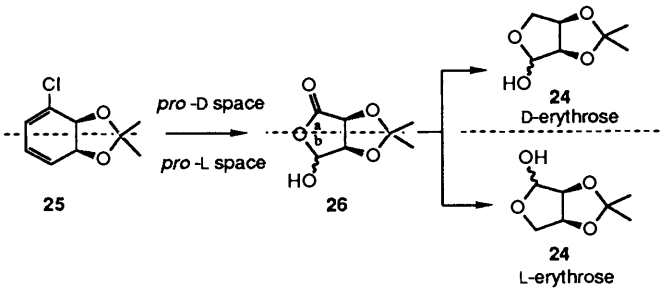


Fig. 1 AM1-calculated atomic charges for chlorobenzene-1,2-diol acetonide[10h,*]

namely those derived from benzene, chloro-, fluoro- and bromo-benzene have become commercially available,[14b] and we would therefore expect an increase in their popularity as starting materials in the enantiomerically controlled synthesis of oxygenated compounds.

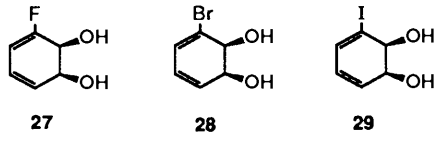
From an analysis of the unique stereoelectronic features of the diols such as **21**, or its acetonide **25**, it can be noted that the two alkenes differ in their electron content as indicated by calculations, Fig. 1. Furthermore, in the rigid acetonides only one face is open to the approach of an electrophilic reagent resulting in a stereocontrolled introduction of the next stereocentre. Finally, the presence of the proenantiotopic plane of symmetry on the molecule allows completely enantiodivergent synthetic design, as shown by the synthesis of both enantiomers of erythrose, Scheme 2. The principles of 'proenantiotopic distinction' in synthetic design have been discussed in connection with our synthesis of (+)- and (−)-pinitols.[10f,h]



Scheme 2 Synthesis of D- and L-erythroses from chlorobenzene

Another aspect of the synthetic strategy lies in the recognition that practically any carbon in the initially formed diol **21** can become any other carbon in any of the final conduritol targets. This is made possible through careful planning of subsequent operations and the placement of new hydroxy groups, or other functionalities, as well as by conversion of the originally created *vic* diol into an alkene in the latter stages of the synthesis. Thus all of the elements of synthetic design, namely regio-, stereo-, and enantio-control are accounted for by precisely defined operations.

The synthesis of dihydroconduritol C and conduritol C from the diol **21** has been reported.[10g] Quite recently, a report appeared describing the preparation of these compounds from the fluoro diol **27**.[8a,†] The use of the bromo diol **28** has been reported[10f] and the preparation of the iodo diol **29** has been achieved.[15] The absolute stereochemistry of these compounds has been determined by direct methods[16,17] or by conversion into known compounds.‡

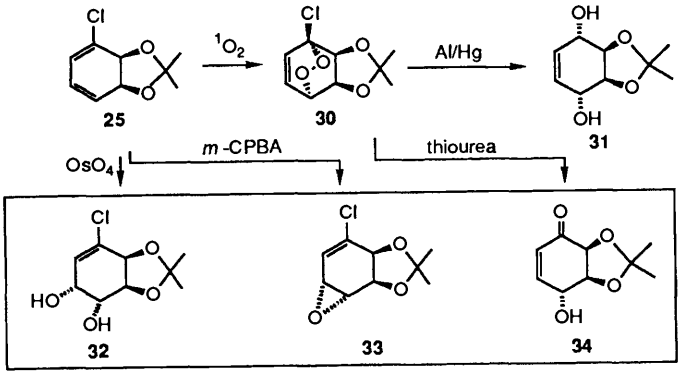


The reactions that are of utmost importance for further functionalization of these diols are epoxidation and osmylation of the more electron-rich double bond, singlet-oxygen addition, and ozonolysis. Diol **32** and epoxide **33** have served as important intermediates in the synthesis of both enantiomers of pinitol.[10f,h] The oxygenation methods shown in Scheme 3 permit the introduction of new centres with relative and absolute stereocontrol, as directed by the agency of the acetonide ring.

* Calculation performed as described by M. J. S. Dewar, E. G. Zoehisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3092.

† Fluorobenzene yields a 2,3-diol in 60% ee. The synthesis published by H. A. J. Carless [ref. 8(*a*)] was performed prior to the paper by D. R. Boyd [ref. 16(*b*)] in which the %ee was determined. We and others assumed that any diastereomers created in the first steps of the Carless synthesis disappeared on purification of intermediates as the final product, conduritol C, was reported to have proper $[\alpha]_D$. Boyd has been able to achieve complete enantiomeric purity in the fluorodiol by crystallization (personal communication).

‡ The stereochemistry of the *cis*-diols has also been proved by conversion of *cis*-chloro- and bromo-benzenediol to both enantiomers of pinitol (ref. 10*f*).



Scheme 3 Control of adjacent stereocentres in further oxidations of cyclohexadienediols

Reliable procedures for the generation of the important synthons **32**, **33**, and **34**, as well as the reduction of **30**, have been published.[10d,f,g,h] The ozonolysis of **25** has been described in detail.[10c]

The availability of these compounds allows a stereorational design of polyhydroxylated cyclohexanes. In each of the synthons, one or more centres have been set relative to the acetonide. The stereo- and regio-controlled opening of the epoxide **33**, as well as previous functionalization of the diol **32**, then allow the precise introduction not only of the next hydroxy centre but also of other functional groups. The following examples underscore the benefits of this strategy.

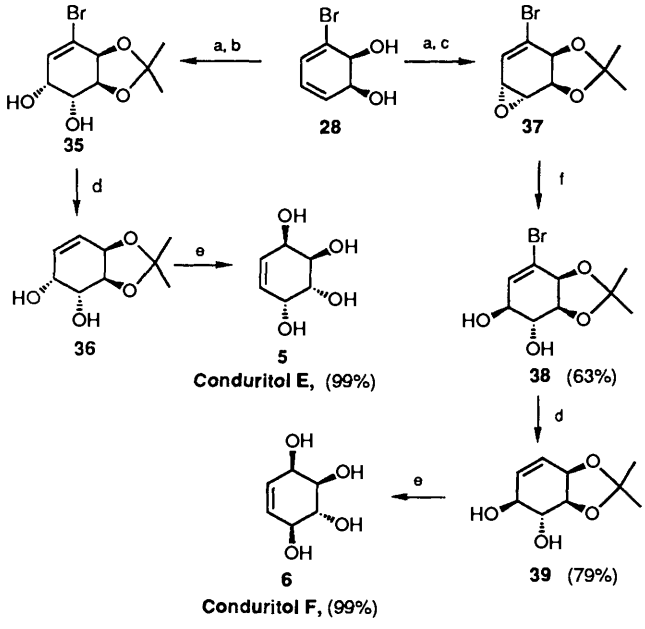
Conduritols E and F.[18]—The *cis* and *trans* disposition of the 2,3-diols in conduritols E **5** and F **6** allowed us to take advantage of the synthons **32** and **33**. Thus reductive dehalogenation of diol **32** with Bu_3SnH and deprotection of the acetonide gave conduritol E **5**, as the enantiomer of the naturally occurring material (confirmed by ^1H NMR spectroscopy and $[\alpha]_D$),[19] (Scheme 4). A preliminary account of this work has appeared.[20]

On the other hand, opening of epoxide **33** with aqueous KOH in dimethyl sulphoxide (DMSO)[21] provided the *trans*-disposition found in conduritol F. The *trans*-bromo diol **38** was reductively debrominated with Bu_3SnH to **39** which was deprotected to give conduritol F **6** (Scheme 4), identical in all respects (^1H NMR, m.p., $[\alpha]_D$) with the natural product.[20]

A strategy for the preparation of conduritols based on epoxide opening, followed by the reductive removal of the halogen, and the regioselective functionalization of the remaining double bond has been advanced and exemplified by the synthesis of (+)- and (−)-pinitol[10f] and the above conduritols. In order to develop a more general synthetic protocol, the opening of epoxides **33** and **37** with variety of nucleophiles has been studied in detail.

Nucleophilic Opening of Epoxides.—The epoxide **33** was subjected to nucleophilic opening under a variety of conditions. Such opening is generally performed with a strong nucleophile assisted by an acid catalyst (either H^+ or Lewis acids). It is also universally accepted that the stereochemistry of the reaction is conducive to the *trans* array of the resulting vicinal substituents through diaxial arrangement of the incoming nucleophile, the incipient OH bond for maximum orbital overlap.[22] It is also known that the regiochemical outcome of the oxirane ring-opening may include a number of possibilities given the presence of groups capable of anchimeric assistance, and the stereochemical course of the reaction can range from complete inversion to complete retention depending on the solvent, nucleophile, electrophilic catalyst, temperature and structure, configuration and conformation of the epoxide.[23]

A rational guide to the factors involved in the reactivity,



Scheme 4 Synthesis of conduritol E **5** and conduritol F **6**. a, DMP–acetone–*p*-TsOH; b, OsO_4–*N*-methylmorpholine *N*-oxide; c, *m*-CPBA–CH_2Cl_2; d, Bu_3SnH–AIBN; e, AcOH–THF–H_2O; f, KOH–DMSO–H_2O

regio-and stereo-chemistry, based on the products of the nucleophilic opening of **33**, would be highly desirable with regard to introduction of further functionalities onto the periphery of the cyclohexane ring. One of the best known principles in this kind of ring-opening reactions is the Fürst–Plattner rule,[24] which states that the opening of an epoxide is expected to take place exclusively in the diaxial mode. This statement therefore requires that a great deal of attention be paid to the stereochemistry of the reacting epoxide, especially that of epoxide **33**, which comprises a very rigid structure.

The structure of epoxide **33** generated by MM2 calculations, in both extreme conformations is shown in Fig. 2. Assuming that the nucleophilic opening occurs from the conformation **A**, the product of the reaction will have the nucleophile vicinal to the acetonide group, in agreement with the Fürst–Plattner rule. But, if the conformation of the reacting epoxide is **B**, then the product will have the nucleophile attached to the allylic position. These arguments assume a strictly S_N2 mechanism with no ionization at C-5. By analysis of ^1H NMR spectra we can assign the conformation **A**, because of the coupling constant between the allyl and vinylic protons.

In the previously reported synthesis of (+)- and (−)-pinitols[10f] we observed that the opening of epoxide **33** by methanol, under acidic conditions, produced a displacement in

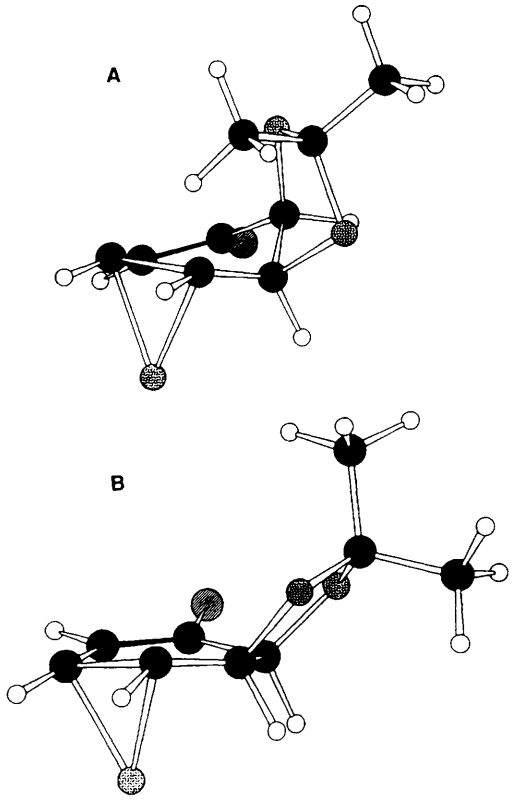
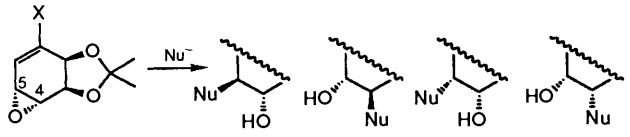


Fig. 2 Conformations of the epoxide **33**

Table 1 Product ratios from the ring-opening reaction of the epoxide **33**



33, X= Cl
37, X= Br

I II III IV

Nucleophile	I	II	III	IV
H_2O/H^+	>95	—	Trace	—
HO^-	100	—	—	—
Cl^-	90	—	10	—
F^-	50	—	50	—
RNH_2	100	—	—	—
N_3^-	—	100	—	—

the allylic position, corresponding to the overall diequatorial opening from conformation **A**. But surprisingly, when alumina was used as a catalyst, the same regio-and stereo-chemistry in the ring opening was observed.

In order to prove the synthetic utility of epoxides **33** and **37** we studied the nucleophilic opening with various nucleophiles (water, halogens, hydride, azide and amines). The results are shown in Table 1, and indicate that some control is available in the procurement of the four possible isomers.

From Table 1 it is clear that the regiochemistry of the ring opening is directed to the allylic position, except in the case of **II**, where nucleophilic attack occurred at the homoallylic position. Our initial interpretation of these results led us to believe that C-4 and C-5 differed in their 'hard/soft' character.[25] This may explain the preference for azide displacement at C-4 but this argument was dispelled by the observation that thiophenol, a softer nucleophile, reacted at C-5 instead. The azide opening was subjected to serious study, the conditions of which are summarized in Table 2. Successful differentiation of C-4 *vs.* C-5 opening would ultimately permit a general synthetic design for aminoconduritols.

To design such a general protocol for aminoconduritol synthesis we wished to explore the possibility of placement of a nitrogenous functionality at either C-5 or C-4 in any of the four possible orientations. We chose to vary the reaction conditions initially searching for regiocontrol in the azide ring opening of the epoxide **33**. Our results are presented in Table 2.

Assuming the mechanism of the reaction with the azide ion may range from a complete S_N1 type to a complete S_N2, the reaction conditions were selected in order to resemble more closely the S_N1 type, thereby maximizing the possibility of formation of an allylic cation, or its predecessor in the transition state. This would lead to the desired regiochemistry at C-5, regardless of the stereochemical consequences.

Entry 1 shows the conditions initially attempted for the expected synthesis of **40**, which led to the regiochemistry found in **41**, in complete agreement with the Fürst–Plattner rule,[24] and also reinforced the conformation **A** as the likely entity in the context of recent work concerning the control of the regiochemistry of the oxirane opening by chelating processes.[33]

The use of Lewis acids as catalysts for the regiocontrolled opening of oxiranes, especially those derived from allylic alcohols is well documented,[34] sometimes even leading to the protected alcohols.[29] We selected the use of $Ti(OPr^i)_4$ in combination with $TMSN_3$ in an attempt to produce **41** as its silyl ether. However, when a catalytic amount of $Ti(OPr^i)_4$ was used (entry 9), azide **41** was again the main product. When 1.5 equiv. of $Ti(OPr^i)_4$ was used (entry 10) the products could not be separated and identified. We also thought that acid conditions might lead to a stable allylic carbocation, and attempted the use of *in situ* generated NH_3 (entries 6 and 7), which again produced **41**.

During our synthesis of pinitols, the epoxide was opened with methanol using neutral alumina as a catalyst. Following a report in the literature[30] we attempted the reaction of HN_3/alumina (entry 12) but the product was again **41**. Even when the nucleophile was $TMSN_3$ (entry 11) in $CHCl_3$, again closely resembling the conditions used in the pinitol synthesis, the result was the same. With more acidic surface catalysts such as silicic acid (pH = 4) in conjunction with HN_3, the product was the *trans*-isomer of diol **32**, which was identified by comparison with a known sample.* Regardless of the conditions used the regioisomer **41** was obtained; the failure of the $Ti(OPr^i)_4$ reaction could be due to the rigidity of the ring system, which did not allow the complexation of the 'allylic' alcohol with the oxygen of the epoxide to take place.

To achieve the regio- and stereo-chemistry of **42**, the epoxide was treated with $FeCl_3$[32a] and the intermediate chlorohydrin reacted further with NaN_3[32b] (entry 16), in 43% overall yield. On the other hand, the reaction with the primary amine, benzylamine with alumina catalysis, produced **43** possessing the regiochemistry observed in the case of methanol or hydroxide under similar reaction conditions.[10f]

* NMR analysis of the product showed it to be in agreement with structure **57**; this compound has been prepared by unambiguous methods to corroborate structure. It was generated from **33** by treatment with silica with or without HN_3.

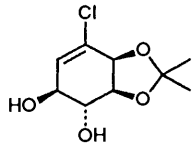


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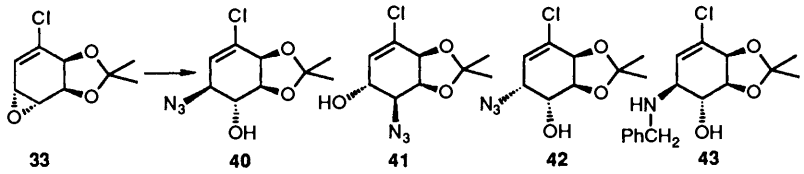
Table 2 Opening of the epoxide **33** with azide



33 **40** **41** **42** **43**

Entry	Reaction conditions[a]	Product (ratio)	Reference
1	NaN_3, NH_4Cl, EtOH–DME–H_2O	**41**	
2	$TMSN_3$, DMF, rt, 9 h	**33**	26
3	$TMSN_3$, DMF, 90 °C, 20 h	**41**	26
4	NaN_3, 18-C-6, rt, 12 h	**33**	27
5	NaN_3, 18-C-6, H_2O, rt, 12 h	**41**	27
6	$TMSN_3$, MeOH, DMF, rt	**33**	26
7	$TMSN_3$, MeOH, DMF	**33**: **41** (70:30)	26
8	NaN_3, dioxane–H_2O, 100 °C, 18 h	**33**:**41** (33:77)	28
9	$TMSN_3$, $Ti(OPr^i)_4$(cat.), THF, rt, 20 h	**33**:**41** (80:20)	29
10	$TMSN_3$, $Ti(OPr^i)_4$, THF, rt, 20 h	Two inseparable products	29
11	$TMSN_3$, neutral alumina, $CHCl_3$, rt, 18 h	**41**	10(*f*)
12	HN_3, neutral alumina, $CHCl_3$, rt, 18 h	**41**	30
13	HN_3, silicic acid (pH = 4), rt, 22 h	**41** + aromatics	30
14	(*a*) HN_3, silicic acid		
	(*b*) **33**, rt, 26 h	**57**	*b*
15	NaN_3, CuI, DMSO, rt, 26 h	mixture (**41**)	31
16	(*a*) $FeCl_3$, Et_2O, rt, 2 h		
	(*b*) NaN_3, DMF, 70 °C, 4 h	**42**	32
17	$PhCH_2NH_2$, neutral alumina, $CHCl_3$, 6 h	**43**	10(*f*)

[a] rt = room temperature, 18-C-6 = 18-crown-6, TMS = trimethylsilyl. [b] See footnote on preceding page.

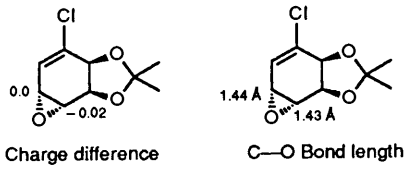


Fig. 3 The chloro epoxide **33**

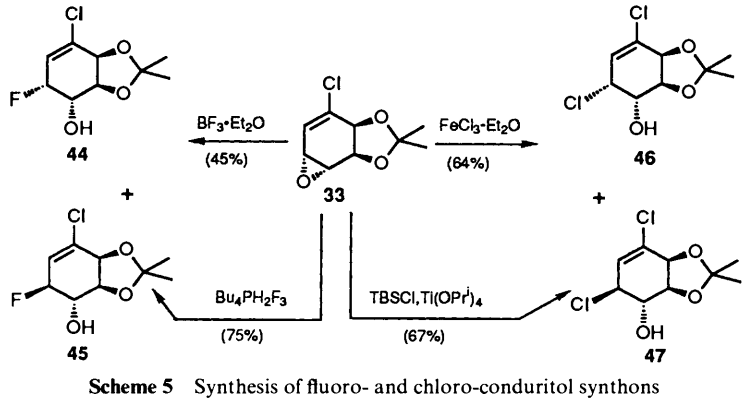
From the data in Table 2 it appears that the only nucleophile not to react at C-5 is the azide ion. A rational explanation of this observation may involve the possible complexation of the azide ion with acetonide oxygens, resulting in the delivery of the azido ion to C-4 from the *endo* surface of the molecule. Azide is also the only nucleophile examined that possesses a formal charge. Thus our initial belief in the hard/soft reasons for the regiochemistry observed is probably incorrect.

A reasonable explanation of the mechanism of the epoxide opening therefore involves an S_N1-like process. (This is reinforced by observation that traces of the *cis*-diol **32** have been detected in the opening of the epoxide **33** under acidic conditions, although the *trans* diol formed almost exclusively).

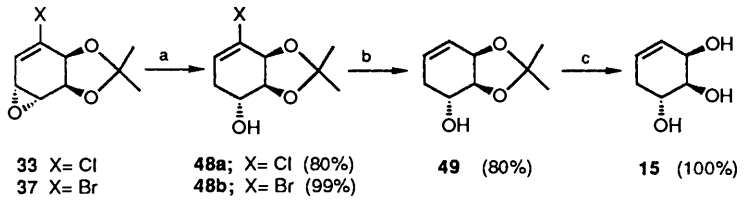
Calculations show a small difference in charge at both carbons of the oxirane ring, lending evidence to the existence of a non-symmetrical oxirane ring, and therefore a highly polarized transition state, resembling an allylic cation, possibly a tight ion pair, Fig. 3. This idea is reinforced by the observation of epoxide opening by attack at the allylic position.

Halogenoconduritols.—In the ring opening by halides, fluoride ion acts as a nucleophile affording both diastereoisomers **44** and **45** in an approximately 1:1 ratio under acid-catalysed conditions in 50% yield, Scheme 5. This result strongly favours an S_N1-type mechanism proceeding *via* an allylic carbocation. On the other hand, tetrabutylphosphonium dihydrogen trifluoride produced only one regio- and stereoisomer **45**, probably because of the decreased hardness of the fluoride ion and the greater probability of a direct S_N2-type displacement.

The use of chloride, considered softer than fluoride, produced mainly the stereoisomer **47** with variable amounts of its epimer **46** at the allylic position. The ratio of both epimers was dependent on the reaction conditions (9:1 under optimum conditions), the amount of the *cis* chloro alcohol increasing with the increased acidity of the reagent. These results reinforce



Scheme 5 Synthesis of fluoro- and chloro-conduritol synthons



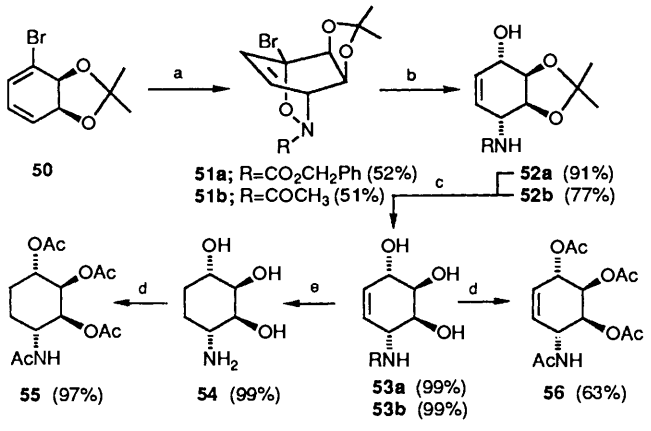
Scheme 6 Opening of the epoxide with hydride as the nucleophile. *Reagents:* a, $LiAlH_4$, ether; b, Bu_3SnH, AIBN, toluene; c, AcOH, THF, H_2O.

our proposal of an S_N1-type mechanism operating during the ring-opening process using halides. The four halogenated conduritols may thus be synthesized with some control of stereochemistry.

Deoxyconduritol E.—When epoxides **33** and **37** were treated with $LiAlH_4$ in ether, the addition of hydride took place at the allylic position presumably by an *anti* displacement at the epoxide ring to give the alcohols **48a** and **48b**, respectively. The bromo alcohol **48b** was reductively debrominated with Bu_3SnH in toluene to afford **49** which was subjected to deprotection in an acid medium to afford the triol **15**, in quantitative yield, Scheme 6.

Aminoconduritols.—Having completed the study of the simple nucleophilic opening of epoxide **33**, we turned to applications of stereocontrol to total synthesis. The synthesis of **42** and **43** allows the conversion of these substances into various aminoconduritols. In the case of **42**, reductive dehalogenation followed by reduction of the azide would produce a structure corresponding to the protected aminoconduritol E-4. In the case of **43**, sequential dehalogenation and debenzylation would provide the acetonide of aminoconduritol F-4.[35]

In addition to the nucleophilic approach, we chose the cycloaddition approach based on a hetero Diels–Alder cycloaddition of acyl nitroso compounds to the bromocyclohexadienediol acetonide **50**. The Diels–Alder reaction of **50** with a nitrosyl dienophile, generated *in situ* from the corresponding hydroxamic acid (*N*-hydroxybenzylurethane and acetohydroxamic acid)[36] led to a single enantiomer with the concomitant establishment of all four contiguous asymmetric centres, Scheme 7. Reductive cleavage[37] of the N–O bond of oxazines



Scheme 7 Synthesis of aminoconduritols. *Reagents:* a, RCONHOH–Bu_4NIO_4; b, Al(Hg); c, AcOH–THF–H_2O; d, Ac_2O–Py; e, H_2–Pd(C).

51a and **51b**, using aluminium amalgam occurred with attendant debromination thereby preserving the *syn* relationship of the hydroxy and the protected amine groups established during the cycloaddition. Deprotection of the acetonide in **52a** followed by hydrogenation led directly to dihydroconduramine A-1 **54** (compound **55** showed $[\alpha]_D$, ^1H and ^{13}C NMR values identical with literature values)[38b] in 46.4% overall yield.[38a] Acid hydrolysis of the acetonide derivative **52b** followed by acetylation gave protected conduramine A-1, **56** (confirmed by $[\alpha]_D$, ^1H and ^{13}C NMR)[38b] in 24.5% overall yield.[38a]

Conclusions

It is evident from the discussion of results above that a fully general synthesis of the conduritol class of cyclitols has been accomplished. The introduction, in a stereocontrolled manner, of almost any heteroatom onto the periphery of cyclohexadienediol bodes well for the expression of this methodology in a system-oriented design for the synthesis of oxygenated compounds. The complete enantiodivergence of our approach is governed by recognition of the proenantiotopic plane(s) present in the two antipodes of any target by appropriate ordering of the chemical sequences to reach each antipode. The diastereoselectivity is achieved by using each functional group in succession as either the element of hindrance (intermolecular) or direction (intramolecular) when setting the next chiral centre relative to the previous one. The regiocontrol is achieved simply by recognizing the polarized electronics of the halogeno diene and by choosing reagents that reinforce reactivity at one or the other terminus. Synthesis of compounds such as aminosugars, fluorosugars, aminoconduritols and other targets form the basis of our current endeavour and will be reported in due course.

Experimental

All non-hydrolytic reactions were carried out under a nitrogen or argon atmosphere, with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried with an internal inert gas sweep. Tetrahydrofuran (THF), diethyl ether, 1,2-dimethoxyethane (DME), and benzene were distilled from sodium–benzophenone; dichloromethane, and toluene from calcium hydride. Analytical TLC was performed on silica gel 60-F_{254} plates. Flash chromatography was performed using Kieselgel 60 (230–400 mesh). Mass spectra were recorded on a DuPont 20-491 or a Varian MAT-112 instrument (low resolution) or on a double-focusing DuPont 21-110C or VGT instrument (exact mass). Infrared spectra were recorded as neat samples (NaCl plates) on a Perkin-Elmer 1600 Series FT spectrometer. Proton and ^{13}C NMR spectra were obtained on a Bruker WP-270 instrument. Proton chemical shifts are reported in parts per million (ppm) relative to chloroform (7.24 ppm). Carbon chemical shifts are reported in parts per million relative to the central line of the $CDCl_3$ triplet (77.0 ppm). The multiplicity is indicated by CH_3, CH_2, CH or C and was determined by INEPT experiments. Coupling constants (J) are given in Hz. Optical rotations are given in 10^{-1} deg cm^2 g^{-1}.

Semiempirical MO calculations were performed using the AM1 approximation developed by Dewar *et al.*[10h] and implemented through MOPAC, v. 5.0 (*QCPE* 455) with full geometry optimization. Molecular-mechanics calculations were performed using MMX, Serena Software, Bloomington, IN 47402-3076.

(1S,2R,3S,4R)-2,3-O-*Isopropylidenecyclohex*-5-*ene*-1,2,3,4-

tetraol, Conduritol A Acetonide **31**.—3-Chlorocyclohexa-3,5-diene-1,2-diol **21** (340 mg, 2.14 mmol) was dissolved in 2,2-dimethoxypropane (DMP, 5 cm^3) and acetone (2 cm^3), with stirring at room temperature; a small crystal of *p*-TsOH was added and stirring was continued for 1 h. 10% Aqueous NaOH (2 cm^3), brine (2 cm^3) and Et_2O (10 cm^3) were added. After 10 min of stirring the layers were separated, the aqueous layer was extracted with Et_2O, and the combined ethereal extracts were washed with brine (3 × 3 cm^3). The organic phase was dried over Na_2SO_4 and evaporated to produce 450 mg of the acetonide **25**. The crude acetonide **25** was dissolved in CCl_4 (50 cm^3) and mixed with tetraphenylporphine (6.1 mg). The solution was irradiated, during which time oxygen was bubbled through, and the process continued at *ca.* 20 °C for 4 h. Evaporation of 90% of the solvent followed by trituration of the green solution with hexane and treatment with activated charcoal (400 mg) produced a light yellow solution which upon evaporation gave the crude crystalline endoperoxide **30** (510 mg, 109%). The crude endoperoxide was dissolved in Et_2O (50 cm^3) and two drops of water were added. The solution was treated with aluminium amalgam (prepared from 0.5 g of aluminium foil). The reaction mixture was stirred for 25 min, whereupon filtration over Celite and evaporation of the solvent gave the essentially pure acetonide of conduritol A **31** (310 mg, 1.67 mmol, 77%), which was recrystallized from CH_2Cl_2–hexane: m.p. 100.5–101 °C (lit.,[39] 101–102 °C); δ($CDCl_3$) 5.88 (2 H, s), 4.20 (4 H, s), 2.49 (2 H, br s), 1.43 (3 H, s) and 1.34 (3 H, s).

(−)-*Conduritol E* **5**.—The acetonide **36**[10f,g] (89 mg, 0.478 mmol) was dissolved in AcOH–THF–H_2O (2:1:1, 3 cm^3). The solution was stirred at 60 °C for 4 h. The solvent was evaporated to yield conduritol E (**5**) (69 mg, 0.475 mmol, 99%). An analytical sample was obtained by recrystallization from MeOH–ether: R_f = 0.18 ($CHCl_3$–MeOH, 4:1); m.p. 192–193 °C (lit.,[40] 193 °C); $[\alpha]_D^{20}$ −330 (*c* 4.5, H_2O) (lit. for enantiomer,[40] +332); ν_{max}(KBr)/cm^{-1} 3382, 2917, 1475, 1097 and 1030; δ_H(D_2O) 5.72 (2 H, m), 4.15 (2 H, m) and 3.76 (2 H, m); δ_C(D_2O; ref. acetone) 127.3 (2 CH), 66.7 (2 CH) and 64.2 (2 CH); *m/z* (CI) (rel. intensity) 147 (M^+, 6), 129 (37), 111 (98) and 83 (100) (Found: C, 49.2; H, 6.9. Calc. for $C_6H_{10}O_4$: C, 49.31; H, 6.90%).

(1S,2R,3S,4S)-5-*Bromo*-3,4-O-*isopropylidenecyclohex*-5-*ene*-1,2,3,4-*tetraol* **38**.—To an ice-cooled solution of (1*R*,4*S*,5*S*,-6*R*)-3-bromo-4,5-*O*-isopropylidene-7-oxabicyclo[4.1.0]hept-2-ene-4,5-diol **37**[10f,g] (465.3 mg, 1.88 mmol) in DMSO (5 cm^3) was added aqueous 10% KOH (5 cm^3). The mixture was refluxed for 6 h. The aqueous solution was extracted with ethyl acetate (6 × 6 cm^3). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by flash chromatography (10% H_2O silica gel; ethyl acetate–hexane 3:1) to afford the diol **38** (316 mg, 63%, 1.19 mmol), which was recrystallized from CH_2Cl_2–hexane: R_f = 0.38 (ethyl acetate–hexane 4:1), m.p. 147.0 °C; $[\alpha]_D^{20}$ −10.7 (*c* 0.35, MeOH); ν_{max}(KBr)/cm^{-1} 3506, 3395, 2984, 1647, 1083 and 1067; δ_H($CDCl_3$) 6.24 (1 H, d, *J* 2.5), 4.66 (1 H, d, *J* 6.1), 4.18 (1 H, dd, *J* 7.9, 6.3), 4.06 (1 H, m), 3.74 (1 H, t, *J* 7.6), 2.92 (2 H, br s), 1.52 (3 H, s) and 1.40 (3 H, s); δ_C($CDCl_3$) 133.8 (CH), 120.2 (C), 111.1 (C), 77.6 (CH), 77.0 (CH), 73.1 (CH), 70.9 (CH), 28.0 (CH_3) and 26.0 (CH_3); *m/z* (CI) (relative intensity 265 (M^+, 6), 249 (14), 189 (100), 170 (50), 161 (20) and 111 (70) (Found: C, 40.5; H, 4.85. Calc. for $C_9H_{13}BrO_4$: C, 40.78; H, 4.94%).

(1S,2R,3R,4R)-3,4-O-*Isopropylidenecyclohex*-5-*ene*-1,2,3,4-*tetraol* **39**.—Bu_3SnH (384 mg, 1.32 mmol) was added to a mixture of azoisobutyronitrile (AIBN) (217 mg, 0.66 mmol) and the vinyl bromide **38** (175 mg, 0.66 mmol) in dry toluene (20 cm^3). The reaction mixture was refluxed for 3 h. The solvent was evaporated and the residue was purified by flash chromatography (silica gel; ethyl acetate–hexane 3:1) to afford the pure product as a white solid (96.9 mg, 0.521 mmol, 79%). An analytical sample was obtained by sublimation (60 °C, bath temp./0.05 Torr): R_f = 0.27 (ethyl acetate–hexane 4:1), m.p. 119.0 °C; $[\alpha]_D^{20}$ −70.8 (*c* 0.25, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3419, 3044, 2988, 1372 and 1053; δ_H($CDCl_3$) 5.83 (2 H, m), 4.62 (1 H, dd, *J* 6.6, 2.3), 4.07 (2 H, dd, *J* 8.7, 6.6), 3.55 (1 H, t, *J* 9.0), 3.23 (2 H, br s), 1.49 (3 H, s) and 1.37 (3 H, s); δ_C($CDCl_3$) 133.5 (CH), 123.5 (CH), 110.5 (C), 77.6 (CH), 75.0 (CH), 72.6 (CH), 70.4 (CH), 28.1 (CH_3) and 25.7 (CH_3); *m/z* (CI) (relative intensity) 187 (M^+, 12), 171 (28), 129 (29), 111 (100) and 83 (36) (Found: C, 58.05; H, 7.65. Calc. for $C_9H_{14}O_4$: C, 58.05; H, 7.58%).

Conduritol F **6**.—Acetonide **39** (209 mg, 1.12 mmol) was dissolved in AcOH–THF–H_2O (2:1:1. 3 cm^3) and the solution was stirred at 60 °C for 6 h. The solvent was evaporated off and conduritol F **6** was obtained (164 mg, 1.1 mmol, 99% yield). An analytical sample was obtained after recrystallization from MeOH–ether: R_f = 0.18 ($CHCl_3$–MeOH 4:1); m.p. 131–132 °C (lit.,[19] 129–130 °C); $[\alpha]_D^{20}$ −84 (*c* 0.71, MeOH) (lit.,[19] −70.5, MeOH); ν_{max}(KBr)/cm^{-1} 3283, 2920, 1420, 1102 and 1061; δ_H($CDCl_3$) 5.79 (1 H, ddd, *J* 10.0, 4.7, 1.9), 5.71 (1 H, dd, *J* 10.0, 1.9), 4.15 (1 H, t, *J* 4.3), 3.92 (1 H, dt, *J* 7.5, 1.6), 3.61 (1 H, dd, *J* 10.4, 7.7), and 3.41 (1 H, dd, *J* 10.4, 4.2); δ_C($CDCl_3$) 133.8 (CH), 128.1 (CH), 74.1 (CH), 73.8 (CH), 72.7 (CH) and 68.0 (CH); *m/z* (EI) (relative intensity) 128 (8), 110 (11), 99 (98) and 86 (100) (Found: C, 49.3; H, 6.95. Calc. for $C_6H_{10}O_4$: C, 49.31; H, 6.90%).

(1S,2S,3R,4S)-3-*Azido*-6-*chloro*-1,2-O-*isopropylidenecyclohex*-5-*ene*-1,2,4-*triol* **41**.—The epoxide **33**[10f,g] (133 mg, 0.657 mmol), sodium azide (2.628 mmol, 171 mg) and dry ammonium chloride (4 equiv., 141 mg) were dissolved in DME–EtOH–H_2O (1.5:1:1), and the solution was heated at *ca.* 80 °C for 1 h. After cooling, brine (15 cm^3) and ethyl acetate (5 cm^3) were added, and the mixture was stirred for 10 min and separated. The aqueous layer was extracted with ethyl acetate (3 × 5 cm^3) and the combined organic extracts were dried with Na_2SO_4 and evaporated to produce a slightly yellow solid (192 mg) which, after flash chromatography (silica gel; hexane–ethyl acetate 7:3), gave the pure azido alcohol **41** (141 mg, 0.574 mmol, 87.8%). An analytical sample was obtained by recrystallization from CH_2Cl_2–hexane: R_f = 0.09 (hexane–ethyl acetate 8:2); m.p. 94–94.5 °C; $[\alpha]_D^{23}$ −10.2 (*c* 0.96, MeOH); ν_{max}(film)/cm^{-1} 3454, 2113, 1250, 1085, 1074 and 869; δ_H($CDCl_3$) 5.87 (1 H, d, *J* 2.0), 4.6 (1 H, d, *J* 6.4), 4.16 (1 H, dd, *J* 8.7, 6.4), 3.96 (1 H, dd, *J* 8.7, 1.4), 3.69 (1 H, td, *J* 8.6, 3.0), 2.88 (1 H, d, *J* 3.0), 1.53 (3 H, s) and 1.40 (3 H, s); δ_C($CDCl_3$) 131.0 (C), 126.6 (CH), 111.5 (C), 77.9 (CH), 75.6 (CH), 73.1 (CH), 61.3 (CH), 28.1 (CH_3) and 25.9 (CH_3) (Found: C, 44.1; H, 4.9; N, 17.05. Calc. for $C_9H_{12}ClN_3O_3$: C, 44.0; H, 4.92; N, 17.10%).

(1R,2R,3R,6R)-6-*Azido*-4-*chloro*-2,3-O-*isopropylidenecyclohex*-4-*ene*-1,2,3-*triol* **42**.—To a solution of chloro alcohol **47** (277.7 mg, 1.59 mmol) in dry DMF (10 cm^3) was added sodium azide (151 mg, 2.324 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 15 h, and then at 80 °C for 4.5 h. The reaction mixture was diluted with Et_2O (20 cm^3) and extracted with 10% aqueous $Na_2S_2O_3$ (1 × 3 cm^3), brine (2 × 5 cm^3), the organic layer was dried with Na_2SO_4 and the solvent evaporated. The oil that resulted was purified by flash chromatography (silica gel; hexane–ethyl acetate 7:3) to produce the azido alcohol **42** (257.9 mg, 1.431 mmol, 66%), R_f = 0.55 (hexane–ethyl acetate 7:3); m.p. 93.5–94 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{27}$ −99 (*c* 0.68, MeOH);

ν_{max}(KBr)/cm^{-1} 3884, 2115, 1651 and 1383; δ_H($CDCl_3$) 5.9 (1 H, dd, *J* 3.6, 0.5), 4.58 (1 H, dd, *J* 5.6, 1.1), 4.39 (1 H, t, *J* 5.6), 4.23 (1 H, m), 4.19 (1 H, m), 2.49 (1 H, br s), 1.42 (3 H, s) and 1.38 (3 H, s); δ_C($CDCl_3$) 134.7 (C), 122.2 (CH), 110.9 (C), 75.9 (CH), 75.0 (CH), 69.4 (CH), 27.6 (CH_3) and 26.0 (CH_3); *m/z* (CI) (relative intensity) 246 (M + 1, 100), 160 (35), 145 (60) and 96 (100) (Found: C, 44.05; H, 4.95; N, 17.05. Calc. for $C_9H_{12}ClN_3O_3$: C, 44.00; H, 4.92; N, 17.10%).

(1R,2S,3S,6S)-6-*Benzylamino*-4-*chloro*-2,3-O-*isopropylidene*-*cyclohex*-4-*ene*-1,2,3-*triol* **43**.—To a stirred solution of the epoxide **33**[10f,g] (140 mg, 0.691 mmol) in $CHCl_3$ (15 cm^3), was added at room temperature, neutral alumina (Fluka, 4.0 g), followed by benzylamine (0.2 cm^3, 1.83 mmol). The reaction mixture was stirred for 4 h after which MeOH (5 cm^3) was added, and stirring was continued for a further 15 min. The mixture was filtered through Celite and the solid was washed thoroughly with 10% MeOH in $CHCl_3$. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (silica gel; hexane–ethyl acetate 7:3) to give the amino alcohol **43** (145 mg, 0.469 mmol, 68%). An analytical sample was obtained by recrystallization from CH_2Cl_2–hexane: R_f = 0.5 (hexane–ethyl acetate 1:1); m.p. 106–106.5 °C; $[\alpha]_D^{23}$ +38 (*c* 0.25, MeOH); ν_{max}(film)/cm^{-1} 3307, 2921, 1217 and 1073; δ_H($CDCl_3$) 7.32–7.30 (5 H, m), 6.06 (1 H, d, *J* 1.6), 4.60 (1 H, d, *J* 6.5), 4.14 (1 H, dd, *J* 8.5, 6.5), 3.93 (1 H, d, *J* 12.9), 3.74 (1 H, d, *J* 12.9), 3.51 (1 H, t, *J* 8.5), 3.16 (1 H, br d, *J* 8.5), 1.51 (3 H, s) and 1.39 (3 H, s); δ_C($CDCl_3$) 139.5 (C), 129.2 (CH), 128.6 (CH), 128.2 (CH), 127.4 (C, CH overlap), 110.9 (C), 78.4 (CH), 75.7 (CH), 71.9 (CH), 58.3 (CH), 50.7 (CH_2), 28.1 (CH_3) and 25.9 (CH_3); *m/z* (CI) (relative intensity) 310 (M$^+$ + 1, 100), 252 (15), 209 (30), 106 (20) and 91 (20) (Found: C, 61.45; H, 6.35. Calc. for $C_{16}H_{20}ClNO_3$: C, 62.03; H, 6.50%).

(1S,2S,3S,6R)- **44** *and* (1S,2S,3S,6S)-4-*Chloro*-6-*fluoro*-2,3-O-*isopropylidenecyclohex*-4-*ene*-1,2,3-*triol* **45**.—*Method A*.[41] To the epoxide **33**[10f,g] (200 mg, 0.987 mmol) in a flame-dried flask under argon were added Et_2O (20 cm^3) and benzene (20 cm^3) at room temperature. Boron trifluoride–diethyl ether (0.483 cm^3, 3.93 mmol) was then added. After being stirred for 15 h the reaction was complete. The reaction solution was washed with aqueous sodium hydrogen carbonate (3 × 5 cm^3) and the organic layer was dried with Na_2SO_4 and evaporated to give yellow oil (205 mg). The crude product was separated by flash chromatography (silica gel; hexane–ethyl acetate 4:1) to give the *cis*-fluoro alcohol **44** as a clear oil (46.8 mg, 0.210 mmol, 21.3%) and the *trans*-fluoro alcohol **45** (51.3 mg, 0.230 mmol, 23.3%). An analytical sample of **45** was accomplished *via* sublimation (70 °C/0.06 Torr) to afford 42.3 mg (0.190 mmol, 19.3%) of a white solid.

Method B. To the epoxide **33**[10f,g] (403 mg, 1.98 mmol, neat) in a flame-dried flask under argon was added tetrabutylphosphonium dihydrogen trifluoride[42] (1.89 g, 5.94 mmol). After 24 h of stirring at 105 °C, the reaction mixture was allowed to cool to room temperature. Water (5 cm^3) was added and the solution was extracted with diethyl ether (4 × 25 cm^3), and the ethereal extracts were combined, dried over Na_2SO_4, and evaporated to give 627.1 mg of residue. Purification by flash chromatography (silica gel; hexane–ethyl acetate 4:1) provided 323 mg (1.50 mmol, 75.2%) of the *trans*-fluoro alcohol **45**.

45: R_f = 0.43 (hexane–ethyl acetate 1:1); m.p. 101–102 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{23}$ −18.0 (*c* 0.9, MeOH); ν_{max}(KBr)/cm^{-1} 3465, 2996, 2871, 1657, 1377 and 1088; δ_H($CDCl_3$) 6.04 (1 H, dd, *J* 12.6, 2.1), 4.92 (1 H, ddm, *J* 49.9, 8.1), 4.62 (1 H, d, *J* 6.4), 4.18 (1 H, dd, *J* 8.6, 6.4), 3.88 (1 H, m), 3.06 (1 H, br s), 1.54 (3 H, s) and 0.91 (3 H, s); δ_C($CDCl_3$) 131.3 (C, d, *J* 12.0), 126.7 (CH, d, *J* 25.1), 111.9 (C), 90.0 (CH, d, *J* 173.5), 76.8 (CH), 75.7 (CH), 72.2 (CH, d, *J* 18.1), 28.0 (CH_3) and 25.9 (CH_3); *m/z* (CI) (relative intensity) 223 (M$^+$ + 1, 100), 207 (86) and 145 (45); δ_F($CDCl_3$) −190.0 (1 F, m) (Found: C, 48.4; H, 5.45. Calc. for $C_9H_{12}ClFO_3$: C, 48.55; H, 5.46%).

44: R_f = 0.49 (hexane–ethyl acetate 1:1); m.p. 77–78 °C; $[\alpha]_D^{23}$ −43.0 (*c* 0.5, MeOH); ν_{max}(film)/cm^{-1} 3410, 2990, 2910, 1750 and 1060; δ_H($CDCl_3$) 6.0 (1 H, dddd, *J* 9.4, 3.1, 1.2, 0.5), 5.2 (1 H, 2 m, $J_{H,F}$ 48.5), 4.6 (1 H, m), 4.5 (1 H, m), 4.4 (1 H, m), 2.3 (1 H, br s), 1.39 (3 H, s) and 1.38 (3 H, s); δ_C($CDCl_3$) 135.3 (C, dd, *J* 13.0, 2.3), 122.5 (CH, d, *J* 24.4), 110.0 (C), 87.1 (CH, d, 169.4), 75.9 (CH), 75.2 (CH), 68.2 (CH), 27.7 (CH_3) and 26.2 (CH_3); δ_F($CDCl_3$) −194.6 (1 F, d, $J_{F,H}$ 48.5) (Found: C, 48.45; H, 5.45. Calc. for $C_9H_{12}ClFO_3$: C, 48.55; H, 5.43%).

(1S,2S,3S,4S)- **46** *and* (1S,2S,3S,4S)-4,6-*Dichloro*-2,3-O-*isopropylidenecyclohex*-4-*ene*-1,2,3-*triol* **47**. *Method A*. A solution of the epoxide **33**[10f,g] (270 mg, 1.33 mmol) in anhydrous Et_2O (4 cm^3), was titrated with a solution of ferric chloride in anhydrous Et_2O, and the reaction was monitored by TLC (silica gel; hexane–ethyl acetate 8:2) for the disappearance of the epoxide. The reaction mixture was cooled in an ice bath, quenched with saturated aqueous $NaHCO_3$ (2 cm^3) and brine (3 cm^3) and diluted with Et_2O (10 cm^3). After being separated, the aqueous layer was extracted with Et_2O (3 × 3 cm^3) and the combined ethereal extracts were washed with brine (1 × 3 cm^3), dried with Na_2SO_4 and evaporated to give 303 mg of a crude material, which was separated by flash chromatography (silica gel, hexane–ethyl acetate 7:3) to produce the *cis*-chloro alcohol **46** (10.6 mg, 0.044 mmol, 3.3%), and the *trans*-chloro alcohol **47** (192 mg, 0.805 mmol, 60.5%).

Method B. To a solution of the epoxide **33**[10f,g] (350 mg, 1.78 mmol) in anhydrous THF (10 cm^3) was added a solution of TBSCl (518 mg, 3.46 mmol) and Et_3N (3 drops) in THF (3 cm^3), at room temperature. After 5 min of stirring under argon, titanium isopropoxide (0.17 cm^3, 0.518 mmol) was slowly added and the stirring was continued for a further 24 h at room temperature. Additional TBSCl (280 mg, 1.86 mmol) and titanium isopropoxide (0.15 cm^3) were added and the reaction was stirred for a further 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (6 cm^3) and brine (4 cm^3) and diluted with Et_2O (30 cm^3). After being separated the aqueous layer was extracted with Et_2O (1 × 10 cm^3) and ethyl acetate (1 × 5 cm^3). The organic extracts were washed with brine (1 × 15 cm^3), dried with Na_2SO_4, and evaporated. The crude product was purified by flash chromatography (silica gel; hexane–ethyl acetate 7:3) to produce the *trans*-chloro alcohol **47** (277 mg, 1.16 mmol, 67.2%) and the epoxide **33** (6.3 mg, 0.03 mmol).

46: R_f = 0.4 (hexane–ethyl acetate 7:3); m.p. 73–74 °C; $[\alpha]_D^{26}$ −120 (*c* 0.12, MeOH); ν_{max}(KBr)/cm^{-1} 3436, 2990, 1649 and 1081; δ_H($CDCl_3$) 6.00 (1 H, d, *J* 3.9), 4.76 (1 H, dd, *J* 3.9, 3.6), 4.65 (1 H, d, *J* 5.6), 4.49 (1 H, t, *J* 6.0), 4.17 (1 H, dd, *J* 6.0, 3.6), 2.48 (1 H, br s), 1.48 (3 H, s) and 1.43 (3 H, s); δ_C($CDCl_3$) 130.6 (C), 128.6 (CH), 111.5 (C), 77.6 (CH), 75.6 (CH), 74.2 (CH), 58.1 (CH), 28.1 (CH_3) and 25.9 (CH_3) (Found: M$^+$, 239.023 682. Calc. for $C_9H_{12}Cl_2O_3$: *M*, 239.024 174).

47: R_f = 0.32 (hexane–ethyl acetate 7:3); $[\alpha]_D^{26}$ −7.3 (*c* 2.08, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3436, 2990, 1649 and 1081; δ_H($CDCl_3$) 6.04 (1 H, dd, *J* 2.0, 1.0), 4.63 (1 H, d, *J* 6.3), 4.38 (1 H, ddd, *J* 8.4, 2.0, 1.0), 4.18 (1 H, dd, *J* 8.4, 8.4), 3.81 (1 H, t, *J* 8.4), 3.11 (1 H, br s), 1.56 (3 H, s) and 1.43 (3 H, s); δ_C($CDCl_3$) 130.5 (C), 128.7 (C), 111.6 (C), 77.5 (CH), 75.7 (CH), 74.3 (CH), 58.2 (CH), 28.0 (CH_3) and 25.9 (CH_3); *m/z* (CI) (relative intensity) 239 (M$^+$ + 1, 100), 223 (20), 145 (20), 89 (18) (Found: M$^+$, 239.021 317. Calc. for $C_9H_{13}Cl_2O_3$: *M*, 239.024 175).

(1S,2S,3R)-4-*Chloro*-2,3-O-*isopropylidenecyclohex*-4-*ene*-1,2,3-*triol* **48a**.—The epoxide **33**[10f,g] (300 mg, 1.48 mmol)

was dissolved in Et_2O (3 cm^3) and added to a solution of $LiAlH_4$ (56.2 mg, 1.48 mmol) in Et_2O (10 cm^3) and the mixture was refluxed for 5 h. Ethyl acetate (5 cm^3) was added, followed by 10% aqueous NaOH solution (10 cm^3). The organic layer was washed with water (5 cm^3) and brine (5 cm^3), and dried with Na_2SO_4. The solvent was evaporated off and the alcohol was purified by flash chromatography (silica gel; hexane–ethyl acetate 6:4) to yield the pure chloro alcohol **48a** (241 mg, 1.18 mmol, 80%); R_f = 0.34 (hexane–ethyl acetate 3:2); $[\alpha]_D^{20}$ −52.5 (*c* 1.9, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3424, 2988, 1654, 1382, 1219 and 1074; δ_H($CDCl_3$) 5.94 (1 H, dd, *J* 5.4, 3.4), 4.56 (1 H, d, *J* 6.0), 4.08 (1 H, dd, *J* 7.4, 6.0), 3.87 (1 H, ddd, *J* 7.8, 7.4, 4.6), 2.47 (1 H, dtd, *J* 17.3, 5.4, 4.6), 2.11 (1 H, ddd, *J* 17.3, 7.8, 3.4), 1.9 (1 H, br s), 1.46 (3 H, s) and 1.38 (3 H, s); δ_C($CDCl_3$) 129.3 (CH), 125.3 (C), 110.1 (C), 78.8 (CH), 75.7 (CH), 67.8 (CH), 30.7 (CH_2), 28.0 (CH_3) and 26.1 (CH_3); *m/z* (CI) (relative intensity) 189 (M^+ − 16, 75), 129 (100), 101 (20) and 59 (50) (Found: C, 52.9; H, 6.4. Calc. for $C_9H_{13}ClO_3$: C, 52.82; H, 6.40%).

(1S,2S,3R)-4-*Bromo*-2,3-O-*isopropylidenecyclohex*-5-*ene*-1,2,3-*triol* **48b**.—The bromo epoxide **37** (202 mg, 0.818 mmol) was dissolved in Et_2O (2 cm^3) and added to a solution of $LiAlH_4$ (31 mg, 0.818 mmol) in Et_2O (6 cm^3). The mixture was refluxed for 5 h, whereupon ethyl acetate (3 cm^3) was added, followed by 10% aqueous NaOH (5 cm^3). The organic layer was washed with water (5 cm^3) and brine (5 cm^3), and dried with Na_2SO_4. The solvent was evaporated to yield the bromo alcohol **48b** (202 mg, 0.81 mmol, 99% yield). A pure sample was obtained by flash chromatography (silica gel; hexane–ethyl acetate 5.5:4.5): R_f = 0.3 (hexane–ethyl acetate 3:2); m.p. 68–69 °C (recrystallized from CH_2Cl_2–hexane); $[\alpha]_D^{20}$ −31 (*c* 1.4, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3422, 2987, 1649 and 1071; δ_H($CDCl_3$) 6.13 (1 H, dd, *J* 5.6, 3.7), 4.63 (1 H, d, *J* 5.9), 4.09 (1 H, dd, *J* 7.2, 6.0), 3.90 (1 H, td, *J* 7.4, 4.7), 2.45 (1 H, dt, *J* 17.4, 4.9), 2.3 (1 H, br s), 2.09 (1 H, ddd, *J* 17.5, 7.5, 3.6), 1.47 (3 H, s) and 1.39 (3 H, s); δ_C($CDCl_3$) 129.4 (CH), 119.6 (C), 109.8 (C), 78.9 (CH), 77.0 (CH), 67.5 (CH), 31.9 (CH_2), 28.0 (CH_3) and 26.1 (CH_3); *m/z* (CI) (relative intensity) 249 (M^+, 68), 233 (100), 191 (55), 175 (73) and 147 (38) (Found: C, 43.4; H, 5.25. Calc. for $C_9H_{13}BrO_3$: C, 43.40; H, 5.26%).

(1R,2S,3R)-2,3-O-*Isopropylidenecyclohex*-4-*ene*-1,2,3-*triol* **49**.—Bu_3SnH (510 mg, 1.75 mmol) was added to a mixture of AIBN (5 mg) and the vinyl bromide **48b** (218.6 mg, 0.878 mmol) in dry toluene (15 cm^3). The reaction mixture was refluxed for 3 h. The solvent was evaporated off, and the residue was purified by flash chromatography (silica gel; Et_2O–hexane 7:3) to afford pure **49** (119.5 mg, 0.702 mmol, 80%): R_f = 0.4 (hexane–ethyl acetate 1:1); $[\alpha]_D^{28}$ −158 (*c* 2.9, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3440, 2900, 1215 and 1055; δ_H($CDCl_3$) 5.88 (2 H, m), 4.61 (1 H, dd, *J* 6.2, 2.6), 3.97 (1 H, dd, *J* 8.5, 6.3), 3.77 (1 H, ddd, *J* 8.8, 5.1), 2.50 (1 H, br s), 2.41 (1 H, ddd, *J* 17.4, 5.1, 4.5), 2.03 (1 H, td, *J* 17.8, 9.8, 1.6), 1.49 (3 H, s) and 1.39 (3 H, s); δ_C($CDCl_3$) 129.3 (CH), 124.2 (CH), 109.1 (C), 79.4 (CH), 72.7 (CH), 69.2 (CH), 30.7 (CH_2), 28.3 (CH_3) and 25.8 (CH_3); *m/z* (EI, 70 eV) (relative intensity) 170 (M^+, 2), 155 (50) and 95 (100) (Found: C, 63.4; H, 8.35. Calc. for $C_9H_{14}O_3$: C, 63.51; H, 8.29%).

(1R,2S,3R)-*Cyclohex*-4-*ene*-1,2,3-*triol* **15**.—The acetonide **49** (32.5 mg, 0.19 mmol) was dissolved in AcOH–THF–H_2O (2:1:1; 3 cm^3). The solution was stirred at 60 °C for 4 h, after which the solvent was evaporated to give the triol **15** (24.7 mg, 0.19 mmol, 100% yield). An analytical sample was obtained after recrystallization from MeOH–Et_2O: R_f = 0.36 ($CHCl_3$–MeOH 4:1); m.p. 130 °C; $[\alpha]_D^{25}$ −194 (*c* 0.3, MeOH); ν_{max}(neat)/cm^{-1} 3209, 3039, 1648 and 1101; δ_H(D_2O) 5.64 (1 H, ddd, *J* 10, 4.4, 2.3), 5.57 (1 H, ddd, *J* 10, 4.1, 2.3), 4.09 (1 H, dd, *J* 4.0, 4.0), 3.74 (1 H, ddd, *J* 8.5, 8.5, 2.0), 3.49 (1 H, dd, *J* 9.5, 4.3), 2.37 (1 H, ddd, *J* 17.7, 5.7, 4) and 1.87 (1 H, ddd, *J* 17.7, 8.5, 4.0); δ_C(D_2O) 126.7 (CH), 123.9 (CH), 70.7 (CH), 64.6 (CH), 64.5 (CH) and 30.5 (CH_2); *m/z* (EI, 70 eV) (relative intensity) 113 (M^+ − 17, 100) and 95 (30) (Found: C, 55.25; H, 7.7. Calc. for $C_6H_{10}O_3$: C, 55.37; H, 7.74%).

3-*Benzyloxycarbonyl*-1-*bromo*-5,6-O-*isopropylidene*-2-*oxa*-3-*azabicyclo*[2.2.2]*oct*-7-*ene*-5,6-*diol* **51a**.—*N*-Hydroxybenzylurethane (1.720 g, 10.3 mmol) was added slowly to a solution of the protected bromo diol **50** (0.915 g, 4.0 mmol) and Bu_4NIO_4 (2.403 g, 5.5 mmol) in CH_2Cl_2 (10 cm^3) in an ice bath. After 1 h, the solution was washed with 20% aqueous sodium thiosulphate (10 cm^3), saturated aqueous Na_2CO_3 (10 cm^3), and brine (10 cm^3). The organic layer was dried over Na_2SO_4, filtered and evaporated. The Diels–Alder adduct **51a** was purified by flash chromatography (silica gel; hexane–ethyl acetate 7:3) (813 mg, 52%): R_f = 0.48 (hexane–ethyl acetate 7:3); $[\alpha]_D^{20}$ +16.1 (*c* 9.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3067, 2992, 1755, 1714, 1607, 1269 and 1212; δ_H($CDCl_3$) 7.33 (5 H, s), 6.49 (1 H, dd, *J* 8.5, 1.4), 6.36 (1 H, dd, *J* 8.5, 5.6), 5.22 (1 H, d, *J* 12.3), 5.15 (1 H, d, *J* 12.3), 5.05 (1 H, m), 4.61 (2 H, m), 1.34 (3 H, s) and 1.31 (3 H, s); δ_C($CDCl_3$) 157.8 (C), 135.4 (C), 134.1 (2 CH), 131.5 (CH), 128.5 (2 CH), 128.4 (CH), 128.0 (CH), 111.5 (C), 87.5 (C), 81.4 (CH), 74.3 (CH), 68.5 (CH_2), 53.3 (CH), 25.7 (CH_3) and 25.4 (CH_3); *m/z* (EI) (relative intensity) 395 (M^+, 1), 100 (10) and 91 (100) (Found: C, 51.4; H, 4.6. Calc. for $C_{17}H_{18}BrNO_5$: C, 51.53; H, 4.58%).

3-*Acetyl*-1-*bromo*-5,6-O-*isopropylidene*-2-*oxa*-3-*azabicyclo*-[2.2.2]*oct*-7-*ene*-5,6-*diol* **51b**.—Acetohydroxamic acid (170.4 mg, 2.27 mmol) was added slowly to a solution of the protected bromo diol **50** (525 mg, 2.27 mmol) and Bu_4NIO_4 (492 mg, 1.136 mmol) in CH_2Cl_2 (10 cm^3) in an ice bath. After 1 h, the solution was washed with 20% sodium thiosulphate solution (10 cm^3), saturated aqueous Na_2CO_3 (10 cm^3) and brine (10 cm^3). The organic layer was dried over Na_2SO_4, filtered and evaporated. The Diels–Alder adduct **51b** was purified by flash chromatography (silica gel; hexane–ethyl acetate 3:1) (350.7 mg, 1.153 mmol, 51%): R_f = 0.34 (hexane–ethyl acetate 4:1); m.p. 99–102 °C; $[\alpha]_D^{20}$ −13.7 (*c* 4.3, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3076, 1657, 1606 and 1384; δ_H-($CDCl_3$) 6.43 (1 H, m), 5.41 (1 H, m), 4.60 (1 H, dd, *J* 7.0, 0.6), 4.53 (1 H, ddd, *J* 7.0, 4.0, 0.6), 2.04 (3 H, s), 1.34 (3 H, s) and 1.31 (3 H, s); δ_C($CDCl_3$) 174.2 (C), 133.8 (CH), 132.5 (2 CH), 111.5 (C), 88.2 (C), 81.4 (CH), 74.1 (CH), 49.8 (CH), 25.6 (CH_3), 25.3 (CH_3) and 21.7 (CH_3); *m/z* (EI) (relative intensity) 304 (M^+, 10), 288 (65), 156 (95), 124 (100) and 94 (85).

(1S,2R,3S,6R)-6-*Benzyloxycarbonylamino*-1,2-O-*isopropylidenecyclohex*-4-*ene*-1,2,3-*triol* **52a**.—To a stirred solution of the Diels–Alder adduct **51a** (221 mg, 0.056 mmol) in aqueous tetrahydrofuran (THF–H_2O, 10:1; 11 cm^3) cooled to 0 °C, was added aluminium amalgam (from 105 mg, 3.9 mmol, 7 equiv. Renolds heavy-duty aluminium foil), and stirring was continued at 0 °C. After 6 h, the reaction was complete. The reaction mixture was diluted with THF (30 cm^3), stirred for 10 min, then filtered through Celite. The filtrate was diluted with toluene and concentrated under reduced pressure to afford the hydroxy carbamate **52a** as a white solid (161 mg, 0.51 mmol, 91%). An analytical sample was obtained by flash chromatography (silica gel, hexane–ethyl acetate 1:1), and recrystallized from CH_2Cl_2–hexane: R_f = 0.32 (hexane–ethyl acetate 1:1); m.p. 113–114 °C; $[\alpha]_D^{20}$ −41 (*c* 0.8, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3338, 2989, 1702, 1522, 1217 and 1064; δ_H($CDCl_3$) 7.37 (5 H, m), 5.96 (1 H, m), 5.83 (1 H, dd, *J* 9.8, 2.2), 5.31 (1 H, br s), 5.13 (2 H, d, *J* 2.8), 4.23 (4 H, m), 4.18 (1 H, m), 2.64 (1 H, br s), 1.47 (3 H, s) and 1.36 (3 H, s); δ_C($CDCl_3$) 155.9 (C), 136.3 (C), 131.1

(CH), 129.8 (CH), 128.5 (3 CH), 128.2 (2 CH), 109.2 (C), 79.2 (C), 77.0 (CH), 69.1 (CH), 67.0 (CH_2), 51.3 (CH), 27.0 (CH_3) and 24.7 (CH_3); *m/z* (CI) (relative intensity) 320 ($M^+ + 1$, 20), 262 (30), 212 (100) and 91 (50) (Found: C, 64.0; H, 6.65. Calc. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63%).

(1S,2R,3S,6R)-6-*Acetamido*-1,2-O-*isopropylidenecyclohex*-4-*ene*-1,2,3-*triol* **52b**.—A solution of the Diels–Alder adduct **51b** (265 mg, 0.87 mmol) in aqueous tetrahydrofuran (THF–H_2O, 10:1; 11 cm^3) was cooled to 0 °C, aluminium amalgam (from 165 mg, 6.1 mmol, 7 equiv. of Reynolds heavy-duty aluminium foil) was added, and stirring was continued at 0 °C. After 6 h, reaction was complete. The reaction mixture was diluted with THF (30 cm^3), stirred for 10 min, then filtered through Celite. The filtrate was diluted with toluene and concentrated under reduced pressure to afford the hydroxy carbamate **52b** as a white solid (152 mg, 0.67 mmol, 77%). An analytical sample was obtained by flash chromatography (silica gel; hexane–ethyl acetate 1:1), and recrystallized from CH_2Cl_2–hexane: R_f = 0.3 ($CHCl_3$–MeOH 9:1); m.p. 113–114 °C; $[\alpha]_D^{20}$ −38 (*c* 8.7, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3300, 1640, 1360 and 1050; δ_H($CDCl_3$) 6.45 (1 H, br s), 5.75 (1 H, ddd, *J* 9.9, 2.8, 2.5), 5.51 (1 H, ddd, *J* 9.9, 2.8, 2.5), 4.34 (1 H, m), 3.6 (1 H, br s), 4.23 (3 H, m), 1.97 (3 H, s), 1.39 (3 H, s) and 1.30 (3 H, s); δ_C($CDCl_3$) 170.1 (C), 131.3 (CH), 129.7 (CH), 109.0 (C), 79.1 (C), 76.6 (CH), 68.3 (CH), 49.3 (CH), 26.9 (CH_3), 24.7 (CH_3) and 23.4 (CH_3); *m/z* (EI, 70 eV) (relative intensity) 212 (M^+ − 15, 25), 168 (35), 140 (50), 127 (90), 98 (75) and 81 (100).

(1S,2R,3S,6R)-6-*Benzyloxycarbonylaminocyclohex*-4-*ene*-1,2,3-*triol* **53a**.—To a solution of the acetonide **52a** (29 mg, 0.09 mmol), in 1:1 acetone–H_2O (5 cm^3), was added concentrated HCl (1 drop). The solution was stirred for 12 h at room temperature and concentrated to afford (25 mg, 0.089 mmol, 99% yield) of the triol **53a**: R_f = 0.44 ($CHCl_3$–MeOH, 4:1); m.p. 122–124 °C; δ_H(CD_3OD) 7.25 (5 H, m), 5.62 (1 H, br d, *J* 10.0), 5.49 (1 H, br d, *J* 10.0), 4.13 (1 H, m), 4.03 (1 H, m), 3.70 (1 H, dd, *J* 6.0, 2.2) and 3.63 (1 H, m).

(1S,2R,3S,6R)-6-*Acetamidocyclohex*-4-*ene*-1,2,3-*triol* **53b**.—The acetonide **52b** (160 mg, 0.7 mmol) was dissolved in AcOH–THF–H_2O (2:1:1; 8 cm^3). The solution was stirred at 60 °C for 4 h. The solvent was evaporated off and the triol **53b** was obtained (130 mg, 0.69 mmol, 99%): δ_H(CD_3OD) 5.53 (1 H, ddd, *J* 10.0, 3.2, 1.9), 5.32 (1 H, ddd, *J* 10.0, 3.1, 1.0), 4.25 (1 H, m), 3.94 (1 H, m), 3.56 (1 H, dd, *J* 5.5, 2.3), 3.49 (1 H, dd, *J* 5.5, 2.3) and 1.75 (3 H, s); δ_C(CD_3OD) 173.1 (C), 130.7 (CH), 128.2 (CH), 73.9 (CH), 71.8 (CH), 69.9 (CH), 51.4 (CH) and 22.4 (CH_3).

(1S,2R,3S,4R)-4-*Aminocyclohexane*-1,2,3-*triol*:*Dihydroconduramine A-1* **54**.[38]—The carbamate **53a** (25 mg, 0.09 mmol), was dissolved in MeOH (5 cm^3). 5% Palladium on charcoal (15 mg) was added, and the mixture was shaken in a Parr hydrogenator for 4 h at 30 psi of H_2. The mixture was then filtered through Celite and the solvent evaporated off to afford dihydroconduramine A-1 **54** (13 mg, 0.089 mmol, 99% yield): δ_H(CD_3OD) (1 H, m), 3.71 (1 H, t, *J* 3.3), 3.49 (1 H, dd, *J* 10.0, 3.1), 2.90 (1 H, td, *J* 10.0, 4.5) and 1.8–1.4 (4 H, m); δ_C(CD_3OD) 74.0 (CH), 73.2 (CH), 71.1 (CH), 51.9 (CH), 26.9 (CH_2) and 26.2 (CH_2).

(1S,2R,3S,4R)-4-*Acetamidocyclohexane*-1,2,3-*triyl Triacetate*: *Dihydroconduramine A-1 Tetraacetate* **55**.[38]—Dihydroconduramine A-1 **54** (17 mg, 0.116 mmol) was stirred in Ac_2O–pyridine (1:1; 2 cm^3), for 3 h at room temperature. The solution was washed with 10% HCl and extracted with ethyl acetate, the organic layer was dried over Na_2SO_4 and filtered and the solvent was evaporated off to afford the tetraacetate **55** (35 mg, 0.112 mmol, 97% yield): R_f = 0.35 (hexane–ethyl acetate 1:1); $[\alpha]_D^{20}$ +42 (*c* 0.9, $CHCl_3$) (lit.,[38] +42.4); δ_H($CDCl_3$) 5.68 (1 H, d, *J* 8.5), 5.22 (1 H, t, *J* 3.8), 5.06 (1 H, dd, *J* 10.4, 3.3), 4.98 (1 H, m), 4.4–4.2 (1 H, m), 2.10 (3 H, s), 2.08 (3 H, s), 1.98 (3 H, s) and 1.93 (3 H, s); δ_C($CDCl_3$) 171.4 (C), 169.7 (C), 169.4 (C), 169.2 (C), 71.0 (CH), 69.4 (CH), 69.3 (CH), 47.9 (CH), 25.9 (CH_2), 24.1 (CH_2), 23.3 (CH_3), 20.9 (2 CH_3) and 20.8 (CH_3); *m/z* (EI) (relative intensity) 315 (M^+, 5), 195 (30), 153 (70) and 94 (100).

(1S,2R,3S,6R)-6-*Acetamidocyclohex*-4-*ene*-1,2,3-*triyl Triacetate*: *Conduramine A-1 Tetraacetate* **56**.—The triol **52b** (72.6 mg, 0.388 mmol) was stirred in Ac_2O–pyridine (1:1; 2 cm^3), for 3 h. The solution was washed with 10% HCl and extracted with ethyl acetate, the organic phase was dried over Na_2SO_4 and filtered, and the solvent was evaporated off to afford the tetraacetate **56** (76 mg, 0.243 mmol, 63%): R_f = 0.38 ($CHCl_3$–MeOH, 95:5); $[\alpha]_D^{20}$ +33 (*c* 0.4, $CHCl_3$) (lit.,[38] +35.6); δ_H($CDCl_3$) 5.78 (2 H, m), 5.75 (1 H, d, *J* 9.0), 5.28–5.15 (3 H, m), 4.80 (1 H, dd, *J* 8.3, 7.5), 2.06 (3 H, s), 2.05 (3 H, s), 2.04 (3 H, s) and 1.96 (3 H, s); δ_C($CDCl_3$) 170.6 (C), 169.8 (2 C), 169.6 (C), 131.1 (CH), 125.0 (CH), 69.6 (CH), 68.3 (CH), 47.8 (CH), 23.2 (CH_3) and 20.8 (3 CH_3); *m/z* (EI) (relative intensity) 254 (M^+ − 59, 100), 151 (95) and 109 (80).

(1S,2R,3S,4S)-5-*Chloro*-3,4-O-*isopropylidenecyclohex*-5-*ene*-1,2,3,4-*tetraol* **57**.—To a solution of the epoxide **33**[10f,g] (1.48 g, 7.31 mmol) in acetone–H_2O (2:1; 30 cm^3) was added HCl in acetone (2% v/v, 0.5 cm^3). The solution was stirred at room temperature for 10 h. The volatile substances were evaporated off under reduced pressure, and the residual solution was saturated with NaCl, and then extracted with ethyl acetate (3 × 10 cm^3). The organic extracts were dried with Na_2SO_4 and evaporated to give the essentially pure diol **57** (1.547 g, 7.13 mmol, 97.6%). The product was recrystallized from CH_2Cl_2–hexane: R_f = 0.38 (hexane–ethyl acetate 2:8); m.p. 106–107 °C; $[\alpha]_D^{25}$ −20.9 (*c* 0.34, MeOH); ν_{max}(film)/cm^{-1} 3386, 2988, 1650 and 1068; δ_H($CDCl_3$) 5.99 (1 H, d, *J* 2.6), 4.59 (1 H, d, *J* 6.2), 4.18 (1 H, dd, *J* 8.0, 6.2), 4.12 (1 H, m), 3.71 (1 H, t, *J* 7.7), 3.21 (1 H, br s), 3.10 (1 H, br s), 1.51 (3 H, s) and 1.39 (s, 3 H); δ_C($CDCl_3$) 129.9 (CH), 128.0 (CH), 111.4 (C), 77.5 (CH), 75.8 (CH), 73.5 (CH), 70.0 (CH), 28.0 (CH_3) and 25.9 (CH_3); *m/z* (CI) (relative intensity) 221 (M^+, 4), 205 (16), 145 (100), 117 (30) and 81 (30); (Found: C, 49.1; H, 5.95. Calc. for $C_9H_{14}ClO_4$: C, 49.19; H, 5.91%).

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