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# Microwave-mediated intramolecular Diels–Alder cyclization of biodihydroxylated benzoic acid derivatives

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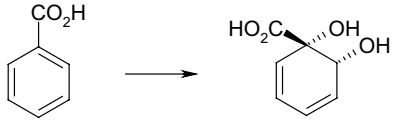
**Abstract**—The synthetic utility of biodihydroxylated benzoic acid derivatives for the construction of bridge bicyclo scaffolds was investigated. Biodihydroxylation of benzoic acid using *Ralstonia eutropha* B9 gave (*1S*,*2R*)-1,2-dihydroxycyclohexa-3,5-diene-1-carboxylic acid (DCD) in high optical purity (>95% ee). Protection of the intermediate and subsequent functional group transformation gave the required cyclization precursors in moderate to excellent overall yields. Subsequent intramolecular Diels–Alder cyclization of biodihydroxylated benzoic acid derivatives was carried out using either thermal or microwave conditions. Enantiomerically pure products with five chiral centers were obtained in 4–6 steps from achiral starting material.


Microbial *cis*-2,3-dihydroxylation of benzene rings functionalized by lipophilic groups has been established as a powerful methodology to access valuable chiral synthetic intermediates over the last years.[1,2] These intermediates have been used for the synthesis of a wide variety of complex target structures.[3–5] In contrast, biodihydroxylation of aryl carboxylates is a much less developed field in synthetic chemistry. In 1971, Reiner and Hegeman first reported the 1,2-biodihydroxylation of benzoic acid using a mutant strain of *Ralstonia eutropha* (strain B9, formerly assigned as *Alcaligenes eutrophus*). (*1S*,*2R*)-1,2-Dihydroxycyclohexa-3,5-diene-1-carboxylic acid **1** (DCD) was secreted into the aqueous media, due to the absence of an enzyme that normally produces catechol in the metabolic pathway of benzoic acid (Scheme 1).[6]




**1**

**Scheme 1.** Biodihydroxylation of benzoic acid.

Subsequent studies by different groups, particularly the groups of Reiner and Knackmuss led to the exploration of a couple of mutant strains, which were able to degrade various kinds of substituted aryl carboxylates.[2,7–9] However, applications in organic synthesis were not reported until 1995, when Widdowson et al. determined the stereochemistry of the *cis*-diol product as (*1S*,*2R*)-DCD. In addition, the group of Widdowson used derivatives of DCD as substrates for intermolecular and hetero Diels–Alder reactions.[10] In 2001, Myers reported the microbial dihydroxylation of benzoic acid in 270 g scale. A large array of highly functionalized synthons was obtained by selective and enantioselective oxidation of DCD.[11] Myers efforts were mainly focused on the potential utilization of the obtained products in synthetic strategies en route to tetracycline.

Based on the previous work of Widdowson, who established the intermolecular Diels–Alder reaction of the metabolized benzoic acid, we report our studies towards highly functionalized bicyclic bridged compounds via intramolecular Diels–Alder cyclizations starting from benzoic acid.

Whole cell biotransformation of benzoic acid using the microbial strain *Ralstonia eutropha* B9 in Hutner's Mineral Base as media and potassium succinate as only

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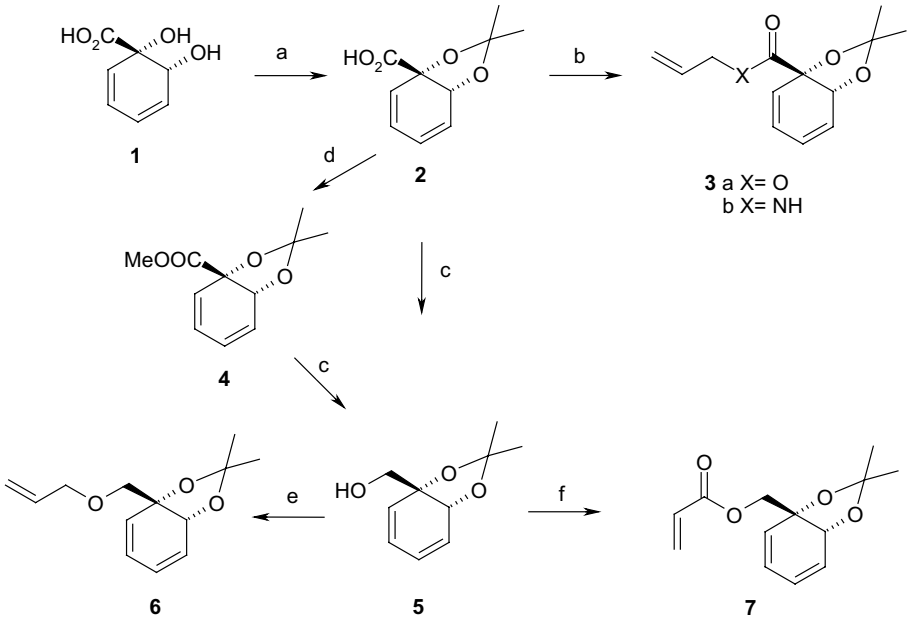
carbon source has been reported previously.[11] Biotransformation has been carried out in a New Brunswick® Benchtop Fermentor with a maximum culture volume of 1.8L. Trituration of the obtained pale yellow solid with dichloromethane gave compound **1** in 4 g per liter culture media in 73% yield. Optical rotation of product **1** agreed with previously reported data (ee >95%).[10,11]

Protection of the 1,2-*cis*-dihydroxylation product was performed according to the literature giving compound **2**[10] as key precursor for the synthesis of various cyclization candidates. Esterification with allylic alcohol and amidation with allylamine, respectively, using 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDC) as activating reagent[12] of the carboxylic acid functionality gave compounds **3a** and **3b** in excellent yields after purification by flash column chromatography (Scheme 2). To access activated dienophiles and more flexible tethers without carbonyl centers, alcohol **5** was prepared. Reduction of the free acid **2** with lithium aluminum hydride yielded 70% of the desired alcohol besides rearomatization product. To circumvent this problem, the reduction of the acetonide protected methyl ester **4**, derived from esterification of compound **2** with methanol, was performed according to a modified procedure of Widdowson.[10] Optimization of the reaction protocol by decreasing the reaction temperature and increasing the reaction time gave a significantly improved yield of 95%. Allylation of alcohol **5** was initially hampered by predominant rearomatization upon etherification conditions. This side reaction could be circumvented by using *tetra*-butyl ammonium iodide ($Bu_4N^+I^-$) as catalyst giving compound **6** in excellent yield. The formation of the 'reversed' ester **7** was established by reacting alcohol **5** with either acryloyl chloride or by using acrylic acid with EDC to form the desired product **7** in 47% and 48% yield, respectively.

With this straightforward strategy, we were able to obtain three different types of precursors with various characteristics for the activation of the dienophile system: activated and nonactivated ester/amide derivatives and a more flexible ether tether without any carbonyl centers. The intramolecular Diels–Alder cyclization represented the key step in the synthesis of the novel scaffolds. Classical thermal reaction conditions (toluene at reflux), were compared with cyclization conditions under microwave irradiation (CEM Discover cavity unit, toluene 135–210 °C). It is noteworthy that all stereocenters of the central six-membered rings of the functionalized cyclohexadiene derivatives could be controlled in a single step.

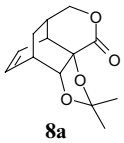
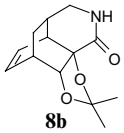
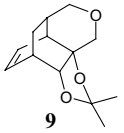
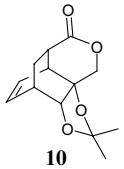
Results for the cyclization experiments are summarized in Table 1.

Cyclization of ester **3a** gave no desired product either under thermal conditions or under microwave irradiation. In both cases, two dimerized compounds could be isolated in a ratio of approximately three to one after flash column chromatography as a result of an intermolecular Diels–Alder reaction. The structural elucidation of these compounds is currently carried out in our laboratory. While amide **3b** was not converted under classical thermal conditions, the desired product **8b**[13] was isolated in 56% yield (based on consumed starting material, 50% conversion), when the reaction was carried out under microwave irradiation (Scheme 3). For both amide and ester precursor formation of dimeric by-products was observed under microwave conditions. The intramolecular Diels–Alder cyclization of allyl ether **6** was straightforward and the bicyclic compound **9**[14] was formed as only reaction product under thermal and microwave conditions. It has to be emphasized that the reaction using microwave is 20 times faster than the

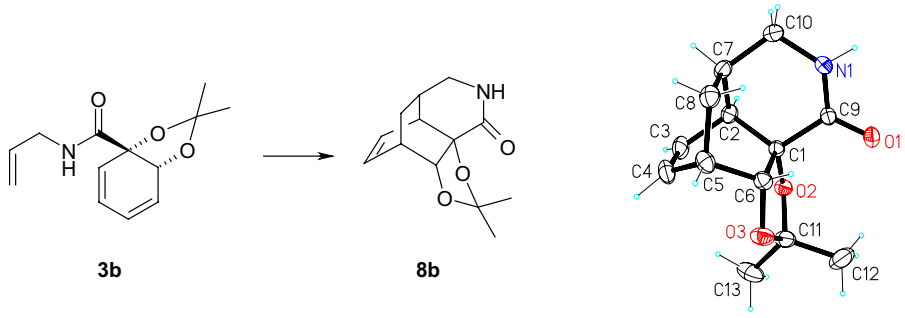



**Scheme 2.** Reagents and conditions: (a) acetone, 2,2-dimethoxypropane, p-TSA, 94%; (b) **3a**: EDC, 2-DMAP, prop-2-en-1-ol, DCM, 87%; **3b**: EDC, Bt-OH, triethylamine, allylamine; DCM, 83%; (c) LAH, $Et_2O$, 0 °C, 20 min, **2** → **5**: 70%, **4** → **5**: 95%; (d) EDC, DMAP, methanol, DCM, 92%; (e) NaH, allylbromide, $Bu_4N^+I^-$, 92%; (f) acryloyl chloride, triethylamine, $Et_2O$, 47%; or acrylic acid, EDC, DMAP, DCM, 48%.

**Table 1.** Results of the intramolecular Diels–Alder reactions

| Products | Reaction conditions | Yield | Dimers |
|---|---|---|---|
|  **8a** | Toluene reflux 7 days | 0% | 56% |
| | Microwave 210 °C 500 min | 0% | 66% |
|  **8b** | Toluene reflux 7 days | No conversion | — |
| | Microwave 210 °C 500 min | 28% (56%*) | 16% (32%*) |
|  **9** | Toluene reflux 3 days | 93% | — |
| | Microwave 135 °C 200 min | 94% | — |
|  **10** | Toluene reflux 7 days | Polymerization | |
| | Microwave 210 °C 500 min | 32% (46%*) | Not determined |

* Yield based on consumed starting material.




**Scheme 3.** Intramolecular Diels–Alder reaction (left) and structural elucidation of cyclization product **8b** by X-ray diffraction (right; 20% ellipsoids, only one of the two independent molecules shown).[16]

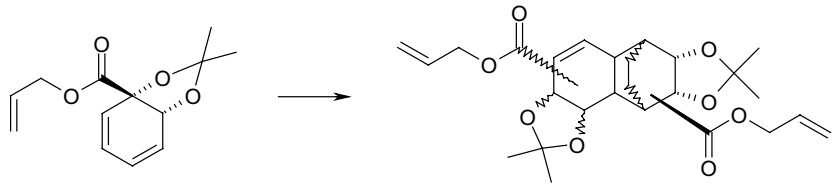
traditional reflux method. The reaction of the reversed ester derivative **7** was much more sluggish. When compound **7** was refluxed in either toluene or chloroform, polymerization was observed. This result can be explained by the high activation of the double bond. However, microwave irradiation (210 °C, 500 min) gave the desired product **10**[15] in 46% yield at 70% consumption of starting material. In addition, dimeric compounds were again isolated as by-products.

It is apparent from the results with precursors bearing the amide and ester functionality that the intramolecular Diels–Alder reaction competes against a dimerization reaction of the precursors, which has yet to be fully characterized. In the case of compound **3a** an appropriate sterical approach of the dienophile toward the cyclohexadiene moiety seems impossible and therefore dimerized products of the general type **11** are formed exclusively (Scheme 4).

Although the dienophile of the allyl ether derivative **6** represents the least activated double bond of all precursors, the intramolecular Diels–Alder reaction gave almost quantitative yields. These results can be explained by the fact that the side chain of allyl ether **6** represents the most flexible system, which obviously plays a significant role in this reaction.

All intramolecular Diels–Alder products were characterized by 2D-NMR techniques. Structural assignment was confirmed by a single crystal X-ray diffraction study of **8b.**[16]

In conclusion, we were able to construct functionalized scaffolds in enantiomerically pure form starting from benzoic acid within a few steps. Chirality was initially introduced by whole-cell biodihydroxylation and structural complexity was achieved in a microwave assisted intramolecular Diels–Alder cyclization controlling five asymmetric centers. Compared to classical thermal conditions, microwave irradiation generally offered the advantages to significantly increase in reaction rate accompanied by a simultaneous decrease of unwanted side-reactions.



**3a** **11**

**Scheme 4.** Cyclization of precursor **3a** yielding dimerized products of general type **11**.

The utilization of DCD in other cycloaddition reactions is currently under investigation in our laboratory.

## Acknowledgements

The authors would like to thank Dr. Christian Hametner (Vienna University of Technology) for his support in NMR based structural assignment. The *Ralstonia eutropha* B9 mutant strain was a generous gift by Prof. Andrew G. Myers, Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts.

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13. Physical data of compound **8b** [*3aR*-(3aα,4β,6aα,7β,10aα)]-3a,4,6a,7,8,9-hexahydro-2,2-dimethyl-4,7-methano-10*H*-[1,3]-dioxole-[4,5-*i*]isochinolin-10-one: colorless crystals; mp = 195–198 °C (EtOAc); $[\alpha]_D^{20}$ −42.3 (*c* 1, $CHCl_3$) $^1H$ NMR ($CDCl_3$, 400 MHz): 1.25–1.32 (m, 1H), 1.37 (s, 3H), 1.55 (s, 3H), 1.75–1.85 (m, 1H), 1.93–2.01 (m, 1H), 2.85–2.90 (m, 1H), 2.97–3.02 (m, 1H), 3.09–3.16 (m, 1H), 3.47 (dd, *J* = 11.8 Hz, *J* = 3.9 Hz, 1H), 4.21 (d, *J* = 3.8, 1H), 6.16–6.22 (m, 1H), 6.26–6.32 (m, 1H), 6.59 (bs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): 25.6 (t), 27.0 (q), 27.2 (q), 30.6 (d), 35.2 (d), 39.6 (d), 46.1 (t), 84.2 (s), 85.2 (d), 112.3 (s), 131.5 (d), 132.1 (d), 175.4 (s).
14. Physical data of compound **9** [*3aR* -(3aα,4β,6aα,7β,10aα)]-3a,4,7,8-tetrahydro-2,2-dimethyl-4,7-methano-6a*H*,10*H*-[1,3]-dioxole-[4,5-*i*][2]benzopyran: colorless oil; $[\alpha]_D^{20}$ −11.95 (*c* 0.95, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): 1.32 (bs, 6H), 1.34–1.40 (m, 1H), 1.49–1.57 (dt, *J* = 3.5Hz, *J* = 12Hz, 1H), 1.68–1.75 (m, 1H), 2.45–2.51 (m, 1H), 2.90–2.97 (m, 1H), 3.36–3.42 (m, 2H), 3.67 (d, *J* = 11.1 Hz, 1H), 3.79 (d, *J* = 10.5 Hz, 1H), 4.22 (d, *J* = 10.5, 1H), 6.17–6.26 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): 25.5 (t), 26.8 (q), 28.4 (q), 33.4 (d), 35.8 (d), 42.5 (d), 71.1 (t), 73.8 (t), 81.2 (s), 83.4 (d), 109.0 (s), 131.4 (d), 132.9 (d).
15. Physical data of compound **10** [*3aR*-(3aα,4β,6aα,7β,10aα)]-3a,4,6a,7-tetrahydro-2,2-dimethyl-4,7-methano-10*H*-[1,3]-dioxole-[4,5-*i*][2]benzopyran-8(8*H*)-one: colorless oil; $[\alpha]_D^{20}$ −80.4 (*c* 0.25, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): 1.34 (s, 3H), 1.36 (s, 3H), 1.48–1.57 (m, 1H), 1.92-2.01 (m, 1H), 2.59 (dt, *J* = 12.4Hz, *J* = 3.8Hz, 1H), 3.01–3.08 (m, 2H), 4.31–4.34 (m, 1H), 4.36 (d, *J* = 12.4 Hz, 1H), 6.13–6.19 (m, 1H), 6.32–6.38 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): 26.7 (q), 28.1 (t), 28.4 (q), 36.9 (d), 35.6 (d), 37.6 (d), 74.3 (t), 79.7 (s), 83.6 (d), 109.9 (s), 128.7 (d), 133.9 (d), 172.9 (s).
16. Crystal data for **8b**: $C_{13}H_{17}NO_3$, *M* = 235.28, orthorhombic, space group $P2_12_12_1$ (no 19), *a* = 8.8241(4) Å, *b* = 11.1952(5) Å, *c* = 24.8843(12) Å, *V* = 2458.3(2) Å$^3$, *Z* = 8, $D_{calcd}$ = 1.271 g/cm$^3$, *T* = 297 K, λ (MoKα) = 0.71073 Å, μ = 0.090 mm$^{-1}$, *F* (000) = 1008. Bruker AXS Smart APEX CCD platform 3-circle diffractometer (Bruker AXS, 2001: programs SMART, version 5.626; SAINT, version 6.36A; SADABS version 2.10; XPREP, version 6.12; SHELXTL, version 6.10. Bruker AXS Inc., Madison, WI, USA). Total/unique reflections 15885/5358, $R_{int}$ = 0.016, $\theta_{max}$ = 27°. Structure solution with direct methods. Final refinement: data/restraints/parameters: 5358/0/409, *GOF* = 1.04, $R_1$ = 0.042, $wR_2$ = 0.099 (all data). Absolute structure known from chemistry. The structure contains two crystallographically independent molecules of similar dimensions and shape mutually linked in pairs via two N-H–O hydrogen bonds, N–O=2.878(2) and 2.904(2) Å. CCDC 242537 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033.