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Enantiospecific synthesis and insect feeding activity of sulfur-containing cyclitols

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ABSTRACT

The first syntheses of two deoxythiocyanocyclitols (4-deoxy-4-thiocyano-L-*chiro*-inositol and deoxythiocyanoconduritol F) and two deoxysulfonylcyclitol acetals are reported by a chemoenzymatic enantioselective route. The compounds were prepared by a sequence of enzymatic and ruthenium-catalyzed dihydroxylations, and the results were studied regarding reaction conditions and co-catalyst for different derivatives. The new compounds were included in a minilibrary of deoxygenated cyclitols and evaluated for their capacity to influence the feeding behavior of *Epilachna paenulata* (Coleoptera: Coccinellidae), a common pest of the Curcubitaceae crops.

1. Introduction

Cyclitols are a group of molecules of particular interest among those in the carbohydrate family of compounds. The biological activity of these compounds, and particularly their role in intracellular communication, has been extensively studied and summarized.[1] In our laboratory, we have developed efficient chemoenzymatic routes for the preparation of *epi*-inositol,[2] (−)-conduramine C-4,[3] phenylthioconduritol F,[4] hydroxythiocyanates, and episulfides.[5] The common starting material for all of these syntheses is the homochiral metabolite **1** produced by whole-cell asymmetric dihydroxylation of bromobenzene with toluene dioxygenase (TDO) (Fig. 1).[6,7] In a continuation of our previous studies on the ring opening of vinyl oxiranes with sulfur compounds,[4,5]

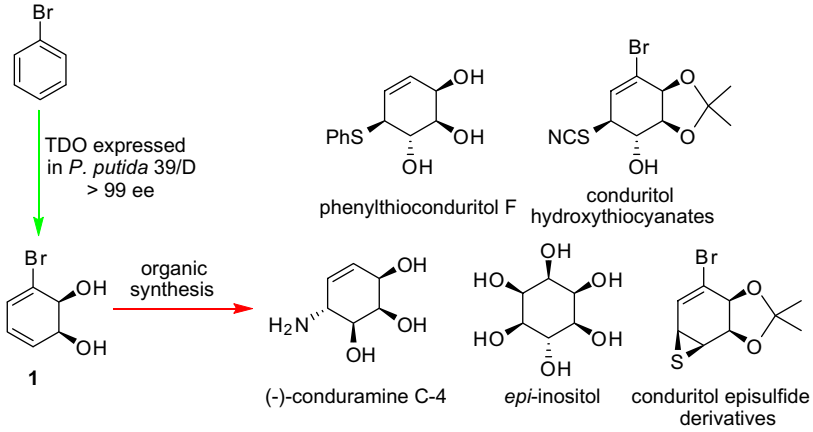

Figure 1. Chemoenzymatic synthesis of cyclitols from bromobenzene.

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we now wish to report the results obtained for the preparation of unnatural cyclitol derivatives containing a –SCN and SO_2Ph group.

We considered the synthesis of these previously unreported molecules based on their similarity to a number of cyclitol derivatives exhibiting antifeedant, antibiotic, antileukemic, and growth-regulating activity.[8,9] In view of their biological potential, we tested some of the cyclitol derivatives as feeding deterrents against *Epilachna paenulata* (Coleoptera: Coccinellidae). Those results, the synthesis of the new sulfur-containing derivatives, and in particular the total synthesis of a thiocyanodeoxy L-*chiro*-inositol are disclosed here.

2. Results and discussion

2.1. Chemistry

To access our target, we proceeded according to the traditional strategy, oxygenation of the *cis*-dienediol **1**.[6] The diol was protected as its corresponding acetonide and the more reactive unsubstituted double bond was epoxidized to furnish the α-oxirane **2**.[10–13] Radical dehalogenation and treatment with ammonium thiocyanate gave thiocyanohydrin **4** as we previously described.[5] Attempts to prepare **4** by radical dehalogenation of hydroxythiocyanate **5** using AIBN or azobiscyclohexane carbonitrile (ABCC) failed. Loss of the thiocyanate group by the action of Bu_3SnH was unavoidable, and therefore compound **6**[13] was obtained as the only identified product in this reaction (Scheme 1).

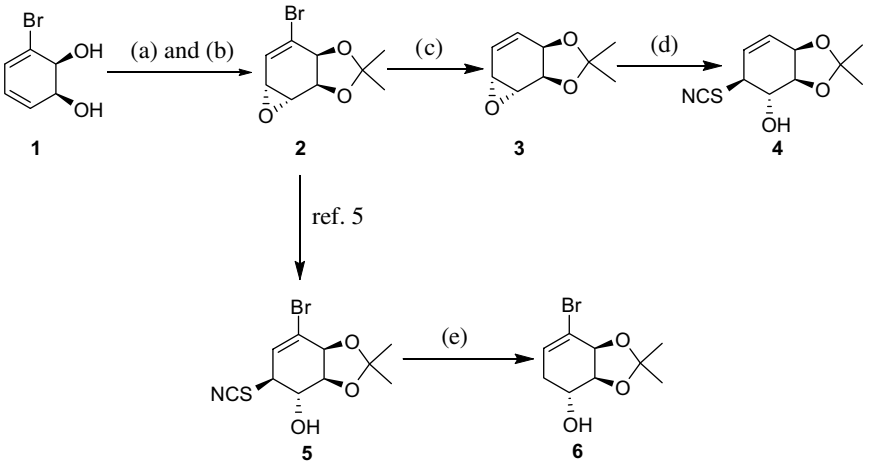
Acetonide **4** was deprotected to render 4-deoxy-4-thiocyanoconduritol F (**7**), the first described SCN-containing deoxyconduritol. Importantly, intermediate **4** was dihydroxylated affording the oxidation level of an inositol, followed by acetonide deprotection to provide the deoxyinositol **8** (Scheme 2).

The reactivity of the olefin toward two dihydroxylating reagents (OsO_4/NMO and $RuCl_3$/$NaIO_4$) under different reaction conditions was studied, and the results are summarized in Table 1. Attempts at the cis-dihydroxylation of **4** using a catalytic amount of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide as co-oxidant were unsuccessful as shown in entries 1 and 2. Experiments utilizing stoichiometric amounts of OsO_4 consumed the starting material in 24 h. However, only minute amounts of the desired product were obtained even after 24 h of reaction time (entry 3). In addition, the high cost of OsO_4, its volatility, toxicity, and the cumbersome recovery of the compound, was not appealing; therefore, we abandoned this methodology.

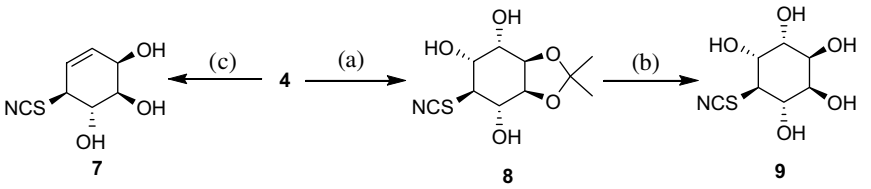
In 1994, Shing reported a dihydroxylation using catalytic amounts of ruthenium tetraoxide.[14] RuO_4 is isoelectronic to OsO_4, and several reports in the literature describe its use as an effective and greener alternative for the dihydroxylation of unreactive alkenes.[15–17] In particular, Hudlicky and Desjardins described the

Table 1
Dihydroxylation of thiocyanoconduritol **4**

Entry	Conditions	*T* (°C)	Time	Isolated yield (%)
1	Catalytic OsO_4–NMO	rt	2 days	No reaction
2		40	1 day	No reaction
3	Stoichiometric OsO_4	rt	1 day	**8** (trace)
4	Catalytic $RuCl_3$ (6%)–$NaIO_4$	−25	10 min	No reaction
5	(1.5 equiv)		20 min	No reaction
6		−12	10 min	No reaction
7			20 min	No reaction
8		0	3 min	**8** (trace)
9		0	9 min	**8** (23)
10		0	15 min	**8** (82)



Scheme 1. Synthesis of thiocyanohydrin **4** and compound **6**. Reagents and conditions: (a) DMP, *p*-TsOH, acetone, rt, 95%; (b) *m*-CPBA, CH_2Cl_2, rt, 80%; (c) Bu_3SnH, ABCC, THF, reflux, 4 h, 70%; (d) NH_4SCN, CH_3CN, 1 h, 85%; (e) Bu_3SnH, AIBN, THF, reflux, 2 h, 50%.



Scheme 2. Synthetic route developed toward thiocyanocondurtiol F (**7**) and 6-thiocyanodeoxy L-*chiro*-inositol (**9**). Reagents and conditions: (a) $RuCl_3$–$NaIO_4$, AcOEt–CH_3CN–H_2O, 15 min, 82%; (b) Dowex 50 (H^+), MeOH–H_2O, rt, 1 h, 93%; (c) Dowex 50 (H^+), MeOH–H_2O, rt, 24 h, 90%.

dihydroxylation of a conduritol acetal with an $RuCl_3$–$NaIO_4$ mixture in their synthesis of *allo*-inositol.[18] It is known that RuO_4 can rapidly cleave C=C bonds.[19,20] However, the nucleophilic addition of water to the intermediate ruthenate is faster in a 3:3:1 mixture of EtOAc, acetonitrile, and water. Any other solvent combination facilitated the scission reaction.[19] As a consequence, we choose this ternary solvent mixture as a starting point. Oxidation of **4** using $RuCl_3$ and $NaIO_4$ (as co-oxidant) furnished *syn*-diol **8** with complete reaction within 15 min as described in entry 10 (Table 1). All attempts to run the reaction below 0 °C resulted in the complete recovery of the starting material (entries 4–7). Dihydroxylation under kinetic control overwhelmingly favored the formation of the less hindered L-*chiro*-inositol substitution pattern (Scheme 2).

Deprotection of **8** under acidic conditions rendered **9** in 36% overall yield from compound **1**. Analysis of the ^1H and ^1H-COSY spectra of the protected inositol **8** identified to be it stereochemically analogous to L-*chiro*-inositol. The spectra of this compound showed that the key proton H4 (cyclitol numbering) is coupled with a large diaxial coupling constant to the neighboring protons H3 and H5 (Table 2). The measured coupling constants are in good agreement with the corresponding large torsion angles (175°, 174°, and 140°) calculated using the Karplus equation for the AM1 minimized structure of **8** shown in Figure 2.

The successful dihydroxylation of **4** prompted us to study the reactivity of the protected derivative of 4-deoxy-4-(phenylthio)conduritol F (**10**) (Scheme 3).[4] We reasoned that **10** could be selectively oxidized to obtain the protected derivative of 4-deoxy-4-(phenylthio)-L-*chiro*-inositol (**14**). However, **10** did not render the expected dihydroxylated compound as deduced from the ^1H NMR data. In fact, the reaction afforded three products (Table 3, entry 1) corresponding to the diastereomeric mixture of sulfoxides **11** and the sulfone **12** as shown in Scheme 3.

Since there were two oxidants involved in the reaction, we decided to determine which of them was responsible of the sulfide oxidation. In order to study the effect of the co-oxidant, we performed the reaction using 1.5 equiv of $NaIO_4$ in the absence of

Table 2
Experimental coupling constants of acetonide **8**

H's	Multiplicity	Experimental values *J*'s (Hz)
H1	dd	3.1 (H1–H6); 5.4 (H1–H2)
H2	dd	5.4 (H2–H1); 5.8 (H2–H3)
H3	ddd	10.6 (H3–H4); 6.1 (H3–H2); 6.0 (H3–OH3)
H4	t	10.2 (H4–H3); 10.2 (H4–H5)
H5	ddd	3.2 (H5–H6); 9.8 (H5–H4); 6.8 (H5–OH5)
H6	dt	3.2 (H6–H5); 3.1 (H6–H1); 3.1 (H6–OH6)
OH3	d	6.0 (OH–H3)
OH5	d	6.9 (OH–H5)
OH6	d	3.8 (OH–H6)

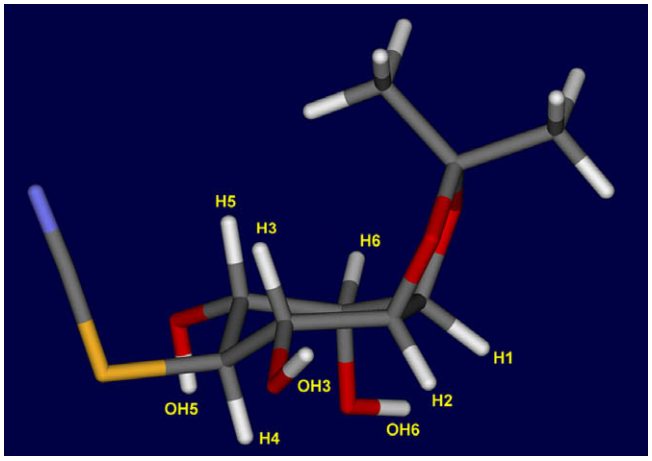
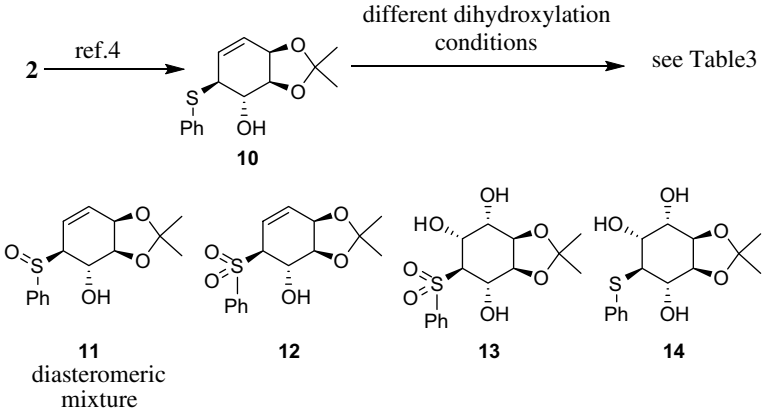


Figure 2. Minimized structure of 4-deoxy-4-thiocyano-L-*chiro*-inositol dimethyl acetal.

Table 3
Dihydroxylation of compound **10**

Entry	Conditions	*T* (°C)	Time	Isolated yield (%)
1	Catalytic $RuCl_3$ (6%)–NaIO4 (1.5 equiv)	0	30 min	**11** (19) **12** (42)
2	$NaIO_4$ (1.5 equiv)	0	10 min	No reaction
3			20 min	No reaction
4			3 h	**11** (trace)
5	$NaIO_4$ (3.0 equiv)	rt	4 h	**11** **12** (trace)
6			24 h	**12**
7	$RuCl_3$ (8%)–$NaIO_4$ (2.0 equiv)	0	30 min	**12** (56) **13** (29)
8	$RuCl_3$ (10%)–$NaIO_4$ (2.0 equiv)	0	30 min	**12** (43)[a]
9	$RuCl_3$ (15%)–$NaIO_4$ (2.0 equiv)	0	30 min	**12** (50)[a]
10	$RuCl_3$ (30%)–$NaIO_4$ (2.0 equiv)	0	30 min	**12** (50)[a]
11	$RuCl_3$ (6%)–*t*-BuOOH (2.0 equiv)	0	2 h	Recovery s.m. **11**
		rt	1 h	(trace)
12	$RuCl_3$ (8%)–*t*-BuOOH (2.0 equiv)	rt	24 h	Recovery s.m. **11** (13)

[a] In these cases, **12** is obtained along with a complex mixture of polar compounds that could neither be isolated in the pure state nor identified.



Scheme 3. Oxidation of compound **10**. The deoxy inositol derivative **14** was never detected in the reaction mixtures.

$RuCl_3$ (Table 3, entries 2–4). Under these conditions even after 3 h, only minute amounts of **11** were formed. The diastereomeric mixture of sulfoxides had identical chromatographic properties, and the individual isomers could not be isolated in the pure state. When we then performed several microscale screening reactions, for example, by increasing the amount of $NaIO_4$ (3.0 equiv), we isolated either a mixture of **11** and **12** after 4 h (entry 5) or the sulfone **12** as the only product after 24 h (entry 6). From these experiments it is clear that compound **12** is formed from **11** by a stepwise sequential oxidation.

In order to study the effect of the amount of $NaIO_4$ in the presence of $RuCl_3$, we carried out several experiments with various combinations of oxidant and co-oxidant. The results shown in entries 7–11 indicated that inositols were formed, but concomitant oxidation of the sulfur atom was unavoidable with these reagents. The results indicated that the dihydroxylation of the olefin was not attainable without altering the sulfur oxidation state. However, this route seems an appealing route toward inositol sulfoxides and particularly sulfones.

Interestingly, inositol derivative **13** is better obtained with a relatively low load of the catalytic oxidant (8 mol %, entry 7). Using a lower (6 mol %, entry 1) or higher (10, 15, 30 mol %, entries 8–10) amount did not render any dihydroxylated product. While it is difficult to justify the great disparity in product formation based on the stated and subtle variance in the $RuCl_3$ catalyst loading, these results were repeatable and occurred when using the same lots of the indicated chemicals.

In a final effort to enable chemoselective oxidation of the olefin in the presence of a thiophenyl residue, we tested *tert*-butylhydrogen peroxide as an alternative stoichiometric oxidant (entries 11–12). *tert*-Butylhydroperoxide is less reactive than periodate since it did not render any product at 0 °C in the presence of 6 mol % $RuCl_3$. When the reaction was warmed up to room temperature, trace amounts of sulfoxide **11** were formed. Increasing the amount of $RuCl_3$ to 8 mol % (which had caused a dramatic change when used in combination with $NaIO_4$) did not yield any sulfone or dihydroxylated products but did again form the sulfoxide **11** in 13% yield.

Overall, these results indicate that successful dihydroxylation of the olefin is dependant of a delicate balance between the stoichiometric oxidant and its ratio to the catalytically active ruthenium. According to our results, the combination of 8 mol % $RuCl_3$ and 2 equiv of $NaIO_4$ is the best fit to achieve the task, although it cannot selectively oxidize the double bond in the presence of the thiophenyl moiety.

As part of our program for the synthesis of cyclitol derivatives to be evaluated for their biological properties, we prepared a small library of analogs (Fig. 3), which was tested for deterrent activity.

2.2. Biological studies

2.2.1. Feeding activity assay: option bioassay using *E. paenulata* (Coleoptera: Coccinellidae)

This bioassay tests feeding deterrence or stimulation of a compound against a special herbivorous insect, *E. paenulata*. Indexes of variability in feeding activity (IFA) were calculated, and the results obtained are shown in Table 4. Preference for the control or the treatment is depicted in Figure 4.

The outcomes of this test revealed that compounds **9, 15, 16, 17**, and **18** were active (p <0.05). Compounds **9, 15**, and **17** showed deterrent activity ($0 < IFA < 1$), while compound **16** and **18** had the opposite phagoestimulant activity ($-1 < IFA < 0$).

Some conclusions can be drawn from this preliminary screening. While sugars and inositols are usually phagostimulants and are well tolerated,[22] substituted deoxygenated inositols can exert a deterrent or phagostimulant effect depending on the nature

Table 4
Index of variability in feeding activity calculated for the compounds tested

Compound	Activity (p values)[a]	IFA[b]
7	None (0.440)	0.6 ± 0.2
9	Deterrent (0.012)	0.90 ± 0.04
15	Deterrent (0.028)	0.82 ± 0.05
16	Phagostimulant (0.029)	−0.71 ± 0.08
17	Deterrent (0.048)	0.7 ± 0.1
18	Phagostimulant (0.002)	−0.8 ± 0.1
19	None (0.233)	0.4 ± 0.1
20	None (0.370)	0.3 ± 0.2
21	None (0.172)	0.7 ± 0.1

[a] p values from Wilcoxon Rank Test.
[b] ±standard error (IFA).

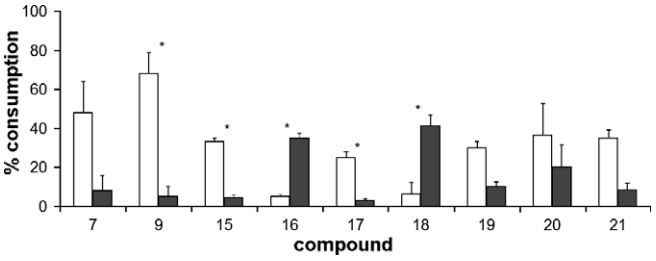


Figure 4. Feeding preferences of *E. paenulata* between control (□) and leaves treated with cyclitol derivatives (■). Bars show standard error; * denotes significant differences (Wilcoxon Rank Test).

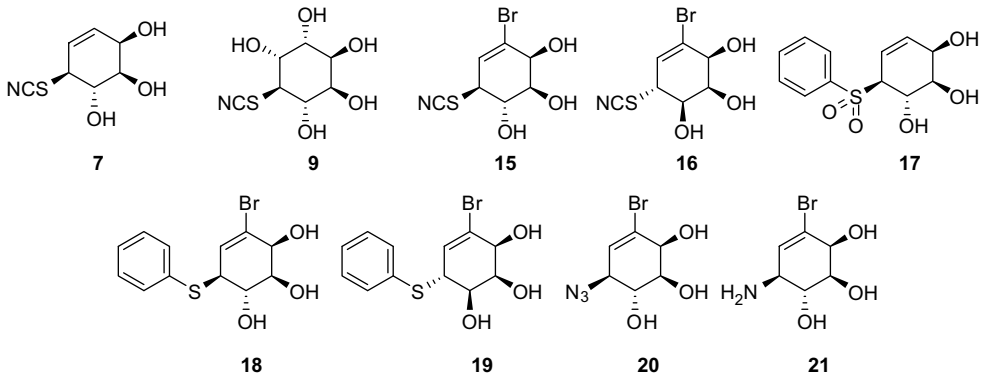


Figure 3. Cyclitols tested for biological activity.

and stereochemistry of the substituent. In general, it was observed that sulfur-containing cyclitols (**9, 15, 16, 17,** and **18**) were more active than nitrogen analogs **20** and **21**. Compounds **9, 15,** and **17** are deterrents, and derivatives **16** and **18** are phagostimulants. The only fully oxygenated analog tested was SCN-inositol **9**, which exhibited the highest deterrent activity (IFA = 0.90 ± 0.04, p = 0.012), and is more active than the corresponding conduritols **7** and **15**. Although **7** showed a tendency toward deterrent activity, the effect was not significant (IFA = 0.6 ± 0.2, p = 0.440); therefore, it appears that the presence of a bromine atom in **15** causes a difference with the dehalogenated analog thiocyanoconduritol **7**. On the other hand, bromothiocyanodeoxyconduritol **16,** which is diastereomeric with **15** but otherwise has the same substitution pattern, induced a completely opposite behavior on *E. paenulata*. Indeed, while **16** was phagoestimulant (IFA = −0.71 ± 0.08, p = 0.029), **15** was deterrent (IFA = 0.82 ± 0.05, p = 0.028). Compound **17**, the only sulfone tested, was shown to be significantly deterrent (IFA = 0.7 ± 0.1, p = 0.048). We assayed two diasteromeric phenylthioconduritols (**18** and **19**). The β-thiophenylconduritol was phagoestimulant (IFA = −0.8 ± 0.1, p = 0.002), but its diastereomer **19** did not show any significant effect according to the Wilcoxon Rank Test. Overall, we have found that several sulfur-containing cyclitols, and particularly L-*chiro*-inositol **9**, are active and can influence the dietary behavior of *E. paeneulata* in this option test. The results suggest that carefully designed carbohydrate analogs could be of potential use in the control of specific herbivores.

3. Conclusions

In conclusion, we have reported the synthesis of a SCN-inositol with the L-*chiro* configuration. Ruthenium catalysis allowed the dihydroxylation of **4** giving a feasible route toward SCN-containing inositols, while osmium tetroxide was unreactive with these types of alkenes. The reaction is under strict steric control furnishing **9** (after deprotection) with excellent facial selectivity. Furthermore, deprotection of **4** rendered the previously unknown thiocyanoconduritol F (**7**) in excellent yield. However, we were unable to establish the best conditions that would lead to the preparation of phenylthioinositol **14**; instead phenylsulfonylinositol **13** was obtained in moderate yield. Overall, our study has disclosed the first available data on the oxidation of sulfur-containing conduritols and their delicate chemistry.

Some of the cyclitols synthesized showed biological activity when subjected to the assay performed. In particular, thiocyanodeoxyinositol **9** proved to be a potential leader for the development of insect deterrents of high selectivity.

4. Experimental

4.1. General

All non-hydrolytic reactions were carried out under a nitrogen atmosphere, with standard techniques for the exclusion of moisture. All solvents were purified prior to use. The commercially available reagents were purchased from Sigma–Aldrich and used without further purification. Optical rotations were measured using a Zuzi 412 automatic polarimeter with a 7-mL cell and a Kruss Optronic GmbH P8000 polarimeter with a 0.5-mL cell (concentration c given as g/100 mL). Melting points were determined on a Gallenkamp apparatus and on a Fisher–Johns apparatus, and are uncorrected. Infrared spectra were recorded using a Shimadzu FTIR 8101A spectrometer, and peaks are reported in reciprocal cm along with relative signal intensities and characteristics: s (strong); m (medium); w (with). Nuclear magnetic resonance spectra were recorded on a Bruker Avance DPX-400 instrument. Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane, and coupling constants (J) are reported in hertz. Low-resolution mass spectra were performed on a Hewlett–Packard 5890 instrument-mass detector 5971, using the electron-impact mode and molecular ion peaks which are listed with relative abundances. Elemental analyses were recorded on a Fisons EA 1108 CHNS-O analyzer. High-resolution mass spectra were performed on a Bruker Daltonics spectrometer model MicrO TofQ (ESI + mode). Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or anisaldehyde–H_2SO_4–AcOH as detecting agent. Flash column chromatography was performed in silica gel (Kieselgel 60, EM Reagents, 230–400 mesh).

4.1.1. (1*S*,2*S*,3*S*,6*S*)-2,3-Isopropylidendioxy-6-thiocyanatocyclohex-4-ene-1-ol (4)

A solution of epoxide **3** (0.105 g, 0.627 mmol) in acetonitrile (2.0 mL) was treated with NH_4SCN (0.238 g, 3.130 mmol) at room temperature. The reaction mixture was stirred for 4 h until consumption of the starting material as monitored by TLC. The solvent was evaporated under reduced pressure, and the residue was diluted with CH_2Cl_2 and sequentially washed with satd aq NH_4Cl, and aq NaCl. The organic layer was dried (anhyd Na_2SO_4) and evaporated to afford a crude oily product that was purified by flash column chromatography (70:30 hexane–EtOAc). Colorless oil (62%); $[\alpha]_D^{20}$ +137 (c 0.85, CH_2Cl_2); IR (neat): 3650–3150 (OH, w), 2155 (SCN, s), 1063 (C–O–C, s); ^{1}H NMR ($CDCl_3$): δ 6.08 (dd, 1H, $J_{4,5}$ 10.0, $J_{4,3}$ 3.7 Hz, H-4), 5.95 (br dd, 1H, $J_{5,4}$ 10.0, $J_{5,6}$ 1.3, H-5), 4.66 (br t, 1H, $J_{3,2}$ 5.0, $J_{3,4}$ 4.8, H-3), 4.14 (dd, 1H, $J_{2,1}$ 8.0, $J_{2,3}$ 5.1, H-2), 3.81 (t, 1H, $J_{1,2}$ 8.2, $J_{1,6}$ 8.4, H-1), 3.70 (dq, 1H, $J_{6,1}$ 8.5, $J_{6,5}$ 1.9, H-6), 3.50 (br s, 1H, OH), 1.52 (s, 3H, CH_3), 1.41 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 129.0 (C (H-4)), 128.1 (C (H-5)), 111.2 (SCN), 111.1 (C isopropylidene), 78.3 (C (H-2)), 72.3 (C (H-1) and C (H-3)), 49.8 (C (H-6)), 28.5 (CH_3), 26.2 (CH_3). EIMS: 212 (M^+-CH_3, 78), 169 (M^+−SCN, 13), 151 ($M^+-C_3H_6O-H_2O$, 21), 58 (SCN, 4); Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77; N, 6.16. Found: C, 52.89; H, 5.95; N, 5.95.

4.1.2. (1*S*,2*S*,3*R*)-4-Bromo-2,3-isopropylidenecyclohex-5-ene-1-ol (6)[13]

Tri-*n*-butyltin hydride (0.1 mL, 0.504 mmol) was added to a mixture of azoisobutyronitrile (AIBN, 44.3 mg, 0.27 mmol)[†] and compound **5** (84.8 mg, 0.277 mmol) in dry THF (10.0 mL). The reaction mixture was refluxed for 2 h. Concentration at reduced pressure and purification of the oily residue by flash chromatography (70:30 hexane–EtOAc) furnished the pure product **6** as a white solid (50%). IR (neat): 3600–3200 (OH, w), 2070 (s), 1381, 1074; ^{1}H NMR ($CDCl_3$): δ 6.17 (dd, 1H, $J_{5,CH2}$ 3.6 and 3.7, H-5), 4.67 (d, 1H, $J_{3,2}$ 5.9, H-3), 4.14 (t, 1H, $J_{2,3}$ 6.2, $J_{2,1}$ 6.9, H-2), 3.96 (m, 1H, H-1), 2.50 (dt, 1H, $J_{6,5}$ 4.7, J_{CH2} 12.6, H-6 (CH_2)), 2.15 (m, 2H, H-6 (CH_2) and OH), 1.52 (s, CH_3), 1.44 (s, CH_3); ^{13}C NMR ($CDCl_3$): δ 130.0 (C (H-5)), 119.9 (C–Br), 110.3 (C isopropylidene), 79.3 (C (H-2)), 77.1 (C (H-3)), 68.1 (C (H-1)), 32.3 (C (H-6)), 28.5 (CH_3), 27.2 (CH_3). (^{1}H and ^{13}C NMR spectral data matched that reported.[13]) EIMS: 235 ((M^++2)−CH_3, 75), 233 (M^+-CH_3, 74), 175 ((M^++2)−$C_3H_6O-H_2O$, 48), 173 ($M^+-C_3H_6O-H_2O$, 46), 94 (M^+−Br−$C_3H_6O-H_2O$, 100).

4.1.3. (1*S*,2*S*,3*S*,6*S*)-6-Thiocyanatocyclohex-4-ene-1,2,3-triol (7)

A mixture of compound **4** (0.032 g, 0.143 mmol), Dowex-50 (H^+ form) resin (0.35 g), and MeOH–H_2O (2.0 mL–0.5 mL) was stirred at room temperature for 24 h. After completion of the reaction,

[†] One equivalent of AIBN was required to complete the reaction in spite of the fact that theoretically only a catalytic amount must suffice.

the resin was filtered off and the solvent was evaporated under reduced pressure. Purification by flash chromatography (20:80 hexane–EtOAc) rendered optically active **7** as a white crystalline solid (90 %). Mp 81–83 °C; $[\alpha]_D^{20}$ +209 (*c* 0.74, MeOH); IR (KBr): 3730–3042 (OH, w), 2157 (SCN, s), 1094 (s); ^{1}H NMR (MeOD): δ 6.02 (dq, 1H, $J_{4,5}$ 10.0, $J_{4,3}$ 4.4, $J_{4,6}$ 2.3, H-4), 5.84 (dd, 1H, $J_{5,4}$ 9.9, $J_{5,6}$ 2.4, H-5), 4.24 (t, 1H, $J_{3,2}$ 4.5, $J_{3,4}$ 4.4, H-3), 3.91 (br t, 1H, $J_{1,2}$ 9.5, $J_{1,6}$ 8.2, H-1), 3.75 (ds, 1H, $J_{6,1}$ 8.0, $J_{6,5}$ 2.3, $J_{6,4}$ 2.3, H-6), 3.57 (dd, 1H, $J_{2,1}$ 9.5, $J_{2,3}$ 4.1, H-2); ^{13}C NMR (MeOD): δ 131.3 (C (H-4)), 127.7 (C (H-5)), 111.4 (SCN), 72.7 (C (H-2)), 70.8 (C (H-1)), 66.36 (C (H-3)), 52.9 (C (H-6)). Anal. Calcd for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48; S, 17.13. Found: C, 44.95; H, 4.65; N, 7.41; S, 17.23.

4.1.4. (1*R*,2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Isopropylidendioxy-6-thiocyanatocyclohexane-1,2,5-triol (8)

A stirred solution of **4** (0.106 g, 0.468 mmol) in a mixture of EtOAc (1.5 mL) and acetonitrile (1.5 mL) was cooled to 0 °C and treated with a mixture of $RuCl_3$ (0.014 g, 6 mol %) and $NaIO_4$ (0.150 g, 0.703 mmol) in water (0.5 mL). After standing at 0 °C for 15 min, 20% aq $Na_2S_2O_3$ was added, and the mixture was filtered using a pad of silica gel and washed several times with EtOAc. Concentration of the filtrate rendered a crude oily product that was purified over a silica flash column using 40:60 hexane–EtOAc as the eluting solvents, affording **8** as a white hygroscopic solid (0.101 g, 82%). Mp 32–35 °C; $[\alpha]_D^{20}$ −82 (*c* 0.63, MeOH); IR (KBr): 3500–3100 (OH, w), 2155 (SCN, s), 1638 (C–O–C, m), 1063 (s); ^{1}H NMR (C_3D_6O): δ 5.05 (d, 1H, $J_{0H,H5}$ 6.0, OH (H-5)), 4.66 (d, 1H, $J_{0H,H1}$ 6.9, OH (H-1)), 4.63 (d, 1H, $J_{0H,H2}$ 3.8, OH (H-2)), 4.31 (dd, 1H, $J_{3,2}$ 3.1, $J_{3,4}$ 5.4, H-3), 4.27 (dt, 1H, $J_{2,1}$ 3.2, $J_{2,3}$ 3.1, $J_{H2,0H}$ 3.1, H-2), 4.14 (dd, 1H, $J_{4,3}$ 5.4, $J_{4,5}$ 5.8, H-4), 3.89 (ddd, 1H, $J_{1,2}$ 3.2, $J_{1,6}$ 9.8, $J_{H1,0H}$ 6.8, H-1), 3.72 (ddd, 1H, $J_{H5,0H}$ 6.0, $J_{5,4}$ 6.1, $J_{5,6}$ 10.6, H-5), 3.32 (t, 1H, $J_{6,1}$ 10.2, $J_{6,5}$ 10.2, H-6), 1.45 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (C_3D_6O): δ 110.8 (C isopropylidene), 109.3 (SCN), 80.5 (C (H-4)), 77.4 (C (H-3)), 73.6 (C (H-5)), 70.3 (C (H-2)), 69.6 (C (H-1)), 55.1 (C (H-6)), 27.9 (CH_3), 25.7 (CH_3). EIMS: 203 (M^+−SCN, 100); HRESIMS: *m/z* calcd for $(C_{10}H_{15}NO_5SNa)^+$: 284.0563; found: 284.0574 and *m/z* calcd for $(C_{10}H_{15}NO_5SH)^+$: 262.0744; found: 262.0756.

4.1.5. (1*S*,2*R*,4*R*,5*R*)-6-Thiocyanatocyclohexane-1,2,3,4,5-pentaol (4-deoxy-4-thiocyano-L-*chiro*-inositol) (9)

To a stirred suspension of **8** (0.095 g, 0.364 mmol) in MeOH–H_2O (3.0 mL–0.5 mL) was added Dowex-50 (H^+ form) resin (0.85 g). After 1 h at rt, the resin was filtered off and washed many times with MeOH. Concentration by evaporation at reduced pressure gave **9** as a syrup (0.074 g, 93%). $[\alpha]_D^{21}$ −21 (*c* 0.50, MeOH); IR (KBr): 3600–3200 (OH, w), 2159 (SCN, s), 1074 (s); ^{1}H NMR (D_2O): δ 4.09 (br dd, 2H, H-2 and H-3), 3.96 (br dd, 1H, $J_{1,2}$ 3.1, $J_{1,6}$ 10.9, H-1), 3.76 (q, 2H, $J_{4,3}$ 3.0, $J_{4,5}$ 9.5, $J_{5,4}$ 9.6, $J_{5,6}$ 10.0, H-4 and H-5), 3.23 (t, 1H, $J_{6,1}$ 10.6, $J_{6,5}$ 10.4, H-6); ^{13}C NMR (D_2O): δ 112.9 (SCN), 72.6 (C (H-4)), 71.9 (C (H-3)), 71.5 (C (H-5)), 70.5 (C (H-2)), 68.5 (C (H-1)), 55.6 (C (H-6)). HRESIMS: *m/z* calcd for $(C_7H_{11}NO_5SNa)^+$: 244.0250; found: 244.0260 and *m/z* calcd for $(C_7H_{11}NO_5SH)^+$: 222.0431; found: 222.0437.

4.2. General procedure for the synthesis of compounds 11 and 12 under catalytic $RuCl_3$–$NaIO_4$ conditions

A solution of **10** (0.050 g, 0.181 mmol) in a mixture of EtOAc (1.5 mL) and acetonitrile (1.5 mL) was cooled to 0 °C and treated with a mixture of $RuCl_3$ (6.0 mg, 6 mol %) and $NaIO_4$ (0.063 g, 0.295 mmol) in water (0.5 mL). After 30 min, 20% aq $Na_2S_2O_3$ was added, and the mixture was filtered through a pad of silica gel and washed several times with EtOAc. The solvent was evaporated to render a crude oily product that was purified by silica gel flash chromatography (50:50 hexane–EtOAc), affording compounds **11** (19%) as an oil and **12** (42%) as a white solid.

4.2.1. (1S,2R,3*R*,6*S*)-2,3-Isopropylidendioxy-6-(phenylsulfinyl)-cyclohex-4-ene-1-ol (1:1 mixture of epimeric sulfoxides) (11)

$[\alpha]_D^{20}$ +85 (*c* 0.23, MeOH); IR (KBr): 3500–3200 (OH, w), 1603 (sulfoxide, s); EIMS: 279 (M^+−CH_3, 8), 167 (M^+−SPh–H_2O, 31), 149 (M^+−SPh–$2H_2O$, 100); ^{1}H RMN ($CDCl_3$): ^{1}H NMR ($CDCl_3$): δ 7.75 (br dd, 2H, *J* 7.8, *J* 1.7, H arom.), 7.65 (dd, 2H, *J* 7.7, *J* 1.7, H arom.), 7.58 (m, 6H, H arom.), 6.08 (tdd, 2H, $J_{4\text{-}5/4'\text{-}5'}$ 9.8, $J_{4\text{-}3/4'\text{-}3'}$ 6.0, H-4 and H-4′), 5.55 (td, 2H, $J_{5,4/5',4'}$ 9.9, $J_{5,6/5',6'}$ 1.8, H-5 and H-5′), 4.59 (br t, 2H, $J_{3,4/3',4'}$ 5.2, $J_{3,2/3',2'}$ 5.2, H-3 and H-3′), 4.16 (dd, 2H, $J_{2,3/2',3'}$ 4.8, $J_{2,1/2',1'}$ 6.4, H-2 and H-2′), 4.05 (td, 2H, $J_{1,6/1',6'}$ 7.2, $J_{1,2/1',2'}$ 6.8, $J_{H1,OH/H1',OH}$ 2.0, H-1 and H-1′), 3.92 (d, 1H, $J_{OH,H1/OH,H1'}$ 2.0, OH (H-1) or OH (H-1′)), 3.68 (d, 1H, $J_{OH,H1/OH,H1'}$ 2.0, OH (H-1) or OH (H-1′)), 3.63 (dq, 1H, $J_{6,5/6',5'}$ 2.0, $J_{6,1/6',1'}$ 7.6, H-6 or H-6′), 3.37 (dq, 1H, $J_{6,5/6',5'}$ 2.0, $J_{6,1/6',1'}$ 7.6, H-6 or H-6′), 1.50 (s, 6H, CH_3), 1.40 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ 132.2 (C-S (C arom.)), 131.2 (C-S (C arom.)), 129.6 (C (H-4) or (H-4′)), 129.3 (C arom.), 129.2 (C (H-4) or (H-4′)), 125.5 and 124.7 (C arom.), 122.6 (C (H-5) or (H-5′)), 121.5 (C (H-5) or (H-5′)), 110.4 (C isopropylidene), 110.3 (C isopropylidene), 78.8 (C (H-2) or (H-2′)), 77.8 (C (H-2) or (H-2′)), 72.0 (C (H-3) or (H-3′)), 71.5 (C (H-3) or (H-3′)), 70.1 (C (H-1) or (H-1′)), 68.6 (C (H-1) or (H-1′)), 65.4 (C (H-6) or (H-6′)), 65.1 (C (H-6) or (H-6′)), 28.2 (CH_3), 25.8 (CH_3). HRESIMS: *m/z* calcd for $(C_{15}H_{18}O_4SNa)^+$: 317.0818; found: 317.0837.

4.2.2. (1*S*,2*R*,3*R*,6*S*)-2,3-Isopropylidendioxy-6-(phenylsulfonyl)-cyclohex-4-ene-1-ol (12)

Mp 135–137 °C; $[\alpha]_D^{26}$ +13 (*c* 0.31, CH_2Cl_2); IR (KBr): 3517 (OH), 1306 and 1146 (sulfone, s); ^{1}H NMR ($CDCl_3$): δ 7.89 (dd, 2H, $J_{o,m}$ 7.2, $J_{o,p}$ 1.7, Ho_{SPh}), 7.69 (dd, 1H, $J_{p,m}$ 7.2, $J_{p,o}$ 1.6, Hp_{SPh}), 7.57 (t, 2H, $J_{m,o}$ 7.5, $J_{m,p}$ 7.9, Hm_{SPh}), 6.05 (dd, 1H, $J_{4,5}$ 10.3, $J_{4,3}$ 3.8, H-4), 5.89 (d, 1H, $J_{5,4}$ 10.2, H-5), 4.50 (br t, 1H, $J_{3,4}$ 3.8, $J_{3,2}$ 5.6, H-3), 4.09 (t, 1H, $J_{2,1}$ 7.5, $J_{2,3}$ 6.3, H-2), 3.79 (m, 3H, H1, H6 and OH (H-1)), 1.38 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 136.1 (C–S (C arom.)), 134.6 (C (Hp_{SPh})), 129.3 (C (Hm_{SPh})), 129.2 (C (Ho_{SPh}), 128.7 (C (H-4)), 122.7 (C (H-5)), 110.5 (C isopropylidene), 77.9 (C (H-2)), 71.3 (C (H-3)), 68.5 and 67.1 (C (H-1) and C (H-6)), 28.1 (CH_3), 25.6 (CH_3). EIMS: 295 (M^+−CH_3, 58), 141 (M^+−SO_2Ph, 21), 125 (M^+−SOPh, 27), 77 (Ph, 67); HRESIMS: *m/z* calcd for $(C_{15}H_{18}O_5S$-$Na)^+$: 333.0767; found: 333.0778.

4.3. General procedure for the synthesis of compounds 12 and 13 under $RuCl_3$–$NaIO_4$ (2.0 equiv) conditions

A solution of **10** (0.042 g, 0.150 mmol) in a mixture of EtOAc (1.5 mL) and acetonitrile (1.5 mL) was cooled to 0 °C and treated with a mixture of $RuCl_3$ (7.0 mg, 8 mol %) and $NaIO_4$ (0.067 g, 0.315 mmol) in water (0.5 mL). After 30 min, 20% aq $Na_2S_2O_3$ was added, and the mixture was filtered through a pad of silica gel and washed several times with EtOAc. The solvent was evaporated to render a crude product that was subjected to flash chromatography on silica gel, eluting first with 50:50 hexane–EtOAc to afford compound **12** (56%) and then with 70:30 EtOAc–hexane to render dihydroxylated compound **13** (29%) as a white syrup.

4.3.1. (1R,2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Isopropylidendioxy-6-(phenylsulfonyl)-cyclohexane-1,2,5-triol (13)

$[\alpha]_D^{20}$ −26 (*c* 1.5, MeOH); IR (KBr): 3500–3100 (OH, w), 1304 and 1144 (sulfone, s); ^{1}H NMR (C_3D_6O) δ 7.97 (br t, 2H, $J_{o,m}$ 7.2, $J_{o,p}$ 1.3, Ho_{SPh}), 7.75 (dt, 1H, $J_{p,m}$ 7.4, $J_{p,o}$ 1.2, Hp_{SPh}), 7.66 (t, 2H, $J_{m,o}$ 7.1, $J_{m,p}$ 7.7, Hm_{SPh}), 4.71 (d, 1H, $J_{0H,H2}$ 3.8 Hz, OH (H-2)), 4.39 (m, 1H, H-3), 4.35 (dd, 1H, $J_{1,2}$ 5.7, $J_{1,6}$ 7.0, H-1), 4.23 (t, 1H, $J_{6,1}$ 7.4, $J_{6,5}$ 7.4, H-6), 4.14 (t, 1H, $J_{5,6}$ 7.8, $J_{5,4}$ 7.8, H-5), 3.84 (dd, 1H, $J_{2,1}$ 5.5, $J_{2,3}$ 2.3, H-2), 3.41 (dd, 1H, $J_{4,5}$ 7.9, $J_{4,3}$ 3.6, H-4), 1.37 (s, 3H, CH_3), 1.28 (S, 3H,

CH_3); ^{13}C NMR (C_3D_6O): δ 139.9 (C-S (C arom.)), 133.7 (C (Hp_{SPh})), 128.9 (di, C (Hm_{SPh})), 128.7 (C (Ho_{SPh}), 108.7 (C isopropylidene), 78.2 (C (H-6)), 77.5 (C (H-1)), 71.6 (C (H-2)), 71.4 (C (H-4)), 68.3 (C (H-3)), 68.0 (C (H-5)), 25.2 (CH_3), 24.2 (CH_3). HRESIMS: *m/z* calcd for $(C_{15}H_{20}NaO_7S)^+$: 367.0821; found: 367.0815.

4.4. Synthesis of some representative compounds evaluated for biological activity

4.4.1. (1*S*,2*S*,3*S*,6*S*)-4-Bromo-6-thiocyanate-cyclohex-4-en-1,2,3-triol (15)

A mixture of compound **5** (0.022 g, 0.072 mmol), Dowex-50 (H^+ form) resin (0.87 g), and MeOH–H_2O (2.0–0.2 mL) was stirred at room temperature for 12 h. After completion of the reaction, the resin was filtered off, washed with MeOH (3 × 5 mL), and the solvent was evaporated under reduced pressure. Purification by flash chromatography (20:80 hexane–EtOAc) rendered optically active **15** as a white solid (96 %): mp 127.2–129.5 °C; $[\alpha]_D^{19}$ +56 (*c* 0.49, MeOH); IR (KBr): 3400–3300 (OH, w), 2159 (SCN, s), 1640 (s); ^1H NMR (MeOD): δ 6.20 (d, 1H, $J_{5,5}$ 2.8, H-5), 4.29 (d, 1H, $J_{3,2}$ 4.1, H-3), 3.90 (t, 1H, $J_{1,2}$ 9.6, $J_{1,6}$ 9.6, H-1), 3.72 (dd, 1H, $J_{6,1}$ 10.1, $J_{6\text{-}5}$ 2.8, H-6), 3.68 (dd, 1H, $J_{2,1}$ 9.6, $J_{2,3}$ 4.1, H-2); ^{13}C NMR (MeOD): δ 128.8 (C (H-5)), 127.3 (C (H-4)), 110.0 (SCN), 73.1 (C (H-3)), 72.8 (C (H-2)), 69.8 (C (H-1)), 53.3 (C (H-6)). EIMS: 98 (M^+−Br–OH, 100), 81 (Br, 6), 58 (SCN, 37); Anal. Calcd for $C_7H_8NBrO_3S$: C, 31.59; H, 3.03; N, 5.26. Found: C, 31.99; H, 3.23; N, 5.15.

4.4.2. (1*R*,2*S*,3*S*,6*R*)-4-Bromo-6-thiocyanatocyclohex-4-en-1,2,3-triol (16)

A stirred solution of (1*R*,2*R*,3*S*,6*R*)-4-bromo-2,3-isopropylidenedioxy-6-thiocyanato-cyclohex-4-ene-1-ol[3,21] (0.051 g, 0.166 mmol) and MeOH–H_2O (3.5–0.5 mL) was treated with Dowex-50 (H^+ form) resin (0.53 g) for 24 h at rt. The resin was filtered off, and washed with MeOH (3 × 5 mL), and the solvent was evaporated under reduced pressure. Purification by flash chromatography 30:70 hexane–EtOAc) gave **16** as a white syrup (0.03 g, 79 %). $[\alpha]_D^{19}$ −78 (*c* 0.26, MeOH); IR (KBr): 3620–3100 (OH, w), 2159 (SCN, s), 1632 (s); ^1H NMR (MeOD): δ 6.20 (t, 1H, $J_{5,3}$ 2.2, $J_{5,6}$ 2.2, H-5), 4.28 (ma, 1H, H-3), 4.17 (dd, 1H, $J_{2,1}$ 5.7, $J_{2,3}$ 3.7, H-2), 3.99 (dt, 1H, $J_{6,1}$ 8.2, $J_{6,5}$ 2.7, $J_{6,3}$ 2.7, H-6), 3.86 (dd, 1H, $J_{1,2}$ 6.3, $J_{1,6}$ 8.2, H-1); ^{13}C NMR (MeOD): δ 130.5 (C 5), 127.4 (C 4), 111.9 (SCN), 72.7 (C 1), 72.3 (C 2), 71.0 (C 3), 51.7 (C 6). EIMS: 183 (M^+−Br, 17), 170 (M^+−2H_2O–SCN, 17), 81 (Br, 39), 58 (SCN, 59); Anal. Calcd for $C_7H_8NBrO_3S$: C, 31.59; H, 3.03; N, 5.26. Found: C, 32.04; H, 3.43; N, 4.84.

4.4.3. (1*S*,2*R*,3*R*,6*S*)-6-(Phenylsulfonyl)cyclohex-4-ene-1,2,3-triol (17)

A mixture of compound **12** (0.021 g, 0.075 mmol), Dowex-50 (H^+ form) resin (0.30 g) and MeOH–H_2O (2.0 mL–0.2 mL) was stirred at room temperature for 48 h. After completion of the reaction, the resin was filtered off, and washed with MeOH (3 × 5 mL), and the solvent was evaporated under reduced pressure. Purification by flash chromatography (20:80 hexane–EtOAc) rendered optically active **17** as a white crystalline solid (95%): mp 76–78 °C; $[\alpha]_D^{20}$ +29 (*c* 0.26, MeOH); IR (KBr): 3500–3300 (OH, w), 1250 and 1020 (sulfone, m); ^1H NMR (MeOD): δ 7.94 (dd, 2H, $J_{o,m}$ 7.2, $J_{o,p}$ 1.3, Ho_{SPh}), 7.72 (dd, 1H, $J_{p,m}$ 7.4, $J_{p,o}$ 1.3, Hp_{SPh}), 7.63 (t, 2H, $J_{m,o}$ 7.7, $J_{m,p}$ 7.7, Hm_{SPh}), 6.08 (ddd, 1H, $J_{4,5}$ 10.1, $J_{4,3}$ 2.8, H-4), 5.92 (dd, 1H, $J_{5,4}$ 9.9, $J_{5,6}$ 3.2, H-5), 4.12 (m, 2H, H-3 and H-2), 3.95 (dt, 1H, $J_{1,6}$ 9.8, $J_{1,2}$ 6.7, H1), 3.95 (dd, 1H, $J_{6,1}$ 9.8, $J_{6,5}$ 3.5, H6); ^{13}C NMR (MeOD): δ 138.2 (C–S (C arom.)), 133.7 (C (Hp_{SPh})), 132.6 (C (H-4)), 128.9 (C (Ho_{SPh}), 128.7 (C (Hm_{SPh})), 121.0 (C (H-5)), 72.2 (C (H-6)), 69.8 (C (H-1)), 65.9 and 67.1 (C (H-2) and C (H-3)). HRESIMS: *m/z* calcd for $(C_{12}H_{14}O_5SNa)^+$: 293.0454; found: 293.0465.

4.4.4. (1*S*,2*R*, 3*S*,6*S*)-4-Bromo-6-(phenylthio)cyclohexene-1,2,3-triol (18)

A mixture of compound (1*S*,2*R*,3*S*,6*S*)-4-bromo-2,3-isopropylidendioxy-6-(phenylthio)cyclohexene-1-ol[3,21] (0.036 mg, 0.102 mmol), Dowex-50 (H^+ form) resin (0.60 g) and MeOH–H_2O (3.0 mL–0.1 mL) was stirred at room temperature for 24 h. After completion of the reaction, the resin was filtered off, and the solvent was evaporated under reduced pressure. Purification by flash chromatography (20:80 hexane–EtOAc) rendered optically active **18** as a white solid (quantitative): mp 114–116 °C; $[\alpha]_D^{20}$ +48 (*c* 1.20, MeOH); IR (KBr): 3500–3400 (OH, w), 2221, 1072, 752; ^1H NMR (CD_3OD): δ 7.53 (dd, 2H, $J_{o,m}$ 8.5, $J_{o,p}$ 1.4, Ho_{SPh}), 7.33 (dt, 3H, $J_{p,m}$ 7.1, $J_{p,o}$ 1.5, $J_{m,\ o}$ 8.6, $J_{m,p}$ 7.2, Hp_{SPh} and Hm_{SPh}), 6.09 (d, 1H, $J_{5,5}$ 2.6, H-5), 4.27 (d, 1H, $J_{3,2}$ 4.1, H-3), 3.80 (t, 1H, $J_{1,2}$ 8.4, $J_{1,6}$ 8.4, H-1), 3.69 (dd, 1H, $J_{6,1}$ 9.0, $J_{6\text{-}5}$ 2.4, H-6), 3.66 (dd, 1H, $J_{2,1}$ 8.3, $J_{2,3}$ 4.9, H-2); ^{13}C NMR (CD_3OD): δ 134.7 (C-S (C arom.)), 132.4 (C (Ho_{SPh}), 132.1 (C (H-5)), 129.4 (C (Hm_{SPh}), 127.6 (C (Hp_{SPh})), 123.6 (C–Br), 73.6 (C (H-2)), 73.2 (C (H-3)), 69.5 (C (H-1)), 53.3 (C (H-6)). EIMS: 282 ((M^++2)−2H_2O, 16), 280 (M^+−2H_2O, 15), 176 (282-SPh, 25), 174 (280-SPh, 26), 77 (Ph, 70); Anal. Calcd for $C_{12}H_{13}BrO_3S$: C, 45.44; H, 4.13. Found: C, 45.33; H, 3.99.

4.5. Biological tests

4.5.1. Tests of feeding activity against *E. paenulata*

Products were evaluated in choice bioassays in Petri dishes (9 cm x 1 cm) lined at the bottom with a layer of agar (2%). *E. paenulata* adults, reared as previously described,[23] were offered four leaf discs (1 cm^2) of an appropriate host plant (*Cucurbita pepo*). Two of the discs (T) were coated with 100 μg of the product (10 μL of a 1% MeOH solution), and the other two (C) were treated with 10 μL of MeOH (5 replicates per product). To measure variability in feeding activity, a visual score of area consumed (0%, 25%, 50%, 75%, or 100%) was assigned for all discs within the plate, every 15 min (total time of the bioassays, 210 min) as described.[24] An index of variability in feeding activity (IFA) was determined for each plate as IFA = [(control consumption-treatment consumption)/(control consumption + treatment consumption)] at final time. Results were analyzed using the Wilcoxon Rank Test.[25]

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Supplementary data

Supplementary data (copies of the ^1H NMR and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.09.026.

References

1. *Biology of Inositols and Phosphoinositides*; Majumder, A. L., Biswas, B. B., Eds.; Springer: New York, 2006; p 340.
2. Vitelio, C.; Bellomo, A.; Brovetto, M.; Seoane, G.; Gonzalez, D. *Carbohydr. Res.* **2004**, *339*, 1773–1778.
3. Bellomo, A.; Giacomini, C.; Brena, B.; Seoane, G.; Gonzalez, D. *Synth. Commun.* **2007**, *37*, 3509–3518.
4. Bellomo, A.; Gonzalez, D. *Tetrahedron: Asymmetry* **2006**, *17*, 474–478.
5. Bellomo, A.; Gonzalez, D. *Tetrahedron Lett.* **2007**, *48*, 3047–3051.
6. Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35–62.
7. Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vogtle, M. *Pure Appl. Chem.* **2003**, *75*, 223–229.

8. Balci, M. *Pure Appl. Chem.* **1997**, *69*, 97–104 and references cited therein.
9. Heo, J.-N.; Holson, E. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1697–1700.
10. Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439–9440.
11. Ramesh, K.; Wolfe, M. S.; Lee, Y.; Vander Velde, D.; Borchardt, R. T. *J. Org. Chem.* **1992**, *57*, 5861–5868.
12. Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510–520.
13. Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T. C.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907–2917.
14. Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312–2313.
15. Plietker, B.; Niggermann, M. *J. Org. Chem.* **2005**, *70*, 2402–2405.
16. Plietker, B.; Niggermann, M. *Org. Biomol. Chem.* **2004**, *2*, 2403–2407.
17. Buschmann, N.; Ruckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325–4329.
18. Desjardins, M.; Brammer, L. E.; Hudlicky, T. *Carbohydr. Res.* **1997**, *304*, 39–42.
19. Plietker, B.; Niggermann, M. *Org. Lett.* **2003**, *5*, 3353–3356.
20. Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814–4818.
21. Hudlicky, T.; Tian, X.; Königsberger; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752–10765.
22. Bernays, E. A.; Chapman, R. F. *J. Insect Physiol.* **2000**, *46*, 905–912.
23. Camarano, S.; González, A.; Rossini, C. *Chemoecology* **2006**, *16*, 179–184.
24. Castillo, L.; González-Coloma, A.; González, A.; Díaz, M.; Alonso-Paz, E.; Bassagoda, M. J.; Rossini, C. *Ind. Crop. Prod.*, in press. doi:10.1016/j.indcrop.2008.05.004.
25. Conover, W. J. *Practical Nonparametric Statistics*; John Wiley & Sons: New York, 1980.