Investigation of steric and functionality limits in the enzymatic dihydroxylation of benzoate esters. Versatile intermediates for the synthesis of pseudo-sugars, amino cyclitols, and bicyclic ring systems†

Fabrizio Fabris,[b] Jonathan Collins,[a] Bradford Sullivan,[a] Hannes Leisch[a] and Tomas Hudlicky*[a]

Received 6th February 2009, Accepted 9th April 2009
First published as an Advance Article on the web 28th April 2009
DOI: 10.1039/b902577b

A series of benzoate esters (methyl, ethyl, *n*-Pr, *i*-Pr, *n*-Bu, *t*-Bu, allyl, and propargyl) were subjected to enzymatic dihydroxylation by *E. coli* JM 109(pDTG 601) strain in a whole-cell fermentation. The *cis*-cyclohexadienediols were obtained in yields of ~1g/L except for *n*-propyl- and *i*-propyl benzoate which were found to be poor substrates. *n*-Butyl and *t*-butyl benzoates were not oxidized at all. The absolute stereochemistry for all metabolites was determined by comparison with a standard prepared from (1*S*-*cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol, whose absolute configuration is well established. The free diols were found to be quite stable compared to other *cis*-dihydrodiols of this type, however, their acetonides underwent a dimerization *via* a regio- and stereoselective Diels–Alder cycloaddition. The diol derived from ethyl benzoate was subjected to a stereo- and regioselective inverse electron demand Diels–Alder cycloadditions with several dienophiles. The new adducts were completely characterized. The hetero-Diels–Alder reaction of this diol with an acyl nitroso dienophile yielded regio- and stereoselectively a bicyclic oxazine, which upon reduction provided a useful derivative of amino shikimate that can be exploited in an approach to oseltamivir (Tamiflu) and other amino cyclitols. The diol was also converted to carba-α-L-galactopyranose to demonstrate its potential utility as a source of pseudo sugars. Experimental and spectral data are provided for all new compounds.

Introduction

The processing of aromatic compounds by bacterial dioxygenases leads to arene *cis*-dihydrodiols, more than 400 of which are known.[1] The most numerous of these metabolites are those derived from monocyclic aromatic compounds by the action of toluene dioxygenase or closely related enzymes. The seminal disclosure of the first stable arene dihydrodiol by Gibson in 1968[2] facilitated the first academic application of such metabolites to synthesis, almost 20 years later, by Ley.[3] This event was preceded in 1983 by the ICI disclosure of polyphenylene synthesis from the *meso* diol derived from benzene.[4] Following these milestones, many new metabolites have been isolated and identified, and the *cis*-dihydrodiols have enjoyed widespread use in the enantioselective syntheses of natural products, carbohydrates, carbohydrate mimics, inositols, and chiral polymers.[5]

Despite the large number of known metabolites, very few have actually been exploited in synthetic ventures. Most of the synthetic applications have been derived from the *cis*-diols originating in the following few arenes: benzene, chloro-, bromo-, iodo-, *m*-dibromo-, and β-bromoethyl- benzene, styrene, toluene, naphthalene, and a few others.[5f] The schematic representation in Fig. 1 shows clearly that the majority of the *cis*-dihydrodiol metabolites remain unexplored in synthetic ventures. The lack of exploitation of the many other known metabolites may be due to their limited availability to the synthetic community. On the other hand the *cis*-diols derived from the arenes mentioned above are obtained in high space-time yields (>20g/L/hour) from the whole-cell fermentations with *Escherichia coli* JM109(pDTG 601), a recombinant organism developed by Gibson.[6] Toluene, chloro- and bromobenzene, and naphthalene are among the best substrates[7] for the toluene (or naphthalene) dioxygenase, and several *cis*-diols are now available commercially.[8]

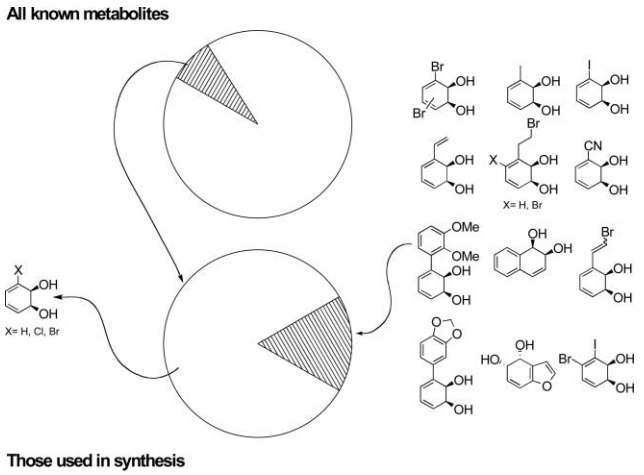


Fig. 1 *cis*-Dihydrodiol metabolites that have been exploited in synthetic ventures as a fraction of the total number of metabolites known to date.

The commercial availability of some of the metabolites provides an opportunity for synthetic chemists to exploit the rich functional

[a]*Department of Chemistry and Centre for Biotechnology, Brock University, 500 Glenridge Avenue, St. Catharines, ON, Canada L2S 3A1*
[b]*Università Ca' Foscari di Venezia, Dipartimento di Chimica, Dorsoduro 2137, I-30123, Venezia, Italy*

† Electronic supplementary information (ESI) available: Experimental data for compounds **11**, **13**, **14** and **15**. See DOI: 10.1039/b902577b

content of these enantiopure building blocks. The whole-cell fermentation of aromatics with the recombinant *E. coli* organism, which requires specialized equipment and rudimentary skills in microbiology, limits wider use of these compounds in synthesis. On the other hand, the blocked mutant, *Pseudomonas putida* 39/D, can be easily cultured and used in a typical synthetic laboratory to provide useful quantities of the *cis*-dihydrodiols.[7c] The only minor disadvantage of using the mutant *versus* the recombinant organism is the fact that the protein synthesis in the mutant must be induced by a known inducer (toluene, chloro-, or bromobenzene, for example), resulting in a mixture of *cis*-dihydrodiols derived from the inducer and the substrate to be tested and therefore necessitating a separation.

The opportunities for application of these metabolites in synthesis are almost limitless. Fig. 2 shows a small sample of targets attained in our group from just two *cis*-dihydrodiols, those derived from chloro- and bromobenzene. Increasing the functional content in homochiral arene *cis*-dihydrodiols would permit more complex chemical operations, for example inter- and intramolecular cycloadditions, sigmatropic processes, and radical cyclizations, and hence expand the number of available targets. To this end, we continue to identify new substrates for toluene dioxygenase (TDO).

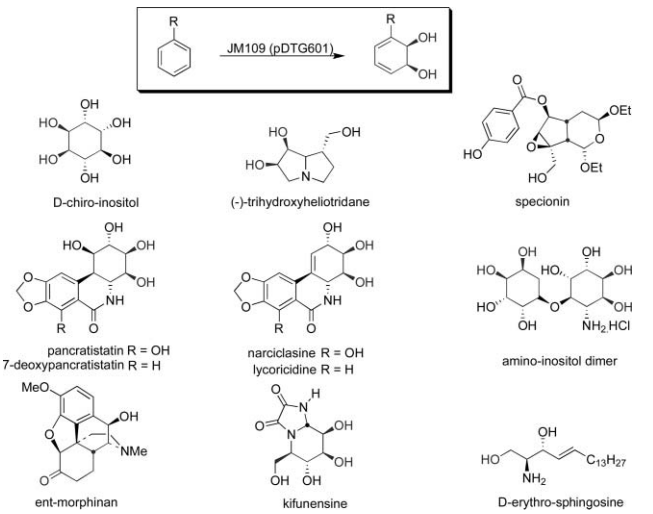


Fig. 2 Selected examples of complex targets synthesized from *cis*-dihydrodiols derived form chloro-, and bromobenzene.[9] The colored portion shows the location of the carbon content of the metabolite retained in the product.

Among the metabolites that have been somewhat underutilized in synthetic ventures are benzoic acids and their esters. Toluene dioxygenase-expressing organisms produce, with remarkable enantioselectivity, *cis*-diols of type **1**[1,5f] from a variety of single-ring aromatics, Fig. 3. The diol functionality is introduced regioselectively to the 2,3-position relative to the largest substituent, according to the model proposed by Boyd.[5e] This model is remarkably valid for a number of substrates and allows for a reasonable level of predictability. On the other hand, benzoic acids yield either diols of type **1** or diols with the "ipso" substitution pattern as in **2**, Fig. 3. The regiochemistry depends on the nature of the substituents on the ring as well as on the particular organism.[10]

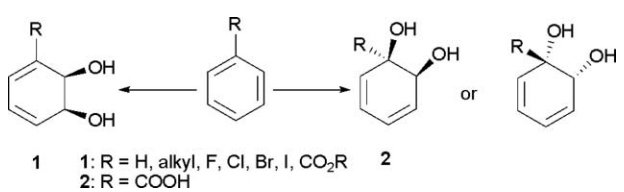


Fig. 3 Regiochemistry of enzymatic dihydroxylation in single-ring arenes.

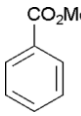
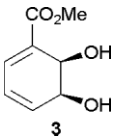
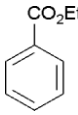
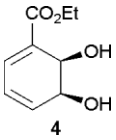
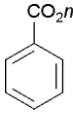
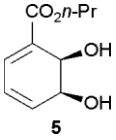
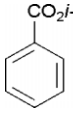
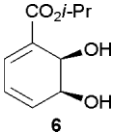
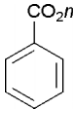
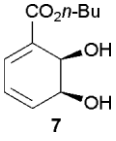
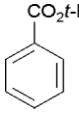
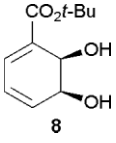
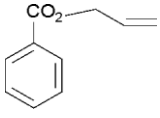
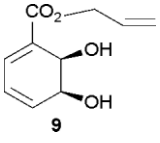
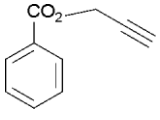
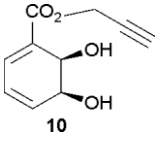
In connection with ongoing projects in our group, we were interested in diols derived form various benzoate esters for several reasons. First, such compounds would be versatile intermediates in the synthesis of pseudo sugars as the required exocyclic carbon is already contained in the metabolite. This avoids the usual introduction of a carboxylate *via* palladium-catalyzed carbonylation of vinyl bromides or iodides as we[11] and others[12] have demonstrated by the conversion of bromo- or iodo-*cis*-dihydrobenzene diol to various pseudo sugars. Second, because the diols derived from benzoates are ideally suited for cycloaddition or cyclization schemes performed in either inter- or intramolecular fashion, they can be exploited in design of polycyclic structures. Herein we report the results of enzymatic dihydroxylation of a series of benzoate esters and provide the absolute stereochemistry of the new metabolites as well as some insight into the limits of the enzymatic oxidation as a function of the steric bulk of the esters. The synthetic utility of the *cis*-dihydrodiols derived from benzoate esters is demonstrated in a short synthesis of carba-α-L-galactopyranose as well as an aminocyclitol derivative that may be used in an approach to oseltamivir.

Results and discussion

Diols derived from otherwise unsubstituted benzoate esters are not as common as those obtained from the free acids. To date there are over 30 known diol metabolites derived from various benzoic, naphthoic or other aromatic acids and their derivatives. Most of the *cis*-dihydrodiols identified contain the ipso substitution pattern shown in **2**, Fig. 3. Benzoate esters that contain additional functionality on the aromatic ring do yield diols of type **1**, Fig. 3. In contrast, only the diol **3** derived from methyl benzoate has been described, albeit incompletely.[13a] This particular transformation was achieved using dioxygenase enzymes present in *Pseudomonas putida* wild strains NCIB 1176 and NCIB 11680 or *Pseudomonas putida* UV4. In this patent an extended range of substrates are claimed but only diol **3** was partially characterized (^{1}H-NMR, MS, optical rotation). The absolute configuration of diol **3** was later established by its conversion to 6β-hydroxyshikimic acid.[13b] In order to more fully explore the potential of these metabolites as synthetically useful intermediates we initiated a more thorough investigation of their production by TDO.

The required benzoate esters were either commercially available (Entries 1, 2, 3, 5) or were prepared by reported procedures, Table 1.[14] In order to determine their suitability as substrates for TDO, preliminary testing was performed in Fernach shake flasks (2 L) with cells grown to optimum optical density in a 15 L Biostat fermentor. Following the detection and isolation of new metabolites, the preparative fermentations were performed under controlled conditions in a 15 L fermentor as previously described.[7] The diols were isolated by extraction (EtOAc) of the broth from which the cells were removed by centrifugation. Diols derived from methyl, ethyl, allyl, and propargyl esters were obtained in

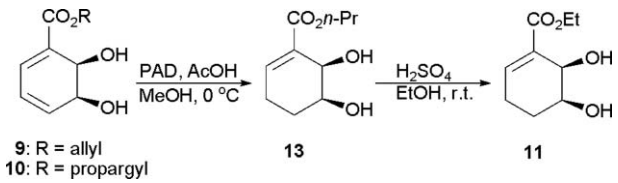
Table 1 Dihydroxylation of benzoate esters[a]

Entry	Substrate	Product	Conversion (%)[b]	Yield (g/L)
1		 **3**	95	1.30
2		 **4**	56	0.80
3		 **5**	78	0.07
4		 **6**	41	0.05
5		 **7**	—	—
6		 **8**	—	—
7		 **9**	89	0.60
8		 **10**	91	1.0

[a] 10.0 g of substrate was slowly injected in the fermentor containing 9 L broth. [b] The percent conversion is defined as (mass substrate fed – substrate recovered)/mass substrate fed × 100.

the yields of ~1 gram/L, while those derived from *n*-propyl and *i*-propyl esters were isolated in trace amounts. Both *n*- and *t*-butyl benzoates were found not to be substrates for TDO.

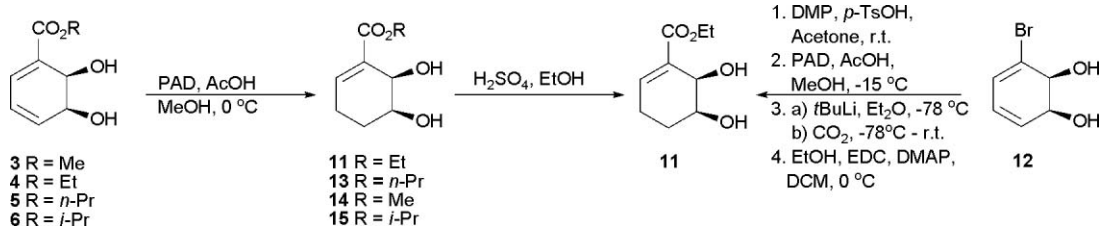
The diols were found to be quite robust, permitting a full physical and spectral analysis, including combustion analysis. To determine (or confirm) their absolute stereochemistry, diols **3**, **5**, and **6** were subjected to chemoselective reduction of the disubstituted olefin with potassium azadicarboxylate (PAD) in acetic acid. This procedure was followed by transesterification to the ethyl ester **11**, obtained by PAD reduction of diol **4**, as shown in Scheme 1. A standard of this material was obtained by carbonylation[11,15] of the vinyl bromide moiety in **12**, whose absolute configuration is securely established.[1,5f] The diols derived from allyl and propargyl benzoates, **9** and **10**, were reduced with excess PAD, with concomitant saturation of the allyl and propargyl functionalities, and matched with **13**, whose absolute configuration had been ascertained by its conversion to the ethyl ester **11** (Scheme 2). Thus we found that the absolute stereochemistry of all diols derived from benzoate esters was identical to the β-configuration of the known diol **12**.



Scheme 2

The synthetic utility of diols obtained from various benzoates may be explored in their conversion to various pseudo-sugars to provide complementary protocols to the sequences originating in diol **12**[11] or its somewhat less stable iodo analog.[12] Only stereoselective introduction of *cis* or *trans* diol at the site of the distal olefin, saturation of the proximal double bond, and reduction of the carboxylate are required to reach various pseudo-sugars shown in Fig. 4. Diols **3** and **4** are obtained in useful yields and their conversion to pseudo-sugars can be achieved in fewer than six synthetic operations, as demonstrated on the synthesis of carba-α-L-galactopryanose (**17**), Scheme 3.

Diol **3** was first protected as its acetonide before dihydroxylation and acylation furnished bis acetate **24** (69% over 3 steps). The olefin of **24** was then catalytically hydrogentated with Rh/Al_2O_3 under 60 psi of H_2 to produce a 4:1 mixture of diastereomers **25** and **26**. Separation by flash column chromatography yielded **25** as a single diastereomer (70%). Treatment of the saturated ester with excess $LiAlH_4$ in refluxing THF provided the fully reduced, protected carbasugar **27**, protected form of



Scheme 1

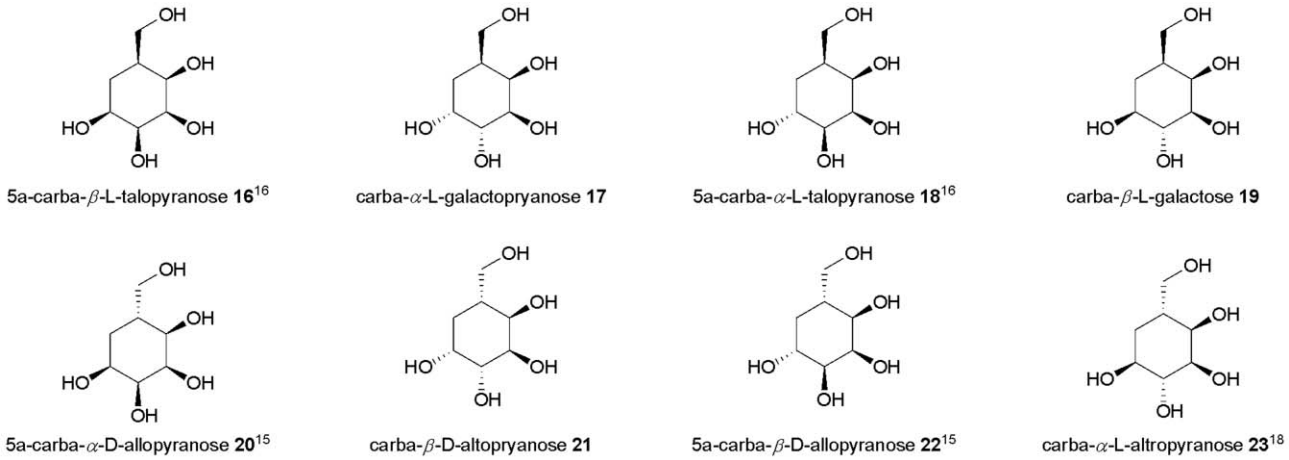
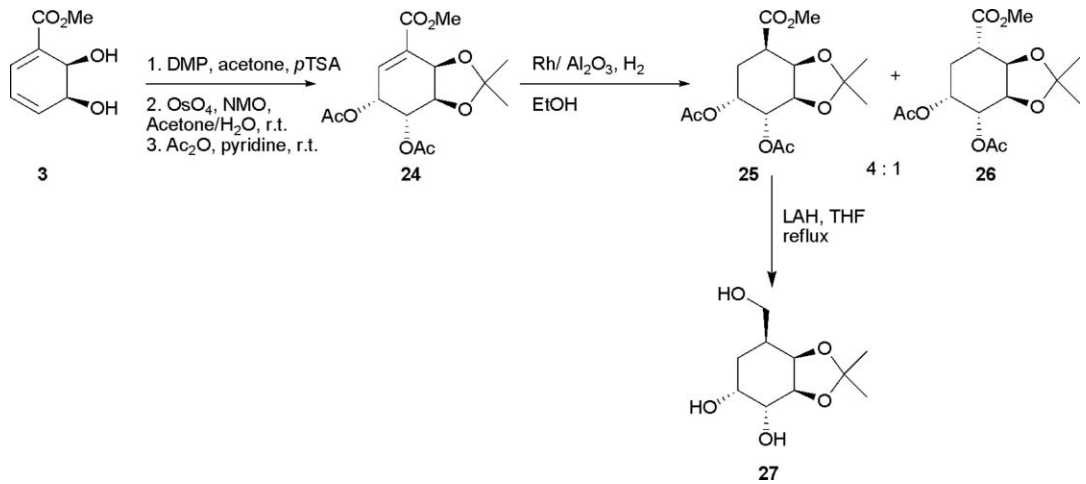


Fig. 4 Isomeric pseudo sugars obtainable from diol **3** and **4**.



Scheme 3

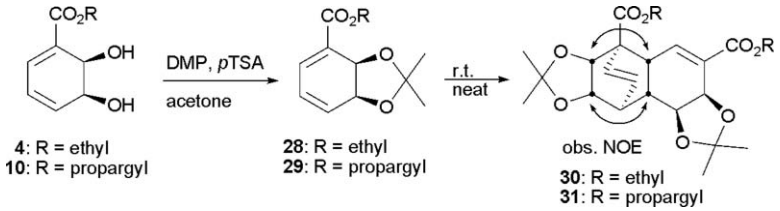
carba-α-L-galactopyranose (**17**), in 86% yield. This material was identical in every respect to the previously reported compound save for a slightly higher optical rotation value ($[\alpha]_D^{20}$ −57.08 vs. $[\alpha]_D$ −47).[10]

Other notable reactive options for the benzoate-derived diols are cycloaddition reactions. Diels–Alder reactions between arene *cis*-dihydrodiols and suitable dienophiles were first reported by Gibson.[19] The diols derived from halobenzene, toluene, or styrene have been exploited in various other cycloaddition schemes.[5f] While the free diols are slow to dimerize *via* regio- and stereoselective Diels–Alder cycloadditions, the corresponding acetonides dimerize easily, even when stored at low temperatures.[20]

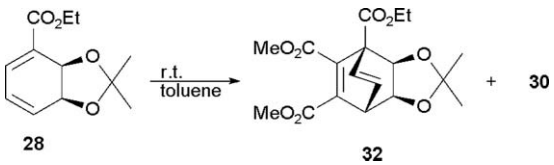
The diol derived from styrene was converted to (–)-zeylena *via* an intramolecular Diels–Alder reaction with cinnamyl ester.[21] The acetonide derived from diol **12** undergoes a regio- and stereoselective [4 + 2] cycloaddition with acylnitroso compounds and this feature was exploited in the synthesis of aminocyclitols and amininositols,[22] and the total synthesis of lycoricidine.[23] The hetero-Diels–Alder cycloaddition of acyl nitroso compounds to the diol derived from *m*-dibromobenzene led to a concise total synthesis of narciclasine.[24] Diols derived from toluene and β-bromoethyl benzene yielded, *via* intramolecular Diels–Alder cycloadditions, concise models for approaches to morphine skeleton.[25] Many elegant examples of [4 + 2][26] and other[27] cycloadditions or annulations have been documented.

The dihydrodiols derived from benzoates contain a diene unit suitable for inverse electon demand cycloadditions. Such reactivity has been observed with the acetonides derived from **4** and **10**, which undergo facile dimerization when maintained at room temperature in the absence of solvent for prolonged times (1 week), or when heated (110 °C) in solution for a shorter time (6 hours). The cycloadducts were formed as single diastereoisomers **30** and **31**, deriving from an *endo*-approach of the dienophile to the less hindered faces of both diene and dienophile, as confirmed by NOESY spectroscopy (Scheme 4). Exposure of the free diols, **4** and **10**, to identical reaction conditions did not produce evidence of dimerization. In the case of the ethyl ester diol, prolonged heating (3 days) at 60 °C produced no change in composition, while heating at elevated temperatures (100 °C, 12 h) resulted in the elimination of water and formation of the corresponding phenol.

Acetonide **28** was reacted with the electron-poor dienophile dimethylacetylenedicarboxylate (DMAD), under conditions that afforded good yields of DMAD cycloadduct with electron-rich dienes, furnishing a 2:1 mixture of cycloadduct **32** and dimer **30**, Scheme 5.[28]

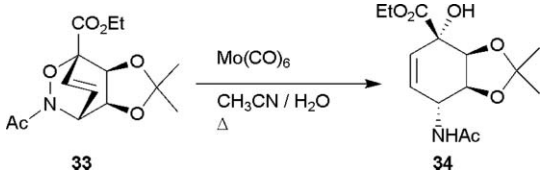


Scheme 4



Scheme 5

In order to take advantage of the inverse electron-demand reactivity, we exposed the acetonide **28** to hetero-Diels–Alder conditions with an acetyl nitroso partner as a dienophile. Absolute regioselectivity was observed, providing the bicyclic oxazine **33** in high yield,[29] Scheme 6.



Scheme 6

While the complete regioselectivity in the production of **33** was not expected, it leads to a valuable and useful intermediate. Reduction of **33** provided the hydroxyl ester **34**, which can and will be exploited in the design of amino pseudo-sugars, derivatives of shikimic acid, aminocyclitols, and other biologically active compounds. For example, the hydroxy ester **34** contains several structural features found in oseltamivir and this feature has been exploited recently in a short approach to this important medicinal agent.[30]

Conclusion

We have isolated new metabolites from the whole-cell fermentation of benzoate esters with the recombinant strain *E. coli* JM 109 (pDTG 601) overexpressing toluene dioxygenase. Following the proof of absolute stereochemistry some of these esters underwent inverse electron demand Diels–Alder reactions and provided useful intermediates for the synthesis of carbohydrate and derivatives, as exemplified in the preparation of a pseudo galactopyranose. While the space-time yields of *cis*-dihydrodiols derived from benzoates are lower than those obtained from, for example, halobenzenes, these new metabolites offer many advantages for further synthetic ventures. The benzoate-derived diols contain all seven carbons present in pseudo sugars and therefore their use in preparation of such targets avoids the extra steps required for the introduction of the carboxylate or hydroxymethyl functionality into the diols derived from bromo- or iodobenzene. The ease with which the benzoate-derived diols undergo regioselective Diels–Alder reaction with dienophiles allows for expansion of their use in the preparation of amino cyclitols and other heteroatom substituted carbohydrate derivatives. Further endeavors will seek to improve the yields of fermentations and exploit these new metabolites in the synthesis of carbohydrates, amino cyclitols, and related compounds.

Experimental section

Viable cells were prepared as previously reported.[7] Substrate was fed in 1 g increments over the course of ~2h with metabolites being harvested in the usual manner. All non-aqueous reactions were conducted in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. Methylene chloride was distilled from calcium hydride, THF and toluene were dried over sodium/benzophenone. Analytical thin layer chromatography was performed on Silicycle 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh). Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer One FT-IR spectrometer. Optical rotation was measured on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm. ^{1}H and ^{13}C spectra were recorded on a 300 MHz and 600 MHz Bruker spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent. Data of proton spectra are reported as follows: chemical shift in ppm (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (δ) relative to solvent resonance as internal standard. Mass spectra and high resolution mass spectra were performed by the analytical division at Brock University.

6-Carboxymethyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (3). (12.92 g, 19.2%, 75.8% based on recovered starting material) Pale yellow oil; R_f 0.33 (1:2 hexanes/ethyl acetate); $[\alpha]_D^{23}$ +71.3 (*c* 1.6, $CHCl_3$); IR (film) ν 3412, 2098, 1690, 1639, 1291, 820, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 5.3 Hz, 1H), 6.17 (dd, J = 0.6, J = 10.3 Hz, 1H), 6.05 (qd, J = 2.2, J = 5.1 Hz, 1H), 4.50–4.56 (m, 1H), 4.41–4.50 (m, 1H), 3.77 (s, 3H), 3.52–3.67 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 138.6, 134.3, 128.4, 122.6, 69.5, 64.8, 52.1 ppm; MS (EI) m/z (%): 170(M^+, 33), 152(61), 139(22), 138(96), 136(71), 121(100), 110(95), 109(66), 105 (23), 93(42), 92(22) 82(57), 81(56), 65(59), 53(49), 51(22); HRMS calcd for $C_8H_{10}O_4$ 170.0579, found 170.0580.

6-Carboxymethyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (4). (8.06 g, 43.4%, 45.6% based on recovered starting material) Colourless crystals, m.p. 48 °C (ethyl acetate/hexanes); R_f 0.31

(1:2 hexanes/ethyl acetate); $[\alpha]_D^{23}$ +54.7 (*c* 3.8, $CHCl_3$); IR (film) ν 3385, 2981, 2934, 1700, 1280, 1243, 1104, 1068, 825, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, *J* = 5.3 Hz, 1H), 6.15 (dt, *J* = 1.1, *J* = 9.4 Hz, 1H), 6.03 (dq, *J* = 2.25, *J* = 9.22 Hz, 1H), 4.49–4.55 (m, 1H), 4.40–4.48 (m, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.65–3.78 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 138.7, 134.1, 128.7, 122.5, 69.8, 64.5, 60.9, 14.2 ppm; MS (EI) *m*/*z* (%): 184(M^+, 9), 166(20), 138(26), 122(33), 121(52), 105(100), 77(39), 51(21), 45(20); HRMS calcd for $C_9H_{12}O_4$ 184.0736, found 184.0731; *Anal.* calcd: C 58.69, H 6.57, found C 58.77, H 6.60.

6-Carboxypropyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (5). (711 mg, 5.8%, 65.0% based on recovered starting material) waxy solid; R_f 0.15 (1:1 ethyl acetate/hexanes); $[\alpha]_D^{22}$ +58.8 (*c* 1.1, $CHCl_3$); IR (film) ν 3398, 2968, 1700, 1280, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 5.4 Hz, 1H), 6.20 (dd, *J* = 9.5, *J* = 2.5 Hz, 1H), 6.09 (ddd, *J* = 9.5, *J* = 5.4, *J* = 2.2 Hz, 1H), 4.58 (d, *J* = 6.3 Hz, 1H), 4.48 (ddd, *J* = 6.3, *J* = 2.5, *J* = 2.2 Hz, 1H), 4.16 (t, *J* = 6.7 Hz, 2H), 3.40 (bs, 2H), 1.72 (qt, *J* = 7.4, *J* = 6.7 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 138.4, 133.9, 128.7, 122.6, 69.4, 66.6, 64.8, 22.0, 10.4 ppm; MS (EI) *m*/*z* (%): 198(M^+, 18), 180(22), 138(100), 121(81), 110 (54), 105 (77); HRMS calcd for $C_9H_{12}O_4$ 198.0892, found 198.0892.

6-Carboxyisopropyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (6). (488 mg, 4.1%, 34.0% based on recovered starting material) colourless crystals; m.p. 83–85 °C (ethyl acetate/hexane); R_f = 0.31 (6:4 ethyl acetate/hexane); $[\alpha]_D^{22}$ +64.70 (*c* 1.1, $CHCl_3$); IR (KBr) ν 3274, 2981, 1698, 1263, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (ddd, *J* = 5.5, 1.0, 0.5 Hz, 1H), 6.20 (ddt, *J* = 9.6, 2,7, 0.9 Hz, 1H), 6.08 (ddd, *J* = 9.6, *J* = 5.5, *J* = 2.2 Hz, 1H), 5.12 (hept, *J* = 6.3 Hz, 1H), 4.58 (dd, *J* = 6.4, *J* = 0.5 Hz, 1H), 4.48 (br m, 1H), 3.60–3.25 (br s, 2H), 1.30 (d, *J* = 6.3 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 138.2, 133.6, 128.9, 122.63, 99.4 69.2, 68.5, 64.9, 21.8 ppm; MS (EI) *m*/*z* (%): 198(M^+, 19), 180(16), 156(14), 138(100); HRMS (EI) calcd for $C_{10}H_{14}O_4$: 198.08921, found: 198.08896. *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.68; H, 7.19.

6-Carboxyallyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (9). (5.79 g, 52.0%, 73.6% based on recovered starting material) colourless crystals; m.p. 48–50 °C (ethyl acetate/hexane); R_f = 0.23 (1:1 ethyl acetate/hexane); $[\alpha]_D^{22}$ +72.54 (*c* 1.6, $CHCl_3$); IR (KBr) ν 3394, 1704, 1273, 1238 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 5.5 Hz, 1H), 6.23 (ddt, *J* = 9.6, *J* = 2,7, *J* = 1.0 Hz, 1H), 6.11 (ddd, *J* = 9.5, *J* = 5.5, *J* = 2.2 Hz, 1H), 5.98 (ddt, *J* = 17.2, *J* = 10,4 *J* = 5.7 Hz, 1H), 5.37 (dt, *J* = 17.2, *J* = 1.5 Hz, 1H), 5.28 (dt, *J* = 10.4, *J* = 1.3 Hz, 1H), 4.72 (ddd, *J* = 5.7, *J* = 1.5, *J* = 1.3 Hz, 1H), 4.61 (br s, 1H), 4.50 (br s, 1H), 3.25 (d, *J* = 3.8 Hz, 1H), 3.18 (bd, *J* = 7.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 138.8, 134.4, 131.9, 128.4, 122.4, 118.3, 69.6, 65.5, 64.5 ppm; MS (EI) *m*/*z* (%): 196(M^+, 20), 178(18), 138(80), 121(95), 41(100). HRMS (EI) calcd for $C_{10}H_{12}O_4$: *m*/*z* 196.07356, found: 196.07364. *Anal.* Calcd. for $C_{10}H_{12}O_4$ + 1/8 H_2O: C, 60.52; H, 6.22. Found: C, 60.52; H, 6.26.

6-Carboxyisopropyl-(1*S*,2*S*)-1,2-dihydroxycyclohex-3-ene (10). (9.20 g, 69.1%, 75.8% based on recovered starting material) colourless crystals; m.p. 70–72 °C (ethyl acetate/hexane); R_f = 0.31 (6:4 ethyl acetate/hexane); $[\alpha]_D^{22}$ +88.20 (*c* 1.6, $CHCl_3$); IR (KBr) ν 3385, 3291, 1707, 1270, 1234 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.01 (dd, *J* = 5.3, *J* = 1.1 Hz, 1H), 6.16 (dq, *J* = 9.5, *J* = 1.4 Hz, 1H), 6.09 (ddd, *J* = 9.5, *J* = 5.3, *J* = 2.2 Hz, 1H), 4.86 (dd, *J* = 15.8, *J* = 2.5 Hz, 1H), 4.80 (dd, *J* = 15.8, *J* = 2.5 Hz, 1H), 4.50–4.23 (m, 2H), 4.10 (d, *J* = 7.4 Hz, 1H), 3.96 (d, *J* = 5.0 Hz, 1H), 3.06 (t, *J* = 2.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6) δ 167.2, 142.5, 136.3, 131.1, 123.5, 80.0, 77.3, 72.5, 65.5, 53.4 ppm; MS (EI) *m*/*z* (%): 194(M^+, 7%), 176(28), 138(47), 121(100); HRMS (EI) calcd for $C_{10}H_{10}O_4$: *m*/*z* 194.0579, found: 194.0581. *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.08; H, 5.18.

General procedure for PAD reduction of diols

To a stirring solution of diene (2.5 mmol) and potassium azodicarboxylate (PAD) (7.5 to 15.0 mmol) in MeOH (4 mL), glacial acetic acid was added (17.5 to 37.5 eq.) dropwise at −15 °C. The reaction was allowed to warm to room temperature slowly over 14 h, then quenched by the addition of Na_2CO_3 (7 to 15 mL) and concentrated under reduced pressure and extracted with ethyl acetate (5 × 5 mL). The combined organic layers were washed with brine (1 × 7 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was recrystalized from ethyl acetate/hexanes. The analytical and spectral data for 6-carboxyethyl-(1*S*,2*S*)-1,2-dihydroxycyclohex-3-ene (**11**), 6-carboxypropyl-(1*S*,2*S*)-1,2-dihydroxycyclohex-3-ene (**13**), 6-carboxymethyl-(1*S*,2*S*)-1,2-dihydroxycyclohex-3-ene (**14**) and 6-carboxyisopropyl-(1*S*,2*S*)-1,2-dihydroxycyclohex-3-ene (**15**) can be found in the ESI.†

6,7-Diacetoxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole-4-carboxylic acid ethyl ester (24). To a solution of diol **3** (300 mg, 1.76 mmol) in 2,2-dimethoxypropane (2 mL) and acetone (1 mL) was added *p*-toluenesulfonic acid (catalytic amount) at room temperature. After complete consumption of starting material (TLC analysis), the solution was diluted with ethyl acetate (60 mL), washed with saturated $NaHCO_3$ (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude acetonide was dissolved in a mixture of acetone:H_2O (5:1, 12 mL) and *N*-methylmorpholine-*N*-oxide (309 mg, 2.64 mmol) was added, followed by a single crystal of OsO_4. The solution was stirred until total consumption of starting material (15 h) as monitored by TLC. The reaction mixture was concentrated to dryness under reduced pressure, suspended in DCM (10 mL), and cooled in an ice bath. To the stirring suspension was added triethylamine (1.1 mL, 8 mmol), Ac_2O (0.60 mL, 6.2 mmol), and DMAP (43 mg, 0.35 mmol). The reaction was stirred overnight (12 h) before being quenched with $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 × 20 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated. The crude material was purified *via* flash column chromatography with a solvent gradient of 5:1–3:1 hexanes-ethyl acetate. (401 mg, 69%), colourless oil. R_f 0.65 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{20}$ −67.54 (*c* 2.5, EtOH); IR (film): ν 2989, 2954, 2938, 1754, 1726, 1661, 1437, 1372, 1303, 1234, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 3.0, *J* = 1.1 Hz, 1H), 5.72 (t, *J* = 3.7 Hz, 1H), 5.53 (ddd, *J* = 5.3, *J* = 3.8, *J* = 1.1 Hz, 1H), 5.07 (dd, *J* = 5.8, *J* = 0.8 Hz, 1H), 4.43 (dd, *J* = 5.6, *J* = 5.3 Hz, 1H), 3.84 (s, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 1.41 (s, 6H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 169.7, 165.4, 136.7,

131.4, 110.2, 72.9, 70.3, 69.6, 66.3, 52.3, 27.4, 25.7, 20.8, 20.7 ppm; MS (EI) *m/z* (%): 313(M^+-CH_3, 52), 211(19), 169(36), 168(12), 137(11), 85(43), 83(58), 47(12), 43(100); HRMS (M^+-CH_3) calcd for $C_{14}H_{17}O_8$ 313.0923, found 313.0919.

6,7-Diacetoxy-2,2-dimethyl-hexahydro-benzo[1,3]dioxole-4-carboxylic acid methyl ester (25). To a solution of ester **24** (40 mg, 0.122 mmol) in ethanol (3 mL) was added 5% Rh/Al_2O_3 (40 mg). The reaction was stirred under an atmosphere of H_2 (60 psi, 24 h). The reaction was filtered through celite by elution with EtOH and concentrated. The crude material was purified *via* flash column chromatography with a solvent gradient of 5:1 hexanes-ethyl acetate. (28 mg, 70%), colorless oil. R_f 0.60 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{20}$ −71.56 (*c* 0.93, $CHCl_3$); IR (film): ν 2976, 2954, 2938, 1750, 1734, 1732, 14337, 1372, 11240, 1221, 1195 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.40 (m, 1H), 4.93 (dd, J = 7.9, J = 2.6 Hz, 1H), 4.69 (t, J = 4.9 Hz, 1H), 4.23 (dd, J = 8.0, J = 5.0 Hz, 1H), 3.78 (s, 3H), 3.13 (dt, J = 12.8, J = 4.5 Hz, 1H), 2.21 (dt, J = 14.9, J = 12.9 Hz, 1H), 2.12–2.06 (m, 4H), 1.52 (s, 3H), 1.38 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 170.3, 169.7, 109.9, 75.5, 73.9, 7.1, 68.7, 52.2, 38.11, 27.9, 26.2, 24.9, 20.9 ppm; MS (EI) *m/z* (%): 313 (M^+-CH_3, 13), 241(15), 171(23), 153(47), 43(100); HRMS (M^+-CH_3) calcd for $C_{14}H_{19}O_8$ 315.1080, found 315.1082.

7-Hydroxymethyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxole-4,5-diol (27). LAH (26 mg, 0.73 mmol) was added to a solution of ester **25** (40 mg, 0.121 mmol) in dry THF (2 mL). The reaction mixture was brought to reflux and stirred for 4 hours, allowed to cool to room temperature, and quenched with a mixture of THF/H_2O. The reaction was filtered, dried over Na_2SO_4, filtered again, and concentrated. The crude material was purified *via* flash column chromatography with a solvent gradient of 5:1 hexanes-ethyl acetate. (23 mg, 86%), colorless oil. R_f 0.14 (9:1 chloroform/methanol); $[\alpha]_D^{20}$ −57.08 (*c* 0.70, MeOH); ^1H NMR (600 MHz, acetone-d_6) δ 4.30 (t, J = 4.4, 1H), 4.01 (dd, J = 6.9, 5.5 Hz, 1H), 4.00–3.94 (m, 2H), 3.70–3.60 (m, 2H), 3.58–3.48 (m, 3H), 2.44–2.37 (m, 1H), 1.75 (dt, J = 13.0, 4.6 Hz, 1H), 1.48 (dt, J = 6.6, 2.8 Hz, 1H), 1.40 (s, 3H), 1.28 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 107.8, 79.4, 74.6, 73.7, 68.9, 63.58, 34.2, 28.3, 27.7, 25.7 ppm; MS (EI) *m/z* (%) 203 (M^+-CH_3, 100), 204(10), 203(100), 125(19), 107(11), 100(13), 97(13), 95(21), 83(32), 79(33), 73(14), 71(11), 70(14), 69(20), 67(16), 60(17), 59(55), 57(18), 55(18), 43(53), 41(22); HRMS (M^+-CH_3) calcd for $C_9H_{15}O_5$ 203.0933, found 203.0926.

General procedure for the trans-esterification of PAD-reduced diols

A solution of PAD-reduced diol (0.79 mmol), conc. H_2SO_4 (5 drops) in dry ethanol (10 mL) was refluxed for 4 days. The mixture was concentrated, diluted in satd. $NaHCO_3$ (2 mL) and extracted with ethyl acetate (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (eluant 1:1 ethyl acetate/hexanes) and recrystallized from ethyl acetate/hexanes.

General procedure for the ketalization of diols

To a stirring solution of diol (0.832 mmol) and 2,2 dimethoxypropane (0.71 mL, 5.83 mmol) in acetone (1 mL) was added a catalytic amount of *p*-TsOH. The reaction was allowed to stir at room temperature for 2h, then it was diluted with ethyl acetate (5 mL) and washed with saturated $NaHCO_3$ (3 × 2 mL). The organic layer was washed with brine (1 × 3 mL) then dried with Na_2SO_4. The crude material was purified *via* flash column chromatography with a solvent gradient of 2:1 hexanes-ethyl acetate.

(3a*R*,7a*S*)-Ethyl-3a,7a-dihydro-2,2-dimethylbenzo[*d*][1,3]dioxole-4-carboxylate (28). (173 mg, 92%) colorless oil; R_f 0.56 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{23}$ +74.6 (*c* 4.02, $CHCl_3$); IR (film): ν 3018, 2987, 2936, 1712, 1651, 1425, 1380, 1259, 1155, 1031, 917, 856, 697, 667, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (dd, J = 5.3, J = 3.1 Hz, 1H), 4.84 (d, J = 5.7 Hz, 1H), 4.28–4.41 (m, 1H), 4.07–4.26 (m, 2H), 2.21–2.45 (m, 1H), 1.99–2.16 (m, 1H), 1.86–1.99 (m, 1H), 1.58–1.72 (m, 1H), 1.33 (d, J = 10.2 Hz, 6H), 1.24 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 142.3, 130.0, 108.5, 72.6, 70.4, 60.5, 27.8, 26.2, 25.1, 20.9, 14.2 ppm; MS (EI) *m/z* (%): 226 (M^+-CH_3), 211(77), 181(15), 169(17), 123(100), 105(17), 95(13), 83(11), 79(76), 67(14), 59(10), 55(11), 43(82), 41(14); HRMS (M^+-CH_3) calcd for $C_{12}H_{16}O_4$ 211.0970, found 211.0969; *Anal.* calcd: C 64.27; H 7.19. Found C 64.52; H 7.08.

(3a*R*,7a*S*)-Prop-2-ynyl-3a,7a-dihydro-2,2-dimethylbenzo[*d*][1,3]dioxole-4-carboxylate (29). (764 mg, 63%) colorless oil; R_f = 0.54 (2:8 ethyl acetate/hexane); $[\alpha]_D^{22}$ +112.70 (*c* 1.3, $CHCl_3$); IR (KBr) ν 2987, 2935, 1718, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, J = 5.3, 1.1 Hz, 1H), 6.19–6.09 (series of m, 2H), 4.95 (d, J = 8.4 Hz, 1H), 4.89 (dd, J = 8.4, J = 2.4 Hz, 1H), 4.84 (dd, J = 2.5, J = 1.0 Hz, 2H), 2.50 (t, J = 2.5 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 134.8, 134.4, 125.5, 121.2, 105.7, 77.7, 74.9, 71.8, 68.0, 52.3, 26.7, 25.0 ppm; MS (EI) *m/z* (%): 219(M^+-Me, 42), 177(41), 163(17), 121(83), 43(100). HRMS (EI) calcd for $C_{12}H_{11}O_4$: *m/z* 219.0657, found: 219.0659. Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.68; H, 6.08.

(1*S*,2*R*,3*S*,4*S*,4a*S*,5*S*,6*R*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-2,3,5,6-tetrahydroxy-*O,O*-diisopropylyden-1,4-ethenonaphthalene-1,7-diethyldicarboxylate (30). Neat **24** (400 mg, 1.78 mmol) was maintained for 7 days at r.t., purified by flash-chromatography (eluant 3:7 ethyl acetate/hexane); $[\alpha]_D^{22}$ +62.90 (*c* 1.3, $CHCl_3$). IR (KBr) ν 2984, 2938, 1722, 1262, 1221, 1071 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.44 (d, J = 3.7 Hz, 1H), 6.39 (d, J = 8.5 Hz, 1H), 6.05 (dd, J = 8.5, J = 6.3 Hz, 1H), 4.61 (dd, J = 7.2, J = 1.2 Hz, 1H), 4.59 (d, J = 4.9 Hz, 1H), 4.43 (ddd, J = 7.2, J = 3.4, J = 0.5 Hz, 1H), 4.36 (qd, J = 7.1, J = 1.7 Hz, 2H), 4.28–4.18 (m, 2H), 4.17 (dd, J = 4.9, J = 2.5 Hz, 1H), 3.02 (1 H, m), 2.95 (ddd, J = 9.2, J = 3.7, J = 1.3 Hz, 1H), 2.34 (ddd, J = 9.2, J = 1.3, J = 1.2 Hz, 1H), 1.37 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 165.8, 136.4, 131.4, 130.2, 128.8, 109.7, 108.2, 80.7, 78.3, 76.9, 69.2, 61.4, 60.7, 53.9, 40.4, 38.6, 34.9, 28.1, 26.5, 25.3, 25.1, 14.20, 14.15 ppm;; MS (EI) *m/z* (%): 433(M^+-Me, 6), 390(8), 375(7), 345(4), 100(17), 61(21), 43(100). HRMS (EI) calcd for $C_{24}H_{32}O_8$: *m/z* 448.20972, found: 448.20863.

(1*S*,2*R*,3*S*,4*S*,4a*S*,5*S*,6*R*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-2,3,5,6-tetrahydroxy-*O,O*-diisopropylyden-1,4-ethenonaphthalene-1,7-dipropargyldicarboxylate (31). A solution of **29** (390 mg,

1.66 mmol) in toluene (1 mL) was maintained at 110 °C for 6 hours, purified by flash-chromatography (eluant 3:7 ethyl acetate/hexane) to afford **27** as a foamy solid (321 mg, 83%); m.p. 43–45 °C. $R_f = 0.32$ (3:7 ethyl acetate/hexane); $[\alpha]_D^{22}$ +53.03 (*c* 1.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (d, $J = 3.8$ Hz, 1H), 6.40 (d, $J = 8.4$ Hz, 1H), 6.08 (dd, $J = 8.4$, $J = 6.4$ Hz, 1H), 4.96 (dd, $J = 15.5$, $J = 2.4$ Hz, 1H), 4.83 (dd, $J = 15.5$, $J = 2.4$ Hz, 1H), 4.82 (dd, $J = 15.6$, $J = 2.4$ Hz, 1H), 4.72 (dd, $J = 15.6$, $J = 2.4$ Hz, 1H), 4.64 (d, $J = 7.2$ Hz, 1H), 4.59 (d, $J = 4.9$ Hz, 1H), 4.45 (dd, $J = 7.2$, $J = 3.5$ Hz, 1H), 4.61 (dd, $J = 4.9$, $J = 2.2$ Hz, 1H), 3.04 (m, 1H), 3.03 (dd, $J = 9.1$, $J = 3.5$ Hz, 1H), 2.64 (t, $J = 2.4$ Hz, 3H), 2.48 (t, $J = 2.4$ Hz, 3H), 2.7 (d, $J = 9.1$ Hz, 1H), 1.37 (s, 3H), 1.309 (s, 3H), 1.303 (s, 3H), 1.29 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 164.9, 137.3, 131.0, 129.6, 129.1, 109.9, 108.3, 80.5, 78.2, 77.6, 77.1, 76.8, 75.7, 75.0, 69.0, 53.8, 52.9, 52.3, 40.4, 38.8, 34.6, 28.1, 26.5, 25.3, 25.1 ppm; IR (KBr) ν 2987, 2938, 1728, 1243, 1217, 1071 cm^{-1}; MS (EI) *m/z* (%): 453(M^+-Me, 26), 395(32), 297(15), 121(31), 100(60), 85(22), 43(100). HRMS (EI) calcd for $C_{24}H_{32}O_8$: *m/z* 453.15494, found: 453.15470. *Anal.* Calcd. for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.61; H, 6.16.

(1*S*,4*S*,5*S*,6*R*)-1-Ethyl-2,3-dimethyl-5,6-dihydroxy-*O,O*-ispropylydenbicyclo[2.2.2]octa-2,7-diene-1,2,3-tricarboxylate (32). A solution of **28** (400 mg, 1.78 mmol), dimethylacetylenedicarboxylate (DMAD) (380 mg, 2.68 mmol) in toluene (1.0 mL) was stirred at rt for 72 hours. The resulting mixture was purified by flash-chromatography (eluant ethyl acetate/hexane in gradient from 2:8 to 3:7) to afford an oil that was purified by crystallization from ethyl acetate/hexane to provide **28** as colourless crystals (210 mg, 57%); m.p. 70–71 °C. $R_f = 0.35$ (3:7 ethyl acetate/hexane); $[\alpha]_D^{22}$ +21.75 (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (ddd, $J = 7.3$, $J = 1.3$, $J = 0.9$ Hz, 1H), 6.44 (dq, $J = 7.3$, $J = 6.0$, $J = 0.7$ Hz, 1H), 4.71 (dd, $J = 6.9$, $J = 0.9$ Hz, 1H), 4.49 (ddd, $J = 6.9$, $J = 3.6$, $J = 0.7$ Hz, 1H), 4.37 (ddd, $J = 6.0$, $J = 3.6$, $J = 1.3$ Hz, 1H), 4.33 (qd, $J = 7.2$, $J = 1.7$ Hz, 2H), 3.77 (s, 6H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.34 (s, 3H), 1.28 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 165.5, 164.1, 144.8, 137.8, 131.4, 130.4, 114.3, 81.8, 78.3, 62.0, 60.0, 52.48, 52.39, 43.7, 25.70, 25.67, 14.0 ppm; IR (KBr) ν 2989, 2953, 1748, 1724, 1261 cm^{-1}; MS (EI) *m/z* (%): 351(M^+-Me, 6), 207(21), 221(62), 175(88), 100(100). HRMS (EI) calcd for $C_{17}H_{19}O_8$: *m/z* 351.10799, found: 351.10811. *Anal.* Calcd. for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.16; H, 6.08.

(1*R*,2*S*,6*S*,7*S*)-9-Acetyl-4,4-dimethyl-3,5,8-trioxa-9-aza-tricyclo[5.2.2.02,6]undec-10-ene-7-carboxylic acid ethyl ester (33). To a stirring solution of diol **4** (5 g, 27.1 mmol) in 2,2-dimethoxypropane (80 mL) was added *p*-toluenesulfonic acid (catalytic amount) at room temperature. After complete consumption of starting material (TLC analysis), the solution was cooled 0 °C before the addition of H_2O (10 mL). On a preparative scale the intermediate acetonide **28** was not isolated.

$NaIO_4$ (5.80 g, 27.1 mmol) was added to the reaction flask prior to the addition of a solution of acetohydroxamic acid (2.03 g, 27.1 mmol) in MeOH (25 mL) dropwise over 5 minutes. The resulting solution was stirred at room temperature for 16 h, quenched by the slow addition of sat. $NaHSO_3$ (10 mL) and extracted into Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over Na_2SO_4. The crude material was purified *via* flash column chromatography with a solvent system of 2:8 (hexanes/ethyl acetate) to yield **29** as a white solid (5.65 g, 70% over 2 steps); R_f 0.33 (3:7 hexanes/ethyl acetate); mp 89–90 °C (hexanes/ethyl acetate); $[\alpha]_D^{23}$ −18.0 (*c* 0.54, $CHCl_3$); IR (film) ν 3466, 2938, 2987, 1747, 1684, 1620, 1372, 1275, 1086 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57–6.65 (m, 2H), 5.47–5.52 (m, 1H), 4.71 (d, $J = 6.8$ Hz, 1H), 4.56 (dd, $J = 4.7$, $J = 6.6$ Hz, 1H), 4.38 (q, $J = 7.2$ Hz, 2H), 2.01 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H), 1.32 (s, 3H), 1.30 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 166.6, 132.4, 128.4, 111.7, 79.2, 76.1, 72.8, 62.7, 50.0, 25.6, 25.4, 21.7, 14.1 ppm; MS (EI) *m/z* (%): 297(M^+), 124(52), 105(35), 100(32), 96(30), 43(100),; HRMS calcd for $C_{14}H_{19}NO_6$ 297.1212, found 297.1215.

7-Acetylamino-4-hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydro-benzo[1,3]dioxole-4-carboxylic acid ethyl ester (34). To a stirred solution of **33** (955 mg, 3.21 mmol) in 15:1 CH_3CN:H_2O (10 mL) was added molybdenum hexacarbonyl (848 mg, 3.21 mmol) at room temperature. The reaction was brought to reflux for 3 h before being allowed to cool to room temperature. The reaction was concentrated and filtered through a plug of celite. The crude material was purified *via* flash column chromatography with a solvent system of 1:9 (hexanes/ethyl acetate) to yield (**19**) (720 mg, 75%) as a white solid; R_f 0.20 (ethyl acetate); mp 97–99 °C (hexanes-ethyl acetate); $[\alpha]_D^{23}$ −94.3 (*c* 0.79, $CHCl_3$); IR (film) ν 3433, 2094, 1644, 1271, 1217, 1060 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.25 (d, $J = 8.7$ Hz, 1NH), 5.98 (dd, $J = 3.8$, $J = 9.8$ Hz, 1H), 5.94 (dd, $J = 0.9$, $J = 9.9$ Hz, 1H), 4.77–4.81 (m, 1H), 4.37 (t, $J = 8.3$ Hz, 1H), 4.34 (dd, $J = 4.3$, $J = 7.7$ Hz, 1H), 4.22–4.29 (m, 2H), 4.12 (s, 1OH), 1.99 (s, 3H), 1.35 (s, 3H), 1.32 (t, $J = 7.4$ Hz, 3H), 1.28 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 170.0, 132.9, 129.6, 109.3, 81.0, 76.3, 74.5, 62.8, 48.8, 26.2, 24.2, 23.5, 14.0 ppm; MS (EI) *m/z* (%): 284 (M^+-CH_3), 199(99), 153(38), 125(36), 96(37), 86(61), 84(100), 83(47), 43(90),; HRMS calcd for $C_{13}H_{18}NO_6$ 284.1130, found 284.1137.

Acknowledgements

The authors are grateful to the following agencies for financial support: Natural Science and Engineering Research Council (NSERC), TDC Research Foundation, Canada Foundation for Innovation (CFI), Ontario Innovation Trust (OIT), Research Corporation, TDC Research, Inc., and Brock University. Prof. Fabrizio Fabris is grateful to Università Ca' Foscari Venezia and Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) within the Progetti di Ricerca di Interesse Nazionale (PRIN) framework for facilitating this collaboration.

References

1 For a recent compilation of arene *cis*-dihydrodiols see: R. A. Johnson, *Org. React.*, 2004, **63**, 117.
2 D. T. Gibson, J. R. Koch, C. L. Shuld and R. E. Kallio, *Biochemistry*, 1968, **7**, 3795.
3 S. V. Ley, F. Sternfeld and S. Talor, *Tetrahedron Lett.*, 1987, **28**, 225.
4 D. G. H. Ballard, A. Cortis, I. M. Shirley and S. C. Taylor, *J. Chem. Soc. Chem. Comm.*, 1983, 954.
5 (*a*) For reviews on applications of the arene *cis*-dihydrodiols in synthesis: H. A. J. Carless, *Tetrahedron: Asymm*, 1992, **3**, 795; (*b*) S. M. Brown, T. Hudlicky, In *Organic Synthesis: Theory and Applications*T. Hudlicky, ed.; JAI Press: London, 1993; Vol. 2, p. 113; (*c*) T. Hudlicky, J. W. Reed, In *Advances in Asymmetric Synthesis*A. Hassner, Ed.; JAI Press: London, 1995; Vol. 1, p 271; (*d*) T. Hudlicky, *Chem. Rev.*, 1996,

96, 3; (*e*) D. R. Boyd and G. N. Sheldrake, *Nat. Prod. Rep.*, 1998, 309; (*f*) T. Hudlicky, D. Gonzalez and D. T. Gibson, *Aldrichimica Acta*, 1999, **32**, 35; (*g*) T. Hudlicky, J. W. Reed, *The Way of Synthesis: Evolution of Design and Methods in Organic Synthesis*Wiley–VCH, Weinheim, Germany, 2007; (*h*) T. Hudlicky and J. W. Reed, *Synlett*, 2009, 685.

6 G. J. Zylstra and D. T. Gibson, *J. Biol. Chem.*, 1989, **264**, 14940.

7 (*a*) For medium-scale preparation of some of the more common *cis*-dihydrodiols see: M. A. Endoma, V. P. Bui, J. Hansen and T. Hudlicky, *Org. Process Res. Dev.*, 2002, **6**, 525; (*b*) For procedures for preparation of diols from benzoic acids see:A. G. Myers, D. R. Siegel, D. J. Buzard and M. G. Charest, *Org. Lett.*, 2001, **3**, 2923; (*c*) For a procedure for the preparation of diols derived from chlorobenzene by means of *Pseudomonas putida* 39/D see: T. Hudlicky, M. Stabile, D. T. Gibson and G. M. Whited, *Org. Synth*, 1999, **76**, 77.

8 Diols derived form chloro- (48,950–6) and bromobenzene (48,949–2), naphthalene (49,032–6), and biphenyl (48,963–8) are available from Aldrich Chemical Company.

9 For the syntheses of these targets see: **(+)-D-*chiro*-Inositol:** M. Mandel, T. Hudlicky, L. D. Kwart and G. M. Whited, *J. Org. Chem.*, 1993, **58**, 2331**(+)-Kifunensine:** J. Rouden and T. Hudlicky, *J. Chem. Soc. Perkin 1*, 1993, 1095; T. Hudlicky, J. Rouden and H. Luna, *J. Org. Chem.*, 1993, **58**, 985; T. Hudlicky, J. Rouden, H. Luna and S. Allen, *J. Am. Chem. Soc.*, 1994, **116**, 5099**(–)-Specionin:** T. Hudlicky and M. G. Natchus, *J. Org. Chem.*, 1992, **57**, 4740 **(+)-Lycoricidine:** T. Hudlicky and H. F. Olivo, *J. Am. Chem. Soc.*, 1992, **114**, 9694 **(+)- Pinitol and (–)-Pinitol:** T. Hudlicky, F. Rulin, T. Tsunoda and J. D. Price, *J. Am. Chem. Soc.*, 1990, **112**, 9439; T. Hudlicky, F. Rulin, T. Tsunoda, H. Luna, C. Andersen and J. D. Price, *Isr. J. Chem.*, 1991, **31**, 229 **D-*erythro*-C_{18}- and L-*threo*-C_{18}-Sphingosines:** T. Hudlicky, T. Nugent and W. Griffith, *J. Org. Chem.*, 1994, **59**, 7944; T. C. Nugent and T. Hudlicky, *J. Org. Chem*, 1998, **63**, 510 **(+)-Pancratistatin:** X. Tian, T. Hudlicky and K. Königsberger, *J. Am. Chem. Soc.*, 1995, **117**, 3643 **(+)-7-Deoxypancaratistatin:** X. Tian, R. Maurya, K. Königsberger and T. Hudlicky, *Synlett*, 1995, 1125; T. Hudlicky, X. Tian, K. Konigsberger, R. Maurya, J. Rouden and B. Fan, *J. Am. Chem. Soc.*, 1996, **118**, 10752**(+)-Narciclasine:** D. Gonzalez, T. Martinot and T. Hudlicky, *Tetrahedron Lett.*, 1999, **40**, 3077 **Morphine alkaloids**: T. Hudlicky, S. P. Fearnley, M. R. Stabile, A. G. Gum and D. Gonzalez, *Synthesis*, 1998, 665; J. Zezula, K. C. Rice and T. Hudlicky, *Synlett*, 2007, **124**, 2863 **(+)-Codeine:** A. T. Omori, K. J. Finn, H. Leisch, R. J. Carroll and T. Hudlicky, *Synlett*, 2007, 2859 **1,2-L-*chiro*-inositol conjugates and oligomers:** T. Hudlicky, K. A. Abboud, J. Bolonick, R. Maurya, M. L. Stanton and A. J. Thorpe, *J. Chem. Soc. Chem. Commun.*, 1996, 1717 ***N*- and *O*-linked Diinositols:** B. J. Paul, J. Willis, T. A. Martinot, I. Ghiviriga and T. Hudlicky, *J. Am. Chem. Soc.*, 2002, 10416.

10 Benzoic acid is oxidized to its 2,3-*cis*-dihydrodiol by *P. putida* JT107:J. J. DeFrank and D. W. Ribbons, *J. Bacteriol.*, 1977, **129**, 1356 Oxidation of benzoic acid to its "ipso" diol is accomplished with *A. ethropus* B9: A. M. Reiner and G. D. Hegeman, *Biochemistry*, 1971, **10**, 2530.

11 (*a*) D. A. Entwistle and T. Hudlicky, *Tetrahedron Lett.*, 1995, **36**, 2591; (*b*) T. Hudlicky, K. A. Abboud, D. A. Entwistle, R. Fan, R. Maurya, A. J. Thorpe, J. Bolonick and B. Myers, *Synthesis*, 1996, 897.

12 (*a*) D. R. Boyd, N. D. Sharma, N. M. Llamas, J. F. Malone, C. R. O'Dowd and C. C. R. Allen, *Org. Biomol. Chem.*, 2005, **3**, 1953–1963; (*b*) D. R. Boyd, N. D. Sharma, G. P. Coen, P. J. Gray, J. F. Malone and J. Gawronski, *Chem. Eur. J.*, 2007, **13**, 5804–5811; (*c*) D. R. Boyd, N. D. Sharma, N. M. Llamas, G. P. Coen, P. K. M. McGeehin and C. C. R. Allen, *Org. Biomol. Chem.*, 2007, **5**, 514–522.

13 (*a*) A. Blacker, S. M. Brown, M. C. Bowden, Hydroxy Derivatives of Cyclohexadiene, International Patent WO 93/17994, September 16, 1993; (*b*) A. Blacker, R. Booth, G. Davies and J. Sutherland, *J. Chem. Soc. Perkin Trans. 1*, 1995, 2861.

14 *t*-Butyl benzoate: S. W. Wright, D. L. Hogeman, A. S. Wright and L. D. McClure, *Tetrahedron Lett.*, 1997, **38**, 7345–7348 allyl benzoate: J. Ramnauth and E. Lee-Ruff, *Can. J. Chem.*, 1999, **77**, 1245–1248 propargyl benzoate: M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, C. Santi and R. Terlizzi, *Eur. J. Org. Chem.*, 2004, 3447–3458 isopropyl benzoate: G. Brown, *Int. J. Appl. Radiation Isotopes*, 1959, **5**, 114–116.

15 R. Knorr and E. Lattke, *Chemische Berichte*, 1981, **114**, 2116–31.

16 Pingli Liu and M. Vandewalle, *Synlett*, 1994, **4**, 228–30.

17 R. Verduyn, S. H. van Leeuwen, G. A. van der Marel and J. H. van Boom, *Rec. Trav. Chim. Pays-Bas*, 1996, **115**, 67–71.

18 T. Suami, K. Tadano, Y. Ueno and C. Fukabori, *Chemistry Letters*, 1985, **10**, 1557–60.

19 D. T. Gibson, M. Hensley, H. Yoshika and R. J. Mabry, *Biochemistry*, 1970, **9**, 1626.

20 (*a*) T. Hudlicky, E. E. Boros, H. F. Olivo and J. S. Merola, *J. Org. Chem.*, 1992, **57**, 1026; (*b*) T. Hudlicky and C. H. Boros, *Tetrahedron Lett.*, 1993, **34**, 2557; (*c*) C. A. Pittol, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sik and J. O. Williams, *J. Chem. Soc. Perkins Trans. 1*, 1989, 1160.

21 T. Hudlicky, G. Seoane and T. Pettus, *J. Org. Chem.*, 1989, **54**, 4239.

22 (*a*) T. Hudlicky, H. F. Olivo and B. McKibben, *J. Am. Chem. Soc.*, 1994, **116**, 5108; (*b*) T. Hudlicky, K. A. Abboud, D. A. Entwistle, R. Fan, R. Maurya, A. J. Thorpe, J. Bolonick and B. Myers, *Synthesis*, 1996, 897.

23 T. Hudlicky and H. F. Olivo, *J. Am. Chem. Soc.*, 1992, **114**, 9694.

24 D. Gonzalez, T. Martinot and T. Hudlicky, *Tetrahedron Lett.*, 1999, **40**, 3081.

25 (*a*) T. Hudlicky, C. H. Boros and E. E. Boros, *Synthesis*, 1992, 174; (*b*) G. Butora, A. G. Gum, T Hudlicky and K. A. Abboud, *Synthesis*, 1998, 275.

26 (*a*) T. A. Reekie, Kerrie A. B. Austin, M. G. Banwell and A. C. Willis, *Austr. J. Chem*, 2008, **61**, 94–106; (*b*) M. G. Banwell, K. A. B. Austin and Anthony C. Willis, *Tetrahedron*, 2007, **63**, 6388–6403; (*c*) M. G. Banwell, P. Darmos and D. C. R. Hockless, *Austr. J. Chem*, 2005, **57**, 41–52; (*d*) M. G. Banwell and G. J. Harfoot, *Austr. J. Chem*, 2004, **57**, 895–897; (*e*) M. G. Banwell, A. J. Edwards, M. D. McLeod and S. G. Stewart, *Austr. J. Chem*, 2004, **57**, 641–644; (*f*) M. G. Banwell, P. Darmos and D. C. R. Hockless, *Austr. J. Chem*, 2004, **57**, 41–52; (*g*) M. G. Banwell, A. J. Edwards, G. J. Harfoot and K. A. Jollife, *J. Chem. Soc. Perkin Trans. 1.*, 2002, **18**, 2194–2203; (*h*) M. G. Banwell, K. J. McRae and A. C. Willis, *J. Chem. Soc. Perkin Trans. 1.*, 2001, **18**, 2194–2203; (*i*) M. G. Banwell, P. Darmos, M. D. McLeod and D. C. R. Hockless, *Synlett*, 1998, **8**, 897–899.

27 T. Hudlicky and B. P. McKibben, *J. Chem. Soc. Perkin Trans. 1*, 1994, 485–486.

28 S. M. Ogbomo and D. J. Burnell, *Org. Biomol. Chem.*, 2006, **4**, 3838–3848.

29 (*a*) T. Hudlicky, I. Carrera, unpublished observations; (*b*) Provisional patent application # 61/052, 435, file date May, 2008.

30 B. Sullivan, I. Carrera, M. Drouin and T. Hudlicky, *Angew. Chem. Int. Ed.*, 2009, DOI: 10.1002/anie.200901345.