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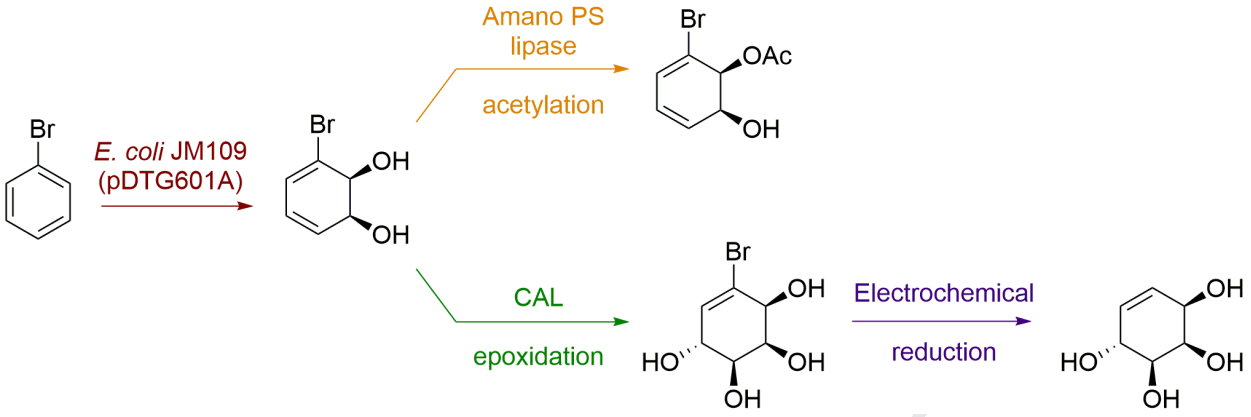

Sequential enzymatic and electrochemical functionalization of bromocyclohexadienediols: Application to the synthesis of (-)-conduritol C

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1. Abstract

cis-Diene diol obtained from the microbial oxidation of bromobenzene was used as a substrate for the chemoenzymatic acetylation and epoxidation with lipases. The model studies showed that the regiochemistry of the acetylation is solvent-dependent. The chemoenzymatic epoxidation followed the expected regiochemistry when compared to the chemical epoxidation with *m*-CPBA, but with the unexpected formation of bromoconduritol-C, an important intermediate whose electrochemical reduction led to the synthesis of (-)-conduritol-C. Experimental and spectral data are provided for all new compounds.

Keywords: enzymatic dihydroxylation, lipases, acetylation, epoxidation, narciclasine, conduritol C

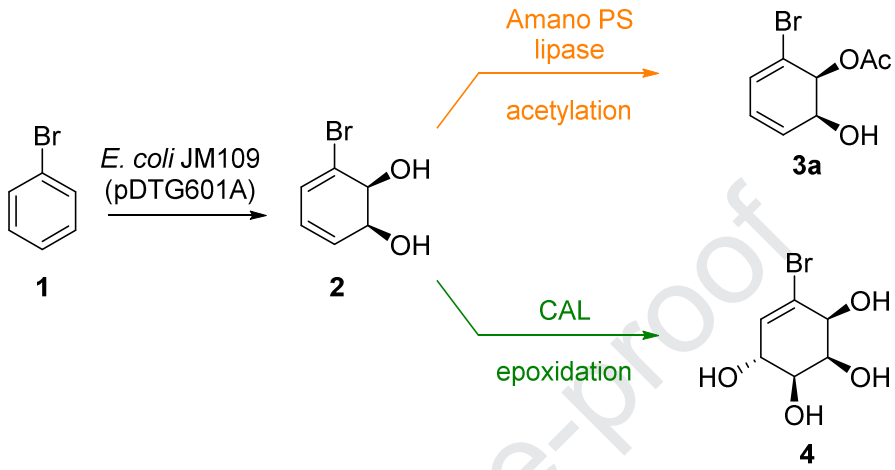
2. Introduction

For more than 30 years, arene *cis*-dihydrodiols obtained from the whole-cell fermentation of aromatics by *E. coli* JM109 (pDTG601A)[1] have been used as building blocks in natural product synthesis. The enantiopure diols have been converted to morphine derivatives, cyclitols, sesquiterpenes, the cytotoxic *Amaryllidaceae* alkaloids, and other complex natural products.[2] This biooxidation process has proven to be scalable and efficient within green chemistry metrics, and it represents a good example of how biocatalysis can be utilized as a potentially sustainable tool in organic synthesis.

Biocatalysis relies on the use of whole microorganisms or isolated enzymes and the tendency of enzymes to control the environment of the reaction rather than the reaction itself to provide outstanding enantio-, stereo- and regioselectivities in fewer steps than traditional chemical strategies.[3] By investigating and adding unconventional methods (e.g. biocatalysis, preparative electrochemistry)[2a] to previously known synthetic routes unexpected results can be attained and shorter synthetic routes can be achieved.

With this reasoning we considered sequential biotransformations applied to one of the ubiquitously used *cis*-diols, namely bromocyclohexadienediol **2**, which is obtained in high yields (>9

g/L) from the dihydroxylation of bromobenzene **1**,[4] Scheme 1. This compound was submitted as a substrate for investigation of lipase-catalyzed acetylation under mild conditions using Amano PS lipase immobilized in diatomite and for chemoenzymatic epoxidation using *Candida antarctica* lipase (CAL). (Scheme 1) Each of these studies provided valuable results and added new options to the repertoire of reactions that could be applied to the homochiral diols such as **2**.

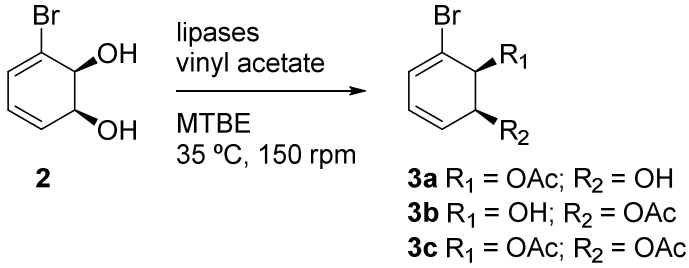


Scheme 1. Chemoenzymatic reactions investigated in this work.

In this work we report the results of chemoenzymatic acetylation of diols in organic media and a short synthesis of (-)-conduritol C by a chemoenzymatic cascade followed by electrochemical reduction of a vinyl bromide. The synthesis of conduritol was subjected to efficiency metric evaluation[5,6] in comparison to previous chemical syntheses. The lipase-catalyzed acetylation was also extended to acetylation of the cytotoxic natural product narciclasine.

3. Results and discussion

a) Lipase–catalyzed acetylation of 2



Scheme 2. Acetylation of bromodiol **(2)** catalyzed by AmanoPS immobilized in diatomite.

Screening of lipases. Initial conditions similar to a previously reported acetylation methodology[7] were used. Three out of nine lipases showed promising activity toward the acetylation of **2**: Lipases from *Pseudomonas fluorescens* (AmanoPF, 20,000 U/g); *Burkholderia cepacia* (AmanoIM, 500 U/g)

and immobilized in diatomite (AmanoPS-d, 500 U/g). The other lipases that were tested are listed in Supporting Information Section I, Part A.

Effect of mass of catalyst and equivalents of acyl donor. The influence of the amount of lipase was evaluated with an initial fixed value at 10 mg/mL with variation in the number of equivalents of acyl donor. The best results are shown in Table 1 (For details and complete results see Supporting Information Section I, Part B). AmanoIM and AmanoPS-d have similar activities with the same fixed load of active enzyme, while the activity for AmanoPF is approximately 40-fold higher. For the tested lipases, there was an increase in the overall conversion when two equivalents (1.0 mmol) of vinyl acetate were used, but the selectivity between **3a** and **3b** was still low.

Table 1. Analysis of varying amount of acyl donor in chemoenzymatic acetylation. Reaction conditions: **2** (0.5 mmol), vinyl acetate (0.5 – 1.0 mmol), lipase (100 mg), Methyl tert-butyl ether (MTBE) (10 mL), 24h, 35 °C, 150 rpm. Conversion values calculated with ^{1}H-NMR

Entry	Lipase	Vinyl acetate (mmol)	Overall Conversion	3a	3b	3c
1	AmanoIM	0.5	22%	64%	36%	-
2		1.0	90%	49%	46%	5%
3	AmanoPF	0.5	38%	69%	31%	-
4		1.0	51%	75%	25%	-
5	AmanoPS-d	0.5	32%	58%	42%	-
6		1.0	90%	49%	46%	5%

A uniform trend among the results presented in Table 1 was not observed. For the second round of experiments the volume of the reaction mixture was lowered from 10 mL of *tert*-butyl methyl ether (MTBE) to 5 mL with variable equivalents of vinyl acetate. The main results are shown in Table 2. (For details and complete results see Supporting Information Section I, Part B)

Table 2. Analysis of varying amount of acyl donor in chemoenzymatic acetylation. Reaction conditions: **2** (0.5 mmol), vinyl acetate (0.5 – 1.5 mmol), lipase (100 mg), Methyl tert-butyl ether (MTBE) (5 mL), 24h, 35 °C, 150 rpm. Conversion values calculated with ^{1}H-NMR

Entry	Lipase	Vinyl acetate (mmol)	Overall conversion	3a	3b	3c
7	AmanoIM	1.0	>95%	48%	32%	20%
8		1.5	>95%	49%	33%	18%
9	AmanoPF	1.0	76%	73%	27%	-
10		1.5	78%	74%	26%	-
11	AmanoPS-d	1.0	>95%	39%	21%	40%
12		1.5	>95%	49%	32%	19%

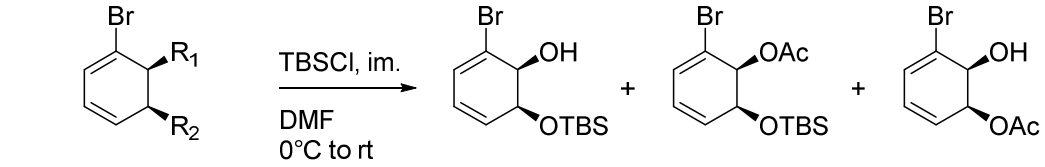
When the volume of the reaction mixture is decreased while keeping the same relative concentration of the substrate, acyl donor and lipases, AmanoIM and AmanoPS-d showed full overall conversion. AmanoIM is less selective and less sensitive to variation of the concentration of

vinyl acetate, while AmanoPF had the best selectivity towards formation of **2**, but without total consumption of starting material. AmanoPS-d was selected for further studies.

By using more concentrated organic media we observed the formation of diacetate **3c** and complete consumption of starting material. To investigate the source of formation of diacetate **3c**, the concentrated crude product from entry 12 was purified by column chromatography and two mixtures of **3a** and **3b** (1:1) were resubmitted in the shaker with conditions from entry 9. The first flask was removed from the shaker after 24 h, and a mixture of **3a** (55%), **3b** (14%) and **3c** (30%) was observed through ^{1}H-NMR. The second flask was removed after 48 h, and the mixture contained **3a** (41%), **3b** (12%) and **3c** (46%). The monoacetate **3b** appears to be the main substrate for the formation of diacetate **3c**.

Effect of solvent. To better understand the effect of biocompatibility of a few organic solvents in the acetylation reaction, two solvents and a mixture of solvents were selected with different logarithm of the partition coefficient (log *P*).[8] Acetonitrile (MeCN) (log *P* = -0.33), MTBE (log *P* = 1.24), and a 4:1 mixture of *n*-hexane (log *P* = 3.5) tetrahydrofuran (THF) (log *P* = 0.46) were selected. An increase in selectivity was observed toward the formation of **3a** when MTBE was switched for MeCN, but with a decrease in the overall conversion. The solvent system *n*-hexane:THF 4:1 presented low selectivity in the acetylation of **2** and is highly dependent on the concentration of vinyl acetate. Because of the observed trend, both MeCN and MTBE were selected for further investigations. (For details and complete results see Supporting Information Section I, Part C)

Because of the intramolecular acyl migration from C-2 to C-3, it is not possible to purify **3a** and **3b** by column chromatography. The crude product containing a mixture of starting material and products **3a** and **3b** was treated with TBSCl and compound **6** was isolated as the major product.



2: R_1 = OH; R_2 = OH
3a: R_1 = OAc; R_2 = OH
3b: R_1 = OH; R_2 = OAc

5 **6** **3b**

Scheme 3. TBS protection of a mixture of **2, 3a** and **3b**.

An acyl migration study was performed by filtering and concentrating the crude product obtained from the chemoenzymatic acetylation in MeCN and submitting it with a fresh load of solvent. After a period of 24h, acyl migration was observed as there was a 11% conversion from **3a**

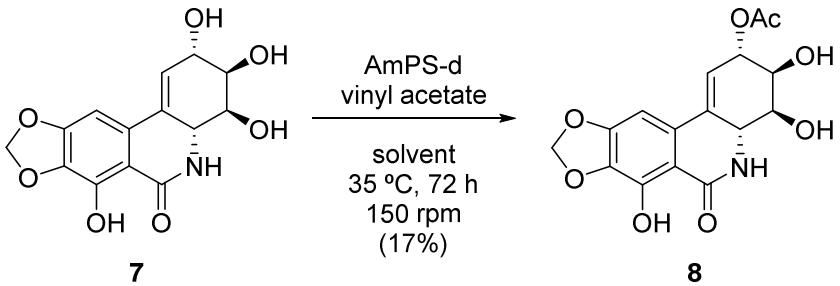
to **3b**. However, further acyl migration studies using imidazole or other suitable bases were not performed.

Effect of temperature. Temperature can often be a key factor in reactions catalyzed by enzymes.[9] To evaluate the effect of temperature in the acetylation of bromodiene diol **2**, reactions were performed using T = 20 °C and T = 45 °C. (For details and complete results see Supporting Information Section I, Part D)

Effect of co-solvents. For the subsequent application of narciclasine as a substrate for the chemoenzymatic acetylation, DMSO (log *P* = -1.3) and dimethylformamide (DMF) (log *P* = -0.829) were evaluated as co-solvents in the model studies, since these solvents are capable of solubilizing narciclasine. Using the two standard MTBE/MeCN conditions, no conversion to any desired product was obtained with DMSO as a co-solvent. However, overall conversions of 31% (**3a** (71%) and **3b** (29%)) and 37% (**3a** (78%) and **3b** (22%)) with MTBE:DMF (4:1) and MeCN:DMF (4:1) respectively were observed.

b) Lipase-catalyzed acetylation of narciclasine.

The reaction conditions for the acetylation of narciclasine were kept similar to the previous study, but with longer reaction time of 72h. After purification, we observed different selectivity than that in the model study regarding the solvents. The reaction in MTBE:DMF was selective in acylating the C-2 position of narciclasine and trace amounts of acylated C-3 and C-4 products were also detected. (Scheme 4) The reaction with MeCN:DMF is less selective towards acetylation of the C-2 position because it was observed the formation of C-3/C-4 monoacetate derivatives of narciclasine. The observed selectivity could be related to the allylic nature of the C-2 position, similar to both allylic alcohols present in the model study with bromodiene diol. No acetylation occurred at the phenolic alcohol at C-7 position, presumably because of the strong H-bond with the neighboring amide.



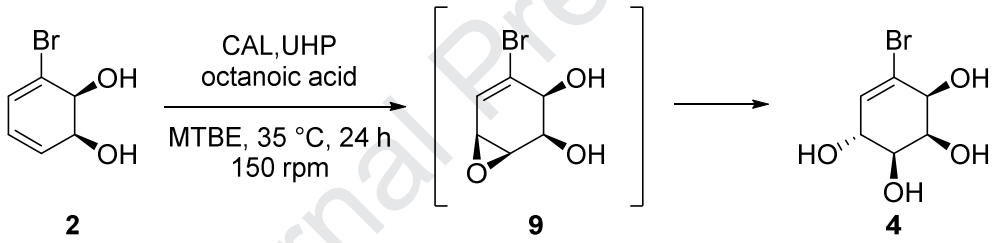
7 **8**

Scheme 4. Chemoenzymatic acetylation of narciclasine. Reaction conditions: **7** (0.16 mmol), vinyl acetate (1.0 - 1.5 mmol), AmanoPS-d (100 mg), MTBE:DMF (4:1) / MeCN:DMF (4:1) (5 mL), 72h, 35 °C, 150 rpm.

c) Epoxidation of bromodienediol 2

Diol **2** was tested as a potential substrate for a chemoenzymatic epoxidation. Chemoenzymatic epoxidations catalyzed by lipases are known to promote the generation of a peracid *in situ* through a cascade reaction, minimizing hazardous risks of handling peracids in stoichiometric ratios.[10] Following a previously reported epoxidation methodology,[11] a few parameters were tested in a similar way to the acetylation study.

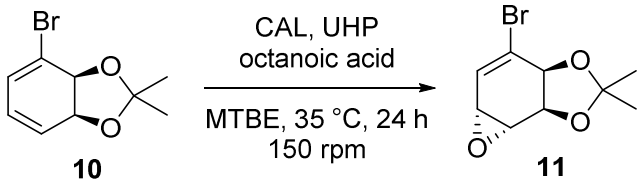
Candida antarctica lipase (CAL) and lipase-B (CALB) were selected for the epoxidations and the initial tests showed that the organic solvent and temperature are key parameters for improving the conversion values. (For details and complete results see Supporting Information Section II, Part A). Surprisingly, the *syn*-epoxide **9** was not observed in the crude product (via ^{1}H-NMR) after full consumption of starting material, and upon purification of the crude product, compound **4** was obtained in 13% yield, the remaining mass balance being unidentified decomposition products. (Scheme 5)



2 **9** **4**

Scheme 5. Formation of tetraol **4** during chemoenzymatic epoxidation of **2**.

Protection of diol **2** yielded acetonide **10**, which was further used as substrate for the chemoenzymatic epoxidation using the previously reported conditions. A 35% conversion was observed for the *anti*-epoxide **11**, formed as a result of the steric hindrance of the acetonide moiety. (Scheme 6) Epoxide **11** is stable and was purified by column chromatography without the opening observed in the *syn*-isomer.

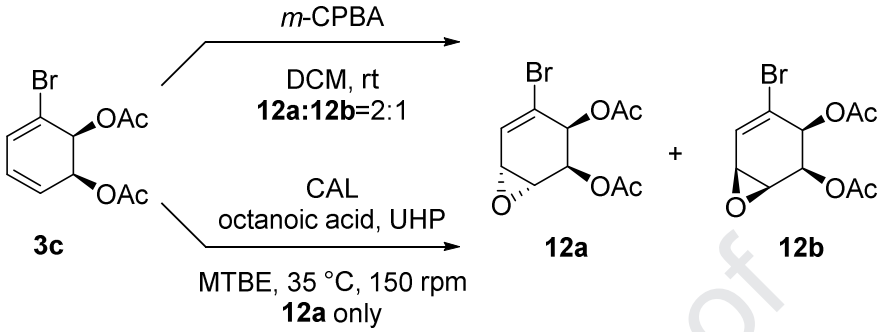


10 **11**

Scheme 6. Chemoenzymatic epoxidation of **10** and formation of *anti*-epoxide **11**

The diacetate **3c** obtained from the chemoenzymatic acetylation of **1** was used in two different approaches to the synthesis of epoxides. By using standard methods with *m*-CPBA, a 2:1 mixture of *anti*- and *syn*-epoxides **12a** and **12b** was obtained, with compound **12b** quickly degrading.

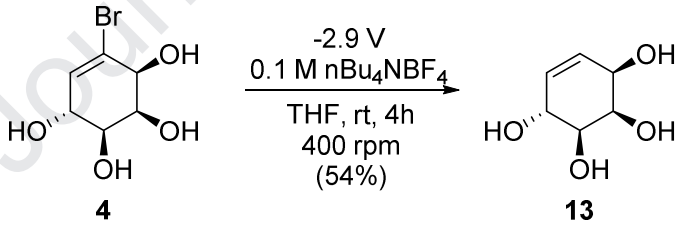
When the chemoenzymatic epoxidation of **3c** was performed, 19% conversion was observed for **12a**, while no conversion was observed for **12b**. The rest of the mass balance was recovered starting material. (Scheme 7). (For details and complete results see Supporting Information Section II, Part A).



Scheme 7. Comparison between chemical and chemoenzymatic epoxidation of **3c**

d) **Electrochemical reduction of 4**.

A methodology for preparative electrochemistry was adapted from a procedure previously published,[12] replacing the mercury pool with a glassy carbon electrode in a "greener" manner and alternating the polarity of the electrodes to reduce the adsorption on the surface of the electrodes. The constant voltage electrolysis of bromo-conduritol C **4** resulted in a 54% yield of (-)-conduritol C **13**. (Scheme 8)



Scheme 8. Preparative electrochemical reduction of **4**.

4. Conclusions

The chemoenzymatic acetylation and epoxidation were performed under mild conditions. The organic medium had the greatest influence on conversions and selectivity. For the acetylation reactions the regioselectivity was initially considered to be influenced only by the lipase, but it was later shown that some migration of the acetyl groups occurred in solution and/or during purification by chromatography. For the epoxidation of the free diol, the release of water in the catalytic cascade reaction performed by the lipase is sufficient to promote opening of the epoxide and formation of the bromo conduritol, but in low yield. The same effect is not observed when the diol moiety is

protected, and the reaction follows the stereochemistry expected from standard chemical epoxidations. The overall yield starting from bromodiene diol is 7%, but there is opportunity to improve the yield of the chemoenzymatic epoxidation, as the standard conditions can be reevaluated and enhanced. Regardless, an old methodology for preparative electrochemistry of conduritol derivatives was adapted for bromo-conduritol C and updated for greener standards. We believe that this route represents a potentially efficient synthesis of a valuable building block. The E-factor for this preparation cannot be contextualized as there are no alternate routes from the same starting material.

5. Experimental section

5.1. General

Analytical thin-layer chromatography was performed using silica gel 60-F_{254} plates. IR spectra were recorded as neat samples. All ^{1}H-NMR spectra were recorded at ambient temperature using Bruker Avance AV 300 (300 MHz) or Bruker Avance AV 600 (600 MHz) spectrometer. All ^{13}C-NMR spectra were recorded at ambient temperature using Bruker Avance AV 300 (75 MHz) or Bruker Avance AV 600 (150 MHz) spectrometer. Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad) coupling constants in Hz, integration. Specific rotation measurements are given in deg.cm^{3}.g^{-1}.dm^{-1}. Mass spectra and high-resolution mass spectra were performed by the analytical division at Brock University. Electrochemical reactions and cyclic voltammetry experiments were carried out in an IKA ElectraSyn 2.0. CV curves were recorded using a three-electrode scheme: The working electrode was a CV glassy carbon electrode and a platinum electrode served as counter electrode. Ag/AgCl was used as the reference electrode with a 3 M NaCl as reference electrolyte. The preparative electrochemistry was performed using a three-electrode scheme: The working electrode was a glassy carbon electrode (d = 3 mm) and a platinum electrode served as counter electrode. Ag/AgCl was used as the reference electrode with a 3 M NaCl as reference electrolyte.

5.2. Chemoenzymatic acetylation

In a typical chemoenzymatic acetylation reaction, a mixture of bromodiene diol **2** (95 mg, 0.5 mmol), vinyl acetate (0.15 mL, 1.5 mmol) and AmanoPS-d (100 mg) in methyl tert-butyl ether (5 mL), or acetonitrile (5 mL) was stirred at 150 rpm, at 35 °C, for 24 h. The crude mixture was filtered to remove the catalyst and concentrated *in vacuo* to afford a mixture of **3a** and **3b** (and **3c** when specified) as a yellow oil.

5.2.1. *(1S,6S)-2-bromo-6-hydroxycyclohexa-2,4-dien-1-yl acetate* **(3a)**

^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 6.51 (dd, *J* = 5.5, 1.1 Hz, 1H), 5.93 – 5.86 (m, 2H), 5.59 (d, *J* = 6.7 Hz, 1H), 4.68 (dt, *J* = 6.7, 2.0 Hz, 1H) , 2.16 (s, 3H).

5.2.2. *(1S,6S)-5-bromo-6-hydroxycyclohexa-2,4-dien-1-yl acetate* **(3b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 6.39 (dd, *J* = 5.2, 0.9 Hz, 1H), 5.94 – 5.80 (m, 2H), 5.48 (ddd, *J* = 6.2, 3.0, 0.9 Hz, 1H), 4.43 (d, *J* = 6.2 Hz, 1H), 2.11 (s, 3H).

5.2.3. *(1S,2S)-3-bromocyclohexa-3,5-diene-1,2-diyl diacetate* **(3c)**

Diene diol **2** (2.0 g, 0.01 mol) was solubilized in dichloromethane (15 mL) and cooled to 0 °C. Triethylamine (4 mL, 0.03 mmol), 4-dimethylaminopyridine (DMAP, cat. amount, 3 crystals) was added to the solution, followed by dropwise addition of acetic anhydride (3 mL, 0.03 mmol). After 1 h, the reaction mixture was quenched with $NaHCO_3$ (15 mL) and extracted with dichloromethane (3x15 mL). The organic phases were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on deactivated silica gel (10%) (hexanes:EtOAc (6:1)) to yield diacetate **3c** as a yellow oil (1.8 g, 65 %).

3c: $[\alpha]_D^{21}$=-71.78 (c 1.0, MeCN); **^{1}H NMR** (300 MHz, $CDCl_3$) δ_{ppm} 6.55 (dd, *J* = 5.7, 0.6 Hz, 1H), 5.97 (ddd, *J* = 9.5, 5.8, 1.6 Hz, 1H), 5.84 (ddt, *J* = 9.6, 2.4, 0.7 Hz, 1H), 5.73 – 5.70 (m, 2H), 2.11 (s, 3H), 2.06 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_{ppm} 170.21, 170.12, 129.56, 125.63, 124.98, 120.32, 70.03, 69.04, 20.89, 20.80; IR ν_{max}: 1739, 1369, 1208, 1068, 1015, 734, 596.

5.3. TBS-protection

5.3.1. *(1S,6S)-2-bromo-6-((tert-butyldimethylsilyl)oxy)cyclohexa-2,4-dien-1-ol* **(5)**[13]

Imidazole (200 mg, 2.9 mmol) and TBSCl (450 mg, 3.0 mmol) were added to a magnetically stirred cold (0 °C) solution of diol **2** (500 mg, 2.6 mmol) in DMF (10 mL) maintained under an atmosphere of nitrogen. After 16 h the reaction mixture was diluted with Et_2O (20 mL) and washed with brine (3x15 mL). The combined organic extracts were then dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a pale-yellow oil. The crude product was purified by flash column chromatography on deactivated silica gel (10%) (hexane:EtOAc (6:1 → 4:1)) to yield **5** (363 mg, 45%).

5: $[\alpha]_D^{21}$=44.60 (c 0.5, MeCN); **^{1}H NMR** (300 MHz, $CDCl_3$) δ_{ppm} 6.37 (dd, *J* = 4.1, 2.5 Hz, 1H), 5.78 (d, *J* = 3.7 Hz, 2H), 4.57 (d, *J* = 6.3 Hz, 1H), 4.14 (dd, *J* = 6.2, 4.6 Hz, 1H), 2.77 (d, *J* = 4.7 Hz, 1H), 0.92 (s, 9H), 0.13 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_{ppm} 129.65, 127.10, 125.64, 123.57, 77.16, 72.80, 70.75, 26.04, 25.90, 18.30, -4.40, -4.71; **IR** ν_{max}: 3548, 2952, 2856, 1571, 1470, 1389, 1253, 1059, 834, 776, 676, 647 cm^{-1}; **HRMS** (EI) Calcd for $C_{12}H_{21}BrO_2Si(M^+)$: 304.0494, found 304.0492; **LRMS** (ESI) found 322 $[M+NH_4]^+$, 327 $[M+Na]^+$, 342.9 $[M+K]^+$.

5.3.2. *(1S,6S)-2-bromo-6-((tert-butyldimethylsilyl)oxy)cyclohexa-2,4-dien-1-yl acetate* **(6)**

A similar procedure was repeated using a crude mixture of **2, 3a** and **3b** (285 mg) from a chemoenzymatic acetylation solubilized in DMF (10 mL). The solution was cooled to 0 °C and imidazole (200 mg, 2.9 mmol) and TBSCl (400 mg, 2.6 mmol) were added. After 16 h the reaction mixture was diluted with Et_2O (20 mL) and washed with brine (3x15 mL). The combined organic extracts were then dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a pale-yellow oil. The crude product was purified by flash column chromatography on deactivated silica gel (10%) (hexane:EtOAc (10:1 → 4:1)) to yield **6** (125 mg).

6: $[\alpha]_D^{21}$=-78.16 (c 1.0, MeCN); **^{1}H NMR** (300 MHz, $CDCl_3$) δ_{ppm} 6.49 (dd, *J* = 4.1, 2.5 Hz, 1H), 5.82 (d, *J* = 3.3 Hz, 2H), 5.56 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 2.10 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_{ppm} 170.17, 131.78, 129.89, 122.46, 120.31, 72.17, 70.01, 25.84, 20.96, 18.29, -4.88, -5.02; **IR** ν_{max}: 2927, 2855, 1736, 1740, 1222, 1119, 1097, 827, 784, 667 cm^{-1}; **HRMS** (EI) Calcd for $C_{14}H_{23}BrO_3Si(M^+)$: 346.0600, found 346.0594; **LRMS** (ESI) found 364 $[M+NH_4]^+$, 369 $[M+Na]^+$, 385 $[M+K]^+$

5.4. (2S,3S,4S,4aR)-3,4,7-trihydroxy-6-oxo-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-2-yl acetate **(8)** [14]

Two reaction mixtures were prepared with **7** (50 mg, 0.16 mmol) each, the first with 0.10 mL (1.0 mmol) of vinyl acetate and 5 mL of MTBE:DMF (4:1) and the second with 0.15 mL of vinyl acetate and 5 mL of MeCN:DMF (4:1). Both had 100 mg of lipase as the biocatalyst. Both reactions were stirred at 150 rpm, at 35 °C, for 72 h. The reaction mixtures were combined and concentrated by rotary evaporation and its crude product was purified by flash column chromatography on deactivated silica gel (10%) (DCM:MeOH (50:1 → 30:1)) to obtain the title compound **8** (20 mg, 17%) as a pale-yellow solid.

8: Rf = 0.21 (DCM:MeOH 10:1); **^{1}H NMR** (300 MHz, DMSO-d_6) δ_{ppm} 13.17 (s, 1H), 8.01 (s, 1H), 6.86 (s, 1H), 6.10 (dd, J = 4.2, 2.5 Hz, 1H), 6.06 (d, *J* = 1.2 Hz, 2H), 5.48 (d, *J* = 4.1 Hz, 1H), 5.33 (d, *J* = 5.4 Hz, 1H), 5.17 (ddd, *J* = 4.4, 2.9, 1.3 Hz, 1H), 4.22 (d, *J* = 8.2 Hz, 1H), 3.78 – 3.65 (m, 2H), 2.00 (s, 3H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ_{ppm} 169.68, 168.92, 152.43, 144.88, 133.97, 133.32, 131.25, 119.32, 105.78, 102.27, 96.19, 71.00, 69.25, 69.14, 52.76, 20.83. The spectral data were matched and are in agreement with the literature data.[14]

5.5. Epoxidation

In a typical chemoenzymatic epoxidation reaction, a mixture of substrate (**2**, **3c** or **10** (0.5 mmol)), urea-hydrogen peroxide (UHP) (94 mg, 1.0 mmol), octanoic acid (80 µL, 0.5 mmol) and *Candida antarctica lipase* (CAL) (10 mg) in methyl tert-butyl ether (5 mL) was stirred at 150 rpm, at 35 °C, for 24 h. The crude mixture was filtered for removal of the catalyst and concentrated *in vacuo* and further analyzed by ^{1}H-NMR.

5.5.1. (1R,2S,3S,4S)-5-bromocyclohex-5-ene-1,2,3,4-tetraol **(4)**[15]

The crude mixture of 6 batches was combined and filtered for removal of the catalyst, and the flasks were washed with MeOH to remove product residues and combined with the MTBE filtrate and concentrated *in vacuo*. The obtained white crude product was adsorbed in 24% deactivated silica gel and purified by flash column chromatography (EtOAc:Hex:MeOH 8:1:1) to yield tetrol as a white solid **4** (88 mg, 13%).

4: $[\alpha]_D^{22}$=-64.53 (c 0.5, MeOH); lit.[15] $[\alpha]_D^{20}$=-50 (c 0.01, MeOH); **^{1}H NMR** (600 MHz, MeOD) δ 6.09 – 6.06 (m, 1H), 4.24 (dt, *J* = 6.5, 2.4 Hz, 1H), 4.20 – 4.17 (m, 1H), 4.06 (dd, *J* = 3.7, 2.0 Hz, 1H), 3.61 (dd, *J* = 6.8, 1.9 Hz, 1H).; **^{13}C NMR** (151 MHz, MeOD) δ 133.04, 127.66, 75.47, 73.10, 72.84, 71.53.; **LRMS** (ESI+/-) Calcd for $C_6H_9BrO_4[M]^+$: 223.9684, found 242 $[M+NH_4]^+$, 246.9 $[M+Na]^+$, 262.9 $[M+K]^+$. The spectral data were matched and are in agreement with the literature data.[15]

5.5.2. *(3aS,7aS)-4-bromo-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole* **(10)**[16]

Diol **1** (2 g, 0.01 mol) was suspended in DCM (10 mL), and 2,2-DMP (5 mL, 0.04 mol) was added followed by the addition of a catalytic amount of *p*-TSA. The reaction mixture was left stirring for 4 h at room temperature and the consumption of starting material was checked with TLC (hexane:EtOAc (4:1)). The reaction was quenched with $NaHCO_3$ and extracted with DCM. The combined organic phases were dried with $MgSO_4$ and concentrated on the rotary evaporator. The residue was adsorbed on deactivated silica gel (10%), and purified by column chromatography (hexane:EtOAc (8:1)) to afford **10** as a colorless oil (1.43 g, 59%). This compound quickly dimerizes and must be used immediately. Otherwise, it is necessary to keep it stored in solution in the freezer (-13 °C).

10: $[\alpha]_D^{21}$= 77.08 (c 1.5, MeCN); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.34 (d, *J* = 6.1 Hz, 1H), 5.97 (d, *J* = 9.5 Hz, 1H), 5.87 (dd, *J* = 9.6, 6.0 Hz, 1H), 4.72 (d, *J* = 1.7 Hz, 2H), 1.44 (s, 2H), 1.43 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 125.90, 124.77, 124.53, 124.22, 106.34, 76.01, 72.60, 26.84, 25.08. The spectral data were matched and are in agreement with the literature data.[16]

5.5.3. *(3aS,5aR,6aR,6bS)-4-bromo-2,2-dimethyl-3a,5a,6a,6b tetrahydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxole* **(11)**[17]

75 mg (0.43 mmol) of recrystallized *m*-CPBA was added to a cold solution of **10** (100 mg, 0.43 mmol) in DCM (5 mL) and left stirring overnight. TLC showed the presence of starting material, so another 35 mg of *m*-CPBA was added to the cold reaction mixture. After 3 h, the reaction was quenched with $NaHCO_3$, extracted with DCM and the combined organic phases were dried with $MgSO_4$ and concentrated. The residue was purified by flash column chromatography with deactivated silica gel (10%) (hexane:EtOAc (8:1)) to yield **11** as a colorless oil (80 mg, 75%).

11: $[\alpha]_D^{21}$= 95.6 (c 0.7, MeCN); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 4.4, 1.1 Hz, 1H), 4.86 (ddd, *J* = 6.8, 1.8, 1.1 Hz, 1H), 4.41 (dd, *J* = 6.8, 0.9 Hz, 1H), 3.58 (dd, *J* = 3.7, 1.9 Hz, 1H), 3.34 – 3.30 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 130.01, 126.61, 111.54, 74.24, 72.74, 49.59, 48.42, 27.63, 26.12. The spectral data were matched and are in agreement with the literature data.[17]

5.5.4. *(1R,2S,3S,6R)-4-bromo-7-oxabicyclo[4.1.0]hept-4-ene-2,3-diyl diacetate* **(12a)**

80 mg (0.46 mmol) of recrystallized *m*-CPBA was added to a cold solution of diacetate **3c** (114 mg, 0.46 mmol) in DCM (5 mL) and left stirring overnight. The reaction was quenched with $NaHCO_3$, extracted with DCM and the combined organic phases were dried with $MgSO_4$ and concentrated. The residue was purified by flash column chromatography with deactivated silica gel (10%) (hexane:EtOAc (8:1)) to yield **12a** as an opaque oil (28 mg, 21%) and **12b** as a yellow solid (14 mg, 10%). Compound **12b** is unstable and quickly decomposes even when kept in the freezer (-15 °C).

12a: $[\alpha]_D^{21}$= 112.8 (c 0.6, MeCN); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 4.3, 2.5 Hz, 1H), 5.79 (ddd, *J* = 4.9, 3.0, 0.5 Hz, 1H), 5.49 (dd, *J* = 4.9, 2.5 Hz, 1H), 3.48 (t, *J* = 3.5 Hz, 1H), 3.37 (t, *J* = 3.8 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.14, 169.31, 127.34, 125.82, 66.86, 66.27, 50.87, 48.33, 20.83, 20.64; **IR** ν_{max}: 1742, 1371, 1210, 1069, 1047, 896, 597, 552, 471 cm^{-1}.

5.5.5. *(1S,2S,3S,6S)-4-bromo-7-oxabicyclo[4.1.0]hept-4-ene-2,3-diyl diacetate* **(12b)**

12b: $[\alpha]_D^{21}$=-230.4 (c 0.6, MeCN); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.65 (d, *J* = 4.4 Hz, 1H), 5.82 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.42 (dd, *J* = 5.5, 1.2 Hz, 1H), 3.59 – 3.54 (m, 1H), 3.46 (t, *J* = 4.4 Hz, 1H), 2.15 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.75, 169.97, 131.45, 123.59, 70.30, 68.90, 53.34, 48.20, 20.88, 20.71. **IR** ν_{max}: 1743, 1368, 1229, 1206, 1051, 897, 728, 552, 603 cm^{-1}.

5.6. Preparative electrochemistry

5.6.1. (1R,2R,3S,4R)-cyclohex-5-ene-1,2,3,4-tetrol **(13) [(-)-conduritol C]**[15,18]

A 0.1 M solution of the charge carrier nBu$_4$NBF$_4$ (TBATFB) in 10mL of THF was added to the IKA ElectraSyn vial. The solution was purged with an argon stream for 10min. Compound **4** (40 mg, 0.17 mmol) was added in the vial and the vial was closed with the three-electrode scheme. The CV was done to obtain the reduction potential (-2.9 V) and the CV electrode was changed to the glassy carbon electrode. The mixture was electrolyzed with constant voltage for 4 h with the polarity being alternated every 5 min. Upon completion of the reaction, the solvent was evaporated, and the resulting green solid was adsorbed in 10% deactivated silica gel and purified by flash column chromatography (EtOAc to remove most of the charge carrier and EtOAc:MeOH 8:1) to yield (-)-conduritol C **13** (14 mg, 54%) as a white solid.

13: $[\alpha]_D^{21}$=-141.13 (c 0.2, MeOH)*; lit.[15] $[\alpha]_D^{20}$=-205 (c 0.2, MeOH); **^{1}H NMR** (300 MHz, MeOD) δ 5.65 (dt, *J* = 10.3, 2.0 Hz, 1H), 5.56 (ddd, *J* = 10.2, 3.5, 1.8 Hz, 1H), 4.27 (dd, *J* = 4.5, 2.3 Hz, 1H), 4.26 – 4.20 (m, 1H), 4.02 (dt, *J* = 3.5, 1.8 Hz, 1H), 3.53 (dd, *J* = 7.4, 2.0 Hz, 1H); **^{13}C NMR** (75 MHz, MeOD) δ 130.84, 130.11, 76.20, 74.05, 70.65, 69.57. *Small amounts of charge carrier still present in the sample. The spectral data were matched and are in agreement with the literature data.[18]

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Highlights:

- arene *cis*-dihydrodiols obtained from whole-cell fermentation were submitted to lipase-catalyzed acetylations;
- The acetylation model was applied to the cytotoxic natural product narciclasine;
- (-)-conduritol C was obtained *via* a chemoenzymatic epoxidation cascade followed by electrochemical reduction.

Declaration of Interest Statement

The authors declare no conflict of interest.