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Efficient, scalable asymmetric synthesis of an epoxy quinol via Noyori desymmetrization of a *meso* diketone

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Abstract

Epoxy quinol **1a** was prepared on a multi-gram scale by Noyori transfer hydrogenative desymmetrization of the readily available *meso* epoxy diketone **4**. Although the intrinsic enantioselectivity for the desymmetrization was modest (82:18 er at 4% conversion), a highly enantiopure product (99.6:0.4 er) could be obtained in one operation in 44% yield *via* kinetic resolution of the minor enantiomer with long reaction times (48 h), or in 73% yield by combination with an enzymatic resolution of a 93:7 er mixture.

1. Introduction

The *trans*-epoxy quinol moiety **1** is present in natural products **1b-h** (Scheme 1),¹ as well as being a useful synthon in complex molecule synthesis.² Asymmetric approaches to these compounds have included whole cell oxidations of arenes to *cis*-arene diols,³ Baker's yeast reduction of β -ketoesters,⁴ stoichiometric⁵ and catalytic⁶ asymmetric Diels-Alder reactions, asymmetric epoxidation,^{2a,7} use of a sulfoxide chiral auxiliary,⁸ enzymatic resolution of racemic⁹ or *meso* diols,¹⁰ from quinic acid,¹¹ and by catalytic alkene isomerization of a *meso* bis-silyl ether.¹²

Over the course of our ongoing synthesis of antascomycin B **2**,^{13,14,15} we identified parent epoxy quinol **1a** as an early intermediate in the asymmetric synthesis of the C29-C34 cyclohexyl moiety (Scheme 2). We would thus need to be able to generate multi-gram quantities of **1a** in an efficient manner. The existing approaches to epoxy quinols suffer from tedious and inefficient protection/deprotection and/or oxidation/reduction sequences, the use of expensive or hard to obtain starting materials, and/or lack of scalability. Thus, while racemic **1a** has been prepared in 4 steps from benzoquinone,¹⁶ the reported asymmetric synthesis of the corresponding silyl ether **1i** required eight steps from benzoquinone, a high enzyme loading for the desymmetrization step (lipase PS-D, 1 eq by weight), and a long reaction time (16 days).^{17,18}

We sought a more efficient approach for preparing large quantities of **1a**, which would be comparable to a short racemic synthesis.^{16,19} Asymmetric transfer hydrogenation offers a mild, readily scalable approach to enantiopure alcohols.²⁰ The asymmetric reduction of *meso*-epoxy diketone **4** (available in two steps from benzoquinone)²¹ would shorten the synthesis of **1a** to four steps (Scheme 3). The *meso* diketones have previously been desymmetrized *via* whole cell reductions,²² asymmetric hydride reductions,²³ and asymmetric deprotonations.²⁴ The asymmetric hydrogenation of *meso* diketones to keto alcohols has apparently not been explored.²⁵

Using formic acid/trialkylamine²⁶ as the stoichiometric reductant, we studied the effect of catalyst loading, the identity of the trialkylamine, acid:amine ratio and acid:ketone ratio on the enantioselectivity of reduction of epoxy diketone **4** using DMF as a cosolvent. The reaction was performed using the Ru(*p*-cymene)[(*S,S*)-TsDPEN] catalyst from -10 °C to rt for approximately 16 h. The desired keto alcohol **5** was formed in 83:17 to 90:10 er (Scheme 3, Table 1). The catalyst loading, identity of the amine, acid:amine and acid:ketone ratio had relatively modest effects on the er.

In contrast to the racemic reduction of **4** with NBu₄BH₄, which gave ca. 6:1 dr,¹⁶ the Noyori reduction gave a single diastereomer. The absolute configuration of alcohol **4** was determined by chiral GC correlation to the compound prepared *via* the enzymatic desymmetrization route.

We then increased the reaction scale to 10 mmol (Table 2). A solvent survey indicated that acetonitrile was the optimal cosolvent for the reduction (entries 1-5). Changing the formic acid/ketone ratio from 3:1 to 1:1 resulted in a significant improvement in er (entries 3 and 6). However, a steady decrease in enantioselectivity was observed upon increasing the reaction scale beyond 10 mmol (entries 6-9). We were ultimately able to achieve a 93:7 er in the reduction on a 60 mmol scale in 85% yield. Chiral GC analysis at 4% conversion under the optimized conditions revealed a modest intrinsic enantioselectivity (82:18 er), which is, however, comparable to other dialkyl ketone transfer hydrogenations.^{25,27}

As expected, increasing the reaction time of the reduction resulted in material with a significantly improved er (99.6:0.4 at 48 h) as a consequence of the kinetic resolution of the minor enantiomer, although the isolated yield dropped to 44%. Alternatively, a 93:7 er mixture (12 h reaction time) could be enriched *via* enzymatic resolution with Amano lipase PS-IM to 99.5:0.5 er in an overall 73% yield.

To complete the preparation of epoxyquinol **1a**, we employed the Taylor variation¹⁹ of the Lubineau procedure¹⁶ for the retro-Diels-Alder reaction of **5** to **1a**. Heating 10 g of keto alcohol **5** at 210 °C in diphenyl ether afforded the desired epoxy quinol **1a** in 80% yield.

3. Conclusion

In conclusion, we have prepared epoxy quinol **1a** in 4 steps from benzoquinone in a concise manner with a synthetically useful yield and high enantiopurity.

4. Experimental

Method A (93:7 er)

At first, Ru(*p*-cymene)[(*S,S*)-TsDPEN] (0.25 g, 0.39 mmol, 0.65 mol %) and epoxy diketone **4** (11.4 g, 60 mmol) were added to a solution of formic acid (3.85 mL), triethylamine (14.3 mL) and acetonitrile (500 mL) at -10 °C. The reaction mixture was allowed to slowly warm to rt and stirred for ca. 16 h. The mixture was concentrated *in vacuo* and then stirred for ca. 16 h in 30/70 ethyl acetate/hexanes (300 mL) with activated charcoal (10 g). The mixture was filtered through a plug of Celite with 30/70 ethyl acetate/hexanes and concentrated *in vacuo*. At this point, the residue could be purified by flash chromatography (20/80 ethyl acetate/hexanes) to give keto alcohol **5** as colorless crystals (9.8 g, 85%, er 93:7). Spectroscopic data matched those previously reported.¹⁶

Method B (99.6:0.4 er)

As in Method A, but the reaction mixture was allowed to stir for 48 h at rt. Flash chromatography (20/80 ethyl acetate/hexanes) gave keto alcohol **5** as colorless crystals 5.1 g, 44%, er 99.6:0.4).

Method C (99.5:0.5 er)

Prior to chromatography, the residue from Method A was purified by enzymatic resolution: vinyl acetate (1.34 mL, 1.26 g, 14.6 mmol), Lipase PS-IM (1.4 g), and keto alcohol **7** (10 g, 52 mmol, 93:7 er) were added to a solution of THF (100 mL) and NEt_3 (10 mL) and stirred at rt for 4 d. The reaction mixture was filtered through a plug of Celite and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexanes to give epoxy keto alcohol **5** as colorless crystals (8.5 g, 73% from **4**, 99.5:0.5 er). The alcohol could be further crystallized to enantiopurity from diethyl ether.

The experimental procedure for the retro-Diels-Alder is as follows. A solution of keto epoxide **5** (10 g, 52 mmol) in diphenyl ether (200 mL) was heated under nitrogen at 210 °C for 2 h. Upon cooling to rt, the mixture was loaded directly on a silica gel column. Hexanes were used to elute the diphenyl ether, followed by 20/80 EtOAc/hexanes to give epoxy quinol **1a** as white crystals (5.2 g, 42 mmol, 80%); mp 84–86 °C; $[\alpha]_D^{19} = +3.8$ (c 1.65, CH_2Cl_2). Spectroscopic data matched those previously reported.¹⁶

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- 1a** R=H
1b (-)-bromoxone, R=Br
1c (-)-epiepoformin, R=Me
1d (-)-epiepoxidon, R=CH₂OH
1e (-)-chaloxone, R=OMe

- 1f** (-)-harveynone, R₁, R₂=H
1g (-)-tricholomenyn A,
R₁=prenyl, R₂=Ac

- 1h** panepoxidon

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Table 1

Optimization of the reduction of diketone **4** on a 1.0 mmol scale.

entry	catalyst (mol %)	acid:amine ratio	amine	acid:ketone ratio	er (5:ent-5)
1	0.4	7:1	NEt(iPr) ₂	5:1	83:17
2	0.8	"	"	"	90:10
3	1.0	"	"	"	90:10
4	1.6	"	"	"	90:10
5	1.0	"	NEt ₃	"	90:10
6	1.2	"	"	"	90:10
7	2.0	"	"	"	90:10
8	1.0	"	"	10:1	83:17
9	0.2	5:2	NEt(iPr) ₂	3.2:1	86:14
10	0.4	"	"	3.2:1	86:14
11	1.0	"	"	3.2:1	86:14
12	"	"	"	2.5:1	80:20
13	"	"	NEt ₃	3.2:1	87:13
14	"	"	"	2.5:1	85:15

Table 2

Optimization of the scale-up of reduction of diketone **4**.

entry	solvent	acid:keto ^a	scale (mmol)	conc (M)	er (5:ent-5)
1	None	3:1	10	"	80:20
2	DMF	"	"	0.5	80:20
3	MeCN	"	"	"	82:18
4	THF	"	"	"	70:30
5	CH ₂ Cl ₂	"	"	"	70:30
6	MeCN	1:1	"	0.15	90:10
7	"	"	30	"	82:18
8	"	"	60	"	79:21
9	"	"	120 ^b	"	77:23

^a Molar ratio.^b Reaction did not proceed to completion.