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Synthesis of (+)-epiepoformin using the base-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone

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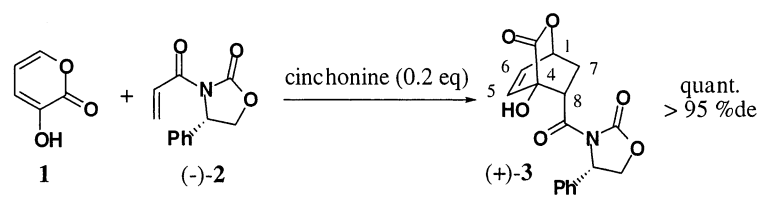
Abstract—Asymmetric total synthesis of (+)-epiepoformin was achieved in short steps using the base-catalyzed asymmetric Diels–Alder (DA) reaction of 3-hydroxy-2-pyrone with chiral acrylate. Since the synthesis produced Ogasawara's intermediate, it is also presented as a formal synthesis of (−)-theobroxide.

Naturally occurring highly oxygenated epoxycyclohexane derivatives, known as cyclohexene oxides, are attractive targets for synthetic chemists because of their various biological activities, including anti-tumor and glucosidase inhibition activities.[1] Construction of the saturated functionalities in the cyclohexane ring system stereoselectively is also of great interest.

The most important point in the efficient synthesis of these small compounds with diverse oxygen functional groups is the choice of a starting material with appropriate functional groups in the appropriate positions in the cyclohexane ring or its equivalent. We reported a base-catalyzed asymmetric Diels–Alder (DA) reaction using 3-hydroxy-2-pyrone (**1**) with optically active acrylate ((−)-**2**), which afforded a highly functionalized adduct ((+)-**3**) in almost quantitative yield as an optically pure form (Scheme 1).[2] As seen by its structure, compound (+)-**3** should be a useful starting material for constructing cyclohexene oxides. The C-5,6 double bond, oxygen functional groups at C-1 and C-4, and carbonyl group at C-8 in **3** might be converted to the respective epoxy group at C-2,3, oxygen functional groups at C-1 and 4, and one-carbon side-chain at C-5 in typical cyclohexene oxides **4**–**7** (Scheme 2). Additionally, since both enantiomers of **3** are easily obtained by changing the chiral auxiliary of **2** and base-catalyst, compound **3** should be a useful starting material for asymmetric synthesis. Indeed, we have already reported the synthesis of both enantiomers of eutypoxide B, a cyclohexene oxide with a C_5 side-chain, from (+)- and (−)-**3**.[3]

In our ongoing study of the application of **3** to cyclohexene oxide synthesis, we chose two compounds, (+)-epiepoformin[4] (**4**) and (−)-theobroxide[5] (**5**) as target molecules. These compounds were isolated as metabolites of phytotoxic pathogens and reported to be an inhibitor of lettuce seed germination[4] and an inducer of



Scheme 1.

Keywords: cyclohexene oxides; asymmetric synthesis; Diels–Alder reaction; base-catalyst.

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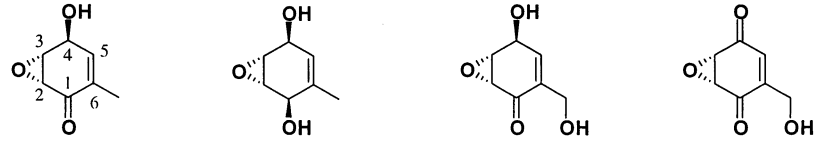

Scheme 2.

potato micro-tubers and morning-glory flower buds,[5] respectively. In 1982, Ichihara's group first reported a short, efficient synthesis of *dl*-**4** using the DA reaction of dimethylfulven with *p*-quinone,[6] and in 1995 Ogasawara's group achieved the first asymmetric synthesis of (+)-**4** and both enantiomers of **5** using asymmetric lipase-mediated asymmetrization of a *meso*-intermediate.[7] Very recently, Maycock's group also reported a synthesis of (+)-**4** and (−)-**5** from (−)-quinic acid.[8]

Our synthesis of (+)-**4** and (−)-**5** started from hydroxyketone (−)-**8**, which was obtained from adduct (+)-**3** following the preceding procedure[3] (Scheme 3). Epoxidation of (−)-**8** was achieved by treatment of hydrogen peroxide under basic conditions. Although the standard H_2O_2–NaOH conditions only provided a complex mixture, the combination of H_2O_2–Triton B was effective in giving the desired epoxide **9**, and the highest yield (up to 92%) was obtained using a catalytic amount (0.3 equiv.) of Triton B.[7,9] The stereochemistry of the epoxy group results from the steric interaction between the hydroperoxide nucleophile and the bulky TBSO-group, which induced α attack of the hydroperoxide. Although the base-induced enolization eliminated the stereochemistry of the hydroxymethyl group at this stage, this was not disadvantageous because the stereochemistry disappeared in the next step.

Dehydroxylation of the primary hydroxyl group in **9** in almost quantitative yield was achieved by tosylation and subsequent elimination. Isomerization of the *exo*-olefin in (−)-**10** was difficult. Several attempts using Rh-complexes were made under various conditions,[10] but no efficient conversion to the *endo*-olefin (+)-**11** was observed. Only treatment with Pd/C that was pretreated in a H_2 atmosphere afforded the desired (+)-**11**.[11] Although the yield was changeable, the isomerized product was obtained in fair yield (up to 70%).

The resulting compound (+)-**11** was the key intermediate of (+)-**4** and (−)-**5** in Ogasawara's synthesis,[7] and the optical rotation showed good agreement. To confirm the structure, (+)-**11** was converted to (+)-**4** in using the reported procedure. Since the optical rotation and ^1H NMR spectrum[12] of the resulting compound showed good agreement with those reported for synthesized (+)-**4**,[7] we accomplished efficient asymmetric synthesis of (+)-**4** and a formal asymmetric synthesis of (−)-**5**.

As shown in this synthesis, compound **3** is a promising starting material for various cyclohexene oxides. For example, introducing a hydroxyl group on the methyl group at C-6 of (+)-**4** and (−)-**5** results in the efficient synthesis of (+)-epiepoxydon[4,13] (**6**) and (−)-phyllostine[14] (**7**), respectively, and further oxidation makes it possible to produce more highly oxidized compounds, such as cyclophellitol[15] and crotepoxide.[16] We are now examining the synthesis of such compounds, including (+)-**6** and (−)-**7**.

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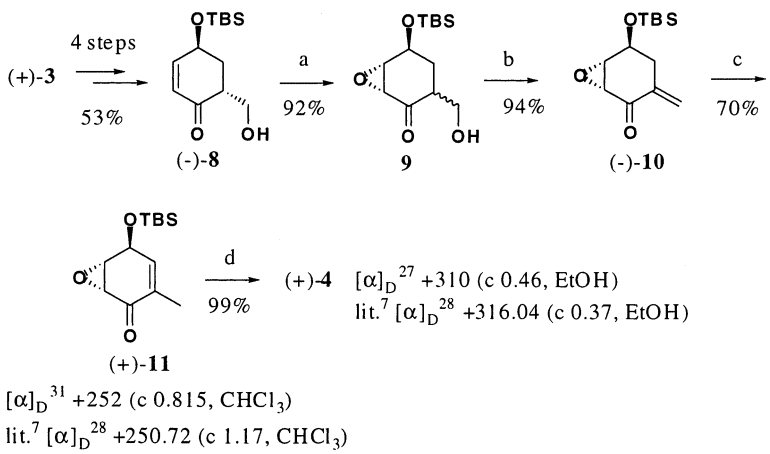

Scheme 3. *Reagents and conditions*: (a) 30% aq. H_2O_2, Triton B; (b) TsCl, Et_3N, DMAP; (c) Pd/C; (d) HF-CH_3CN.

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