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Oxidation of Diols to Lactones by *Nocardia corallina* B-276

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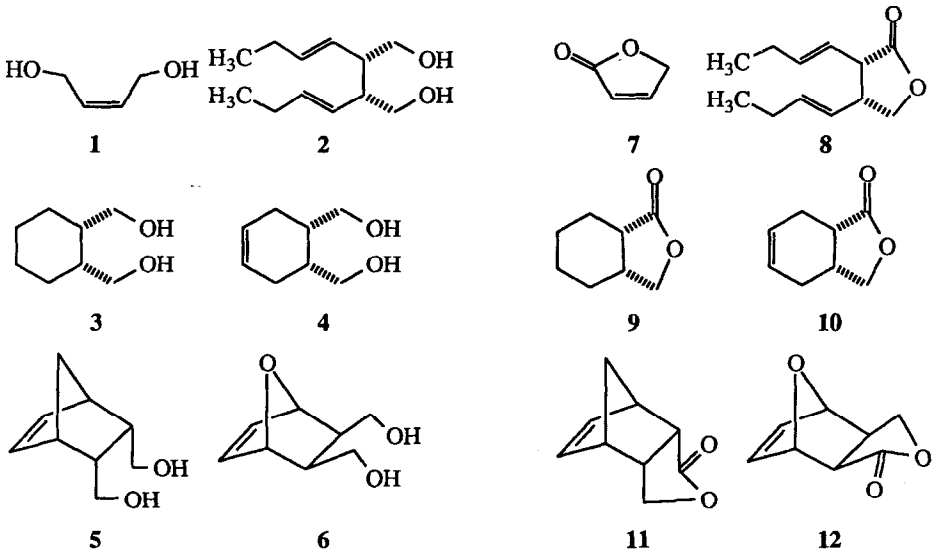
Abstract: Several synthetically useful achiral and chiral lactones with high optical purity were prepared by whole-cell oxidation of diols with *Nocardia corallina*. The absolute stereochemistry of the newly created stereogenic centers was established by comparison with known compounds. In all cases the products were derived from the oxidation of the *pro-S* hydroxymethylene group.

The classical resolution of racemic compounds leads to an economically undesirable maximum yield of only 50% of one enantiomer, unless the undesired enantiomer can be productively recycled. On the other hand, asymmetrization of symmetric compounds offers an enantiomerically pure derivative in 100% yield, at least theoretically. Such asymmetrization reactions become even more attractive with the advent of biocatalysis as these reactions provide ecologically clean conditions.

An interesting example of the asymmetrization process is the preparation of chiral lactones from *meso* diols using horse liver alcohol dehydrogenase.[1] One drawback of this reaction is the cost and recycling of the cofactor, NAD^+/NADH, which makes this method uneconomical. Oxidation with whole cells, which is practically more valuable, has not been well explored for this purpose. In 1982, Otha reported that various strains of *Gluconobacter* and *Acetobacter* were able to oxidize prochiral diols to corresponding lactones.[2] More recently, Patel reported the screening of some *Nocardia* and *Rhodococcus* strains for the preparation of **12** as an intermediate in the synthesis of a cardiovascular agent.[3]

Asymmetric epoxidation of isolated olefins with *Nocardia corallina* is well documented in the literature.[4] Upon extending this work to allylic alcohols, we found that *Nocardia corallina* was able to oxidize allylic alcohols to corresponding aldehydes and/or acids.[5] As a result of this finding we decided to extend these investigations to symmetric diols which led to products widely used in the synthesis of prostaglandins, pyrethroids and polyether ionophores.



In the current studies we investigated simple diols like **1** to **6**, and the results obtained are listed in the Table. Subjecting **1** to standard whole-cell oxidation conditions (see Experimental) yielded 2(5H)-furanone **7**, an

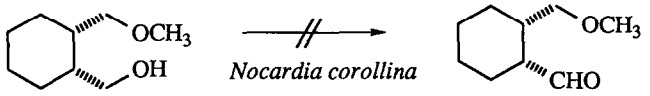
TABLE

Entry No.	Substrate	Reaction time (hr)	Product	Yield (%)	Configuration (lit.)	*ee* (%)
1	**1**	24	**7**	50		
2	**2**	149	**8**	71	3*S*,4*R* (ref. 6)	55[a]
3	**3**	48	**9**	50	3a*R*,7a*S* (ref. 1)	60[b]
4	**4**	47	**10**	50	3a*R*,7a*S* (ref. 7)	>99[b]
5	**5**	48	**11**	60	3a*R*,7a*S* (ref. 8)	95[b,c]
6	**6**	48	**12**	95	3a*R*,7a*R* (ref. 9)	>91[b,c]

a: Determined by GC on Cyclodex-B column; b: determined by HPLC on Chiracel-OD column; c: >99% *ee* after one recrystallization.

expensive but highly useful synthetic intermediate. Acyclic *meso* diol **2**, a precursor for the synthesis of a pheromone,[10] under the same oxidation conditions yielded **8** in 71% yield. The stereoselectivity in this case is a modest 55% *ee*, and the absolute stereochemistry was deduced by comparison with the lactone obtained from the natural pheromone.[6]

Application of this methodology to cyclic *meso* diols turned out to be even more interesting. In most cases the lactones were obtained in good yield and with excellent enantioselectivity. Perhaps the most interesting is the optical purity of lactone **10** obtained from cyclohexenedimethanol **4** (99% *ee*, entry 4), compared to the corresponding saturated analog **3** (60% *ee*, entry 3). Bicyclic dimethanols **5** and **6** afforded lactones **11** and **12** respectively, and in both circumstances the optical purity was enriched to >99% *ee* by one recrystallization. The absolute stereochemistry of lactones **9-12** was assigned by correlating to literature data. The stereochemical outcome in these asymmetrizations in all cases was derived from the initial oxidation of the *pro-S* hydroxymethylene group. These results are analogous to those observed using horse liver alcohol dehydrogenase. A detailed investigation of this oxidation process with example **3** revealed that the presence of both hydroxy groups in free-form is essential for asymmetrization. The monomethylated **3** failed to yield the



corresponding oxidized product suggesting that the oxygenase enzyme in *Nocardia corallina* does not oxidize saturated primary alcohols. This is in contrast to horse liver alcohol dehydrogenase which is also able to oxidize isolated primary hydroxy groups.[11]

Efforts to extend these whole cell oxidation conditions with *Nocardia corallina* to other related systems, especially to epoxy alcohols, are currently underway, and the results will be reported in due course.

Experimental:

The bacteria *Nocardia corallina* B-276 (ATCC 31338) was purchased from American Type Culture Collection. The bacteria was grown under standard sterile conditions at 30 °C on agar plates [beef extract, 3.0 g/L; peptone, 5.0 g/L; agar, 15 g/L at pH=6.8]. The broth composition was: Solution A: $FeSO_4 \cdot 7H_2O$ (0.05 g/L), K_2HPO_4 (1.74 g/L), $(NH_4)_2SO_4$ (2.0 g/L), yeast extract (1.0 g/L); Solution B: $MgSO_4$ (1.5 g/L); Solution C: glucose (2.0 g/L). Each solution was sterilized separately, later combined and the pH was adjusted to 8.0 (±0.5). All substrates and the reference racemic lactones used for HPLC determinations were either prepared according to reported procedures or purchased from commercial sources. All products were compared with authentic samples or data reported in the literature.

General procedure: *Preculture I:* A 125-mL Erlenmeyer flask containing 50 mL of sterile culture medium was inoculated with 1/4 of the cell content from an agar plate (2 weeks old) and incubated at 30 °C (± 0.5 °C) on a rotary shaker (200 rpm) for 24-30 h.

Preculture II: The contents of Preculture I were aseptically poured into a 1-L Erlenmeyer flask containing 425 mL of sterile culture medium. The flask was incubated at 30 °C (± 0.5 °C) on a rotary shaker (200 rpm) for 60-64 h. Then the pH was adjusted to 8.0-8.5 for the next stage.

Biotransformations: Under aseptic conditions the substrate (0.1 mmol) was added to the flask containing preculture II. The mixture was incubated at 30 °C (± 0.5 °C) on a rotary shaker (200 rpm) for the duration of the reaction (monitored by TLC). The reaction mixture was acidified (pH=5), then saturated with sodium chloride and extracted with dichloromethane (4x100 mL). The organic extract was filtered through Celite, dried, and evaporated. The crude products were purified by flash chromatography (silica gel; hexane/ethyl acetate).

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