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Chemoenzymatic synthesis of conduritol analogues

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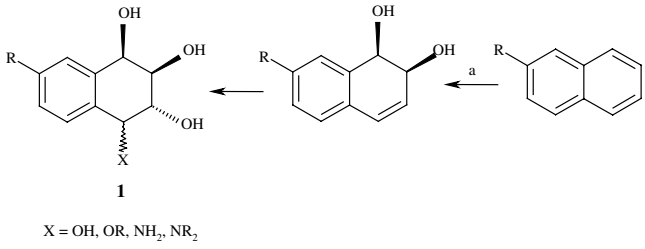
Abstract—Several conduritol and conduramine analogues have been synthesized from β-substituted naphthalenes via a chemoenzymatic approach, in a high regio- and stereocontrolled way.

1. Introduction

Cyclohex-5-ene-1,2,3,4-tetrols are an important class of cyclitols named conduritols. Ten different stereoisomers exist of which six are diastereoisomers (conduritols A–F) indicated by alphabetical letters in order of their discovery.[1] Only conduritol A and (+) conduritol F have been found in nature, albeit in small amounts. All 10 stereoisomers of conduritols have been prepared by multi-steps chemical syntheses in nonracemic form.[1,2] Several chemoenzymatic syntheses have also been performed, based on the ability of some microbial dioxygenases to convert aromatic compounds to *vic*-diols in a high stereospecific manner.[3] Some conduritol derivatives have shown antibiotic, antileukemic and growth regulating activity.[1] In view of their promising therapeutic potential in the management of disorders like diabetes, viral infections (including HIV) and cancer, many analogues and structural variants of conduritols have been synthesized, including nonnatural bicyclic and tricyclic mimics[4–6] and their biological activities evaluated, in particular glycosidase inhibition which plays a fundamental role in the development of new drugs. The promising results stimulated the study of other bicyclic compounds of general formula **1**,[7] where the double bond of conduritols is formally replaced by an aromatic ring, which may confer valuable properties to the molecule and enhance its lipophilicity, that can be further modulated by properly located substituents. Furthermore, a substituent on the aromatic ring could be used to introduce additional functionalities properly devised and tailored to fit specific biological targets. In retrosynthetic analysis compounds of general formula **1** can be prepared from 7-substituted (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalenes (*cis*-diols) that we previously obtained by bioconversion of the corresponding naphthalenes using the naphthalene dioxygenase from *Pseudomonas fluorescens N3* expressed in *E. coli* JM109 (Scheme 1).[8]



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X = OH, OR, NH_2, NR_2

Scheme 1. (a) *E. coli* JM109 (pVL1343A + pMS13).

2. Result and discussion

We already reported the conversion of 1,2-dihydroxy-1,2-dihydronaphthalene **2a** to the 3,4-epoxide **4a** in two steps (80% total yield).[9a] The *cis*-diol **2a** was first converted to isopropylidene derivative **3a** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid and then the double bond was oxidized in a high stereospecific manner at 0 °C with *m*-chloroperbenzoic acid in methylene chloride. The ketalization and epoxidation steps were therefore applied to the 7-substituted *cis*-diols **2b–f**, obtained as single stereoisomers by bioconversion of the corresponding β-substituted naphthalenes.

Keywords: 1,2-Dihydroxy-1,2-dihydronaphthalenes; Diastereoselective synthesis; 1,2,3,4-Tetrahydro-1,2,3,4-tetrahydroxynaphthalenes; 1,2,3-Trihydroxy-4-aminonaphthalenes.
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Whereas the isopropylidene derivatives **3a**–**f** were always obtained in quantitative yields, the expected 3,4-epoxides were obtained with variable yields, depending on the substituent R: generally in good yields (70–80%), albeit lower with respect to the unsubstituted ketal **3a**, but with some exceptions. Ketals **3e**,**f**, having in position 7 an electron-donating substituent (MeO- or Et-), able to stabilize by resonance an incipient carbocation in position 4, afforded derivatives **8e**,**f**. The reported relative *cis*-stereochemistry of the substituents in position 3 and 4 is relative to the main product (85/15 *cis*/*trans* for **8e** and 78/22 *cis*/*trans* for **8f**) and is consistent with the ^{1}H NMR coupling constant ($J_{3,4}$ = 2.8 Hz observed for *cis* product and 7.6 Hz observed for the minor *trans* product).

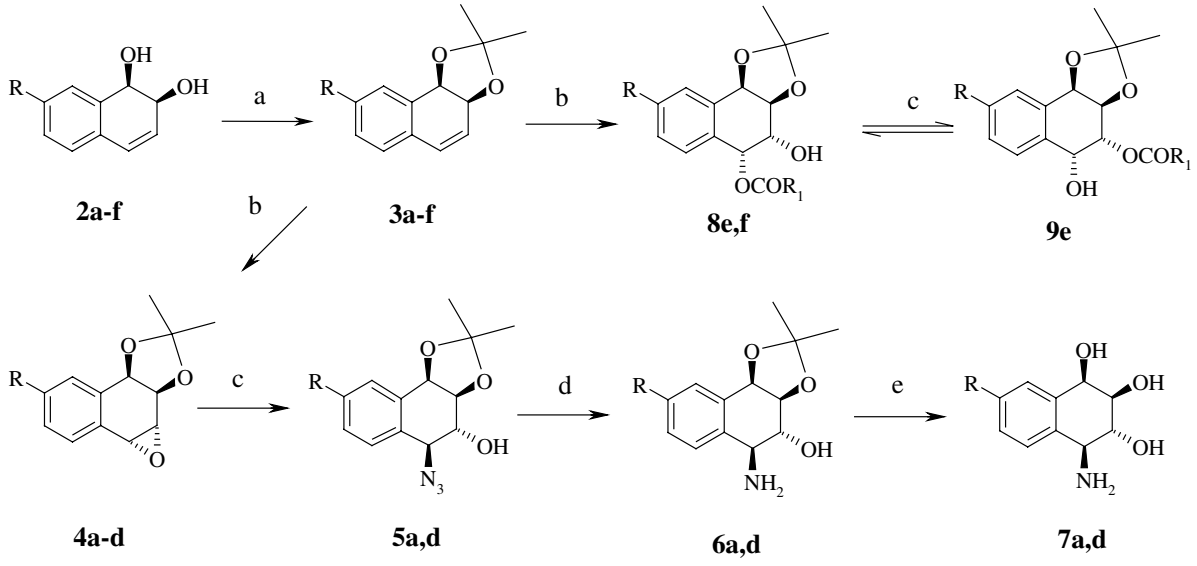
Epoxides **4a**–**d** are useful intermediates for the synthesis of conduritols and conduramine analogues.

Stereospecific ring opening of the 3,4-epoxides **4a**,**c** and **d** at the benzylic position was achieved with sodium azide in dimethylformamide at 110 °C and afforded the corresponding azides **5a** (86%), **5c** (85%) and **5d** (50%) (only one diastereoisomer was obtained in these cases). The nitro epoxide **4b** afforded a mixture of unidentified products (Scheme 2). Catalytic reduction of the azides **5a**,**d** in methanol in the presence of palladium on carbon afforded the amines **6a**,**d** (90–95%) which were deprotected in excellent yields (85–90%) to the corresponding 1,2,3-trihydroxy-4-amino-derivatives **7a**,**d** upon treatment with either hydrochloric acid in methanol or trifluoroacetic acid in tetrahydrofuran–water (4:1). The same protocol (sodium azide in dimethylformamide) applied to the *m*-chlorobenzoate **8e** afforded the derivative **9e** (55 % with 35% recovery of starting **8e**), reasonably coming from an intramolecular transesterification involving the free hydroxyl function in position 3.

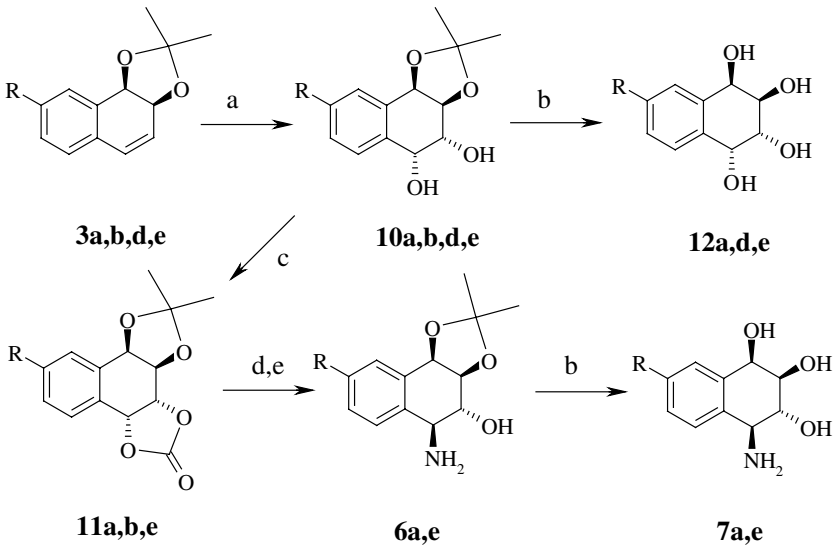
The difficulties encountered in the synthesis of the azides **5b**,**e**,**f** prompted us to devise a different and alternative synthetic strategy, by opening of a carbonate **11** with sodium azide (Scheme 3). The carbonate was obtained from the protected *cis*-diols **3** via di-hydroxylation with β-AD-mix,[10] followed by reaction with triphosgene.

This new protocol was first tested on **3a** and then extended to **3d** and **3e**. The reaction with AD-mix afforded the *cis*-diols **10a**,**b**,**d**,**e** in good yields (70–90%). As observed in the epoxidation step, also in this case oxidation of the 3,4-double bond proceeded in a high stereospecific way on the side of the molecule opposite to the sterically demanding 1,2-ketalic function. Upon treatment with triphosgene (solid and more convenient to use with respect to the toxic phosgene) in methylene chloride at 0 °C in the presence of pyridine, diols **10a**,**b**,**e** afforded, in almost quantitative yields, the corresponding carbonates **11a**,**b**,**e** (Scheme 3). With the exception of the nitro-derivative **11b** (which once again afforded a mixture of unidentified products), they were subsequently converted to the corresponding azides with better yields (80–85%) with respect to those observed via epoxides. The hydrolysis of diols **10a**,**d**,**e** by hydrochloric acid in methanol or by trifluoroacetic acid in THF–water gave tetrols **12a**,**d**,**e**.

Synthetic work is now in progress in order to: (a) extend the synthetic sequences reported above to regioisomeric 8- and 5-substituted (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene diols obtained by bioconversion of α-substituted naphthalenes;[9] (b) obtain a different relative stereochemistry of the stereo centers in the molecule and (c) test their influence on biological activity. To satisfy the point (b), the epoxidation reaction has been directly tested on 1,2-dihydroxy-1,2-dihydronaphthalenes obtained by bioconversion, without any protection of the *cis*-diol function. Diol **2a**, chosen as model compound to optimize the reaction protocol, has been treated with *m*-chloroperbenzoic acid in methylene chloride in the presence of sodium monohydrogenphosphate[11] and afforded the epoxide with the diol and epoxy functions on the same side in quantitative yield. The presence



Scheme 2. Reagents and conditions: R = (**a**) H, (**b**) NO_2, (**c**) Br, (**d**) $COOCH_3$, (**e**) OCH_3, (**f**) CH_2CH_3; R_1 = *m*-Cl–C_6H_5 (a) DME, PTS, CH_2Cl_2, rt; (b) *m*-chloroperbenzoic acid, 0 °C; (c) NaN_3, DMF, 110 °C; (d) H_2, Pd/C, MeOH, rt; (e) HCl, MeOH, 0 °C.



Scheme 3. Reagents and conditions **3** (a): β-AD-mix, *tert*-BuOH, H_2O, 0 °C; (b) HCl, MeOH, 0 °C; (c) triphosgene, pyridine, CH_2Cl_2, 0 °C; (d) NaN_3, DMF, 110 °C; (e) H_2, Pd/C, MeOH, rt.

of the free diol function oriented the epoxidation providing an entry to inverted stereochemistry at positions 3 and 4.

3. Conclusions

We have devised synthetic chemoenzymatic strategies to obtain bicyclic conduritols and conduramine analogues, namely 7-substituted 1,2,3,4-tetrahydroxy-1,2,3,4-tetrahydronaphthalenes (R = H, OCH_3, $COOCH_3$) and 7-substituted 1,2,3-trihydroxy-4-amino-1,2,3,4-tetrahydronaphthalenes (R = H, OCH_3, $COOCH_3$) with different relative configurations.

Work is also in progress to verify if some of the synthesized compounds possess biological activities, screening them against commercial glycosidases that accept *p*-nitrophenyl glycosides as substrates.

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References and notes

1. (a) Balci, M. *Pure Appl. Chem.* **1997**, *69*, 97–104; (b) Gultekin, M. S.; Celik, M.; Balci, M. *Curr. Org. Chem.* **2004**, *8*, 1159–1186.
2. (a) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*(7), 795–826; (b) Balci, M.; Sutbeyas, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715–3742; (c) Jorgensen, M.; Iversen, E. H.; Paulsen, A. L.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4630–4634; (d) Arcelli, A.; Cere', V.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2001**, *57*, 3439–3444; (e) Metha, G.; Ramesh, S. *Chem. Commun.* **2000**, 2429–2430; (f) Angelaud, R.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, *64*, 9613–9624; (g) McDonouhh, N.; Stick, R. V.; Tilbrook, D. M. *Aust. J. Chem.* **1999**, *52*, 143–147; (h) Desjardins, M.; Lallemand, M. C.; Freeman, S.; Hudlicky, T.; Abboud, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 621–628; (i) Leung-Toung, R.; Liu, Y.; Muchowski, J.; Wu, Y. L. *J. Org. Chem.* **1998**, *63*, 3235–3250.
3. (a) Sanfilippo, C.; Patti, A.; Piattelli, M.; Nicolosi, G. *Tetrahedron: Asymmetry* **1997**, *8*(10), 1569–1573; (b) Carless, H. A. J.; Busia, K.; Dove, Y.; Malik, S. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, (21), 2505–2506; (c) Carless, H. A. J. *Tetrahedron Lett.* **1992**, *33*(42), 6379–6382; (d) Carless, H. A. J. *J. Chem. Soc., Chem. Commun.* **1992**, (3), 234–235; (e) Carless, H. A. J.; Oak, O. Z. *J. Chem. Soc., Chem. Commun.* **1991**, (2), 61–62; (f) Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907–2917; (g) Hudlicky, T.; Price, J. D.; Olivo, H. F. *Synlett* **1991**, 645–646; (h) Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D. *Isr. J. Chem.* **1991**, *31*, 229–238; (i) Ley, S. V.; Redgrave, A. J. *Synlett* **1990**, (7), 393–394; (j) Carless, H. A. J.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*(13), 1719–1720.
4. Kara, Y.; Balci, M.; Bourne, A. S.; Watson, N. H. *Tetrahedron Lett.* **1994**, *35*, 3349–3352.
5. Mehta, G.; Ramesh, S. S. *Chem. Commun.* **2000**, 2429–2430.
6. Billington, D. C.; Peoour Sierra, F.; Picard, I.; Beaubras, S.; Duhualt, J.; Espinal, J.; Challal, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2307–2312.
7. Some of them (R = H, X = OH, F, OMe, N_3) have been already synthesized and have given interesting results: Ref. 2h.
8. Di Gennaro, P.; Galli, E.; Albini, G.; Pelizzoni, F.; Sello, G.; Bestetti, G. *Res. Microbiol.* **1997**, *38*, 6267.
9. (a) Orsini, F.; Pelizzoni, F. *Tetrahedron: Asymmetry* **1996**, *7*, 1033–1040; (b) Orsini, F.; Rinaldi, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1039–1048; (c) Orsini, F.; Sello, G.; Bestetti, G. *Tetrahedron: Asymmetry* **2001**, *12*, 2961–2969; (d) Orsini, F.; Sello, G.; Travaini, E.; Di Gennaro, P. *Tetrahedron: Asymmetry* **2002**, *13*, 253–259.
10. Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
11. Ganey, M. V.; Padykula, R. E.; Berchtold, G. A. *J. Org. Chem.* **1989**, *54*, 2787–2793.