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Studies on the resorcylates: biomimetic total syntheses of (+)-montagnetol and (+)-erythrin

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ABSTRACT

6-(2,4-Dioxopentyl)-2,2-trimethyl-4*H*-1,3-dioxin-4-one on reflux in toluene gave $MeCOCH_2COCH_2COCH{=}C{=}O$, which cyclized to 6-(2-oxopropyl)-4-hydroxy-2*H*-pyran-2-one or was trapped with alcohols to produce resorcylate esters. The method was used for the synthesis of both enantiomers of montagnetol and erythrin.

The orsellinic acid unit **1** occurs widely in natural products, including montagnetol (**2**) and the anti-oxidant[1] erythrin (**3**), both isolated from the lichen *Roccella montagnei* (Fig. 1).[2] The structures of montagnetol (**2**) and erythrin (**3**) were confirmed by synthesis,[3] although the absolute stereochemistry has not yet been assigned. Herein, we report a convergent, novel synthesis of diketo-1,3-dioxinone **10**, its varied cyclization reactions, and its application to the synthesis of both enantiomers of (+)-montagnetol (**2**) and (+)-erythrin (**3**) thereby determining the absolute configuration of these natural products.

Recently, we reported efficient biomimetic syntheses of bioactive resorcylate natural products **4** via thermolysis, ketene trapping, and aromatization, starting from dioxinones **5** (Scheme 1).[4]

In the process of optimizing the aromatization step in the synthesis of these natural products, a model system, diketo-1,3-dioxinone **10** was examined. It was found that **10** can undergo different cyclization reactions depending on the reaction conditions.

Dioxinone **10** was synthesized by thermolysis of commercially available dioxinone **6**, which underwent a retro-Diels–Alder[5] reaction at 90 °C to form acyl-ketene **7**, which was trapped with benzotriazole **8** to form amide **9** in quantitative yield.[6] Subsequent crossed Claisen condensation[7] via reaction of the lithium enolate from dioxinone **6** with amide **9** gave diketo-1,3-dioxinone **10** as a 5:95 mixture of keto–enol tautomers in 53% yield over two steps (Scheme 2).[8]

Dioxinone **10** undergoes cyclization using triethylamine, 1,4-diazabicyclo(2.2.2)octane, or *N*,*N*-4-dimethylaminopyridine to give the benzo[1,3]dioxinone **11** (Scheme 3). Alternatively, thermolysis in toluene containing methanol and aromatization with cesium carbonate followed by acidification gave the resorcylate **13** (87%). Finally, thermolysis of dioxinone **10** alone in toluene solution gave the pyrone **14** (68%).

The thermolytic ketene generation, trapping, and aromatization were applied to the total synthesis of (+)-montagnetol (**2**) and (+)-erythrin (**3**), respectively.

Thermolysis of dioxinone **10** in the presence of benzyl-protected erithritols **15a**[10] and **15b** gave the triketo-esters **16a** and **16b**, respectively.[11] NMR analysis in $CDCl_3$ showed these compounds to exist as mixtures of keto and enol tautomers.[12] Aldol cyclization and aromatization followed by hydrogenolysis of the benzyl groups gave **18** and (+)-montagnetol (**2**), respectively (Scheme 4).

Reaction between dioxinone **10** and phenol **17a** at 110 °C failed to give the corresponding aryl triketo-ester, indicating that the

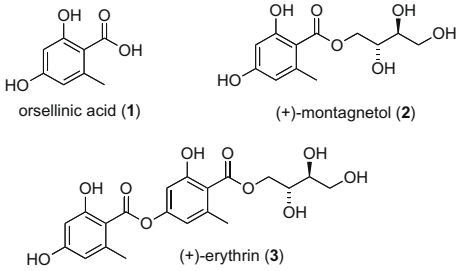

Figure 1. Natural products containing the orsellinic acid unit.

Scheme 1. Retrosynthetic approach to build 6-alkyl-2,4-dihydroxybenzoic acid unit **4**.

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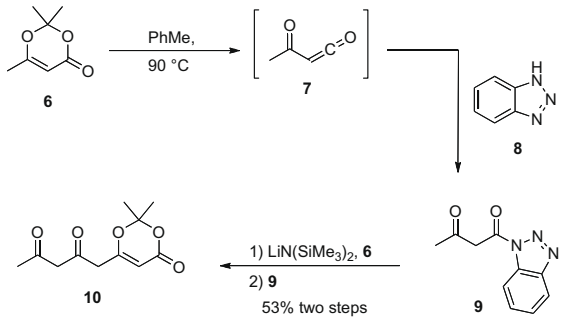
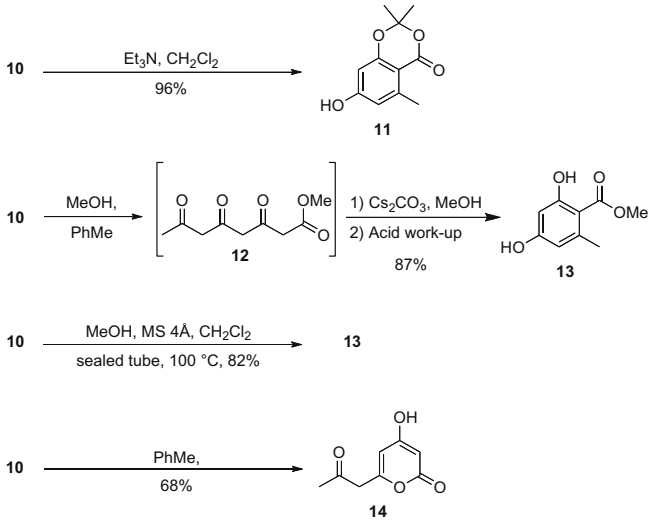
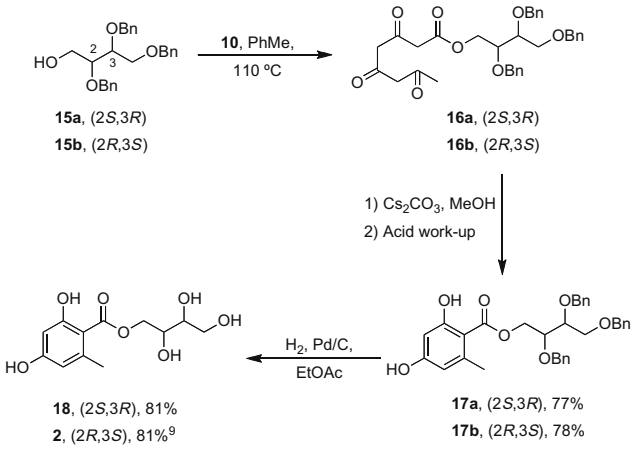


Scheme 2. Synthesis of diketo-1,3-dioxinone **10**.

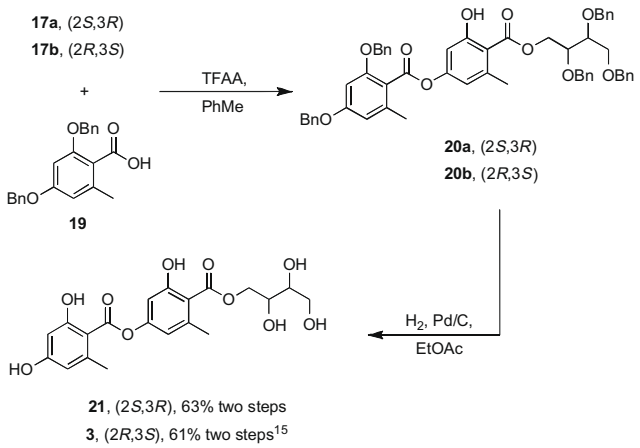


Scheme 3. Different cyclization reactions of diketo-1,3-dioxinone **10**.



Scheme 4. Synthesis of (−)-montagnetol (**18**) and (+)-montagnetol (**2**). (see above-mentioned reference for further information.)

phenol in **17a** was of insufficient nucleophilicity. Consequently, a more classical approach was applied starting from the protected orsellinic acid **19**[13] which underwent an esterification reaction with phenol **17a** or **17b** using activation with trifluoroacetic anhydride[14] to provide the diesters **20a** and **20b**, respectively. Debenzylation by hydrogenolysis afforded **21** and **3**, respectively (Scheme 5).



Scheme 5. Synthesis of (−)-erythrin (**21**) and (+)-erythrin (**3**). (see above-mentioned reference for further information.)

The two enantiomers of montagnetol, **18** and **2,** were examined for their optical rotations, compared with the natural product, showing **2** (2*R*,3*S*) to have the true configuration. Both enantiomers (−)-erythrin (**21**) and (+)-erythrin (**3**) were compared with an authentic sample of erythrin, and chiral HPLC analysis was fully consistent with the natural product configuration being (2*R*,3*S*)-erythrin (**3**).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.134.

References and notes

1. Choudhary, M. I.; Ali, S.; Thadani, V. M.; Karunaratne, V. U.S. Patent application publication 0,048,332 A1, 2009.
2. Rao, S. V.; Seshadri, T. R. *Proc. Ind. Acad. Sci. Sect. A* **1941**, *13A*, 199.
3. Manaktala, S. K.; Neelakantan, S.; Seshadri, T. R. *Tetrahedron* **1966**, *22*, 2373.
4. Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Bräckow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293.
5. Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.
6. This activated amide intermediate exists as a 1:1 mixture of keto and enol forms. As benzotriazole **9** is prone to decomposition, it was used directly in the next step. The NMR analysis of intermediate **9** was measured in THF-d_8.
7. Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854.
8. It was observed that the yield decreased if benzotriazole was not removed before column chromatography, due to aromatization to **11**. To avoid this side product, the mixture was washed with a pH 9 buffer solution to remove benzotriazole and suppress the rate of the aromatization reaction.
9. The optical rotations of compounds **18**, (2*S*,3*R*) and **2**, (2*R*,3*S*) were $[\alpha]_D^{20}$ −10.1 (acetone, *c* 0.5) and $[\alpha]_D^{20}$ =+11 (acetone, *c* 0.4), respectively; these data were compared with those of the isolated natural (+)-montagnetol[2] $[\alpha]_D^{20}$ +12.6 (acetone).
10. Soriente, A.; De Rosa, M.; Trincone, A.; Sodano, G. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2321.
11. Compounds **16a** and **16b** are stable at room temperature, but are very sensitive to base or acid.
12. Deuterium exchange occurs in methanol-d_4 leading to the disappearance of the keto–enol proton in the proton NMR spectrum.

13. Vicart, N.; Ortholand, J.-Y.; Emeric, G. Y.; Greiner, A. *Tetrahedron Lett.* **1994**, *35*, 3917.
14. This is a modified procedure of: Wang, P.; Zhang, Z.; Yu, B. *J. Org. Chem.* **2005**, *70*, 8884.
15. The optical rotations of compounds **21**, (2*S*,3*R*) and **3**, (2*R*,3*S*) were $[\alpha]_D^{20}$ −8.2 (MeOH, *c* 0.2) and $[\alpha]_D^{20}$ +9 (MeOH, *c* 0.2), respectively; these data were compared with those of the isolated natural (+)-erythrin, kindly provided by Professor V. Karunaratne, $[\alpha]_D^{20}$ +7.3 (MeOH, *c* 0.2).