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COMMUNICATION

Catalytic asymmetric synthesis of butane diacetal-protected (4*S*,5*S*)-dihydroxycyclohexen-1-one and use in natural product synthesis†

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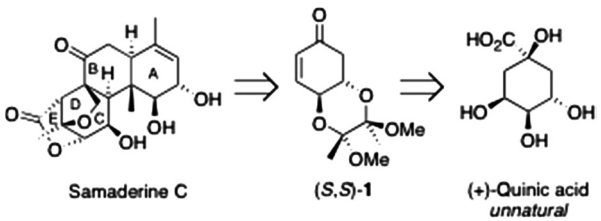
Due to the lack of availability of unnatural (+)-quinic acid as a starting material, a 6-step synthesis of butane diacetal-protected (4*S*,5*S*)-dihydroxycyclohexen-1-one (formally derived from (+)-quinic acid) has been devised. The key catalytic asymmetric step involves a chiral Co-salen-catalysed epoxide ring-opening reaction. (4*S*,5*S*)-Dihydroxycyclohexen-1-one was utilised in the synthesis of two cyclohexenone natural products isolated from the mycelia of *Lasiodiplodia theobromae*.

Synthesis employing chiral pool starting materials such as amino acids and sugars represents one of the seminal strategies for the preparation of enantiopure natural products and pharmaceuticals. Nowadays, despite the plethora of asymmetric synthesis methods that are at our disposal, readily available chiral pool compounds are still important for the total synthesis of complex natural products. A representative recent example is provided by Gademann's total synthesis of cyrneine A from (*R*)-carvone.[1] Notwithstanding the numerous successful examples of chiral pool syntheses, a significant limitation is the commercial availability of only one, naturally occurring stereoisomer.[2] We encountered exactly this problem during the development of methodology for a projected total synthesis of samaderine C. Our plan (Scheme 1) was to construct the A ring of samaderine C starting from (4*S*,5*S*)-dihydroxycyclohexen-1-one (*S*,*S*)-**1** with the *trans*-diol functionality conveniently protected as a butane diacetal (BDA)[3] which could, in principle, be derived from (+)-quinic acid, the unnatural and unavailable stereoisomer.

Enone (*R*,*R*)-**1**, prepared in three steps from (−)-quinic acid,[4] is a well-established chiral building block used in a number of synthetic applications.[4b,c,5] Indeed, we have previously used enone (*R*,*R*)-**1** to prepare the cyclohexenone core of scyphostatin.[6] However, the lack of availability of (+)-quinic acid means that enone (*S*,*S*)-**1** has not previously been considered a viable starting material in synthesis. To address this issue, we report herein the development of a catalytic asymmetric synthetic route to enone (*S*,*S*)-**1** and demonstrate its usefulness in the preparation of naturally occurring methylated enones (*S*,*S*)-**2**[7] and (*S*,*S*)-**3**,[8] structurally related to theobroxide (Fig. 1).

Our synthetic approach to enone (*S*,*S*)-**1** is outlined in Scheme 2. It was envisaged that (*S*,*S*)-**1** would be prepared from BDA-protected chiral epoxide **4** *via* lithium amide-mediated epoxide rearrangement[9–11] and oxidation of the allylic alcohol. Epoxide **4** would be generated from mono-protected dihydroxycyclohexene (*S*,*S*)-**5** which would in turn be the product of a Jacobsen desymmetrisation of *meso*-epoxide **6** using benzoic acid in the presence of a chiral Co-salen catalyst.[12]



Scheme 1

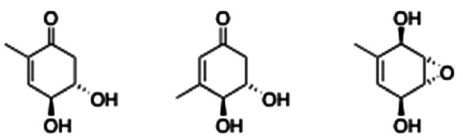
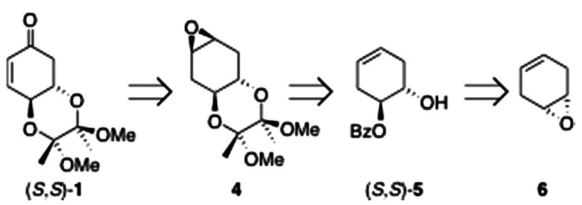


Fig. 1 Theobroxide-related natural products.



Scheme 2

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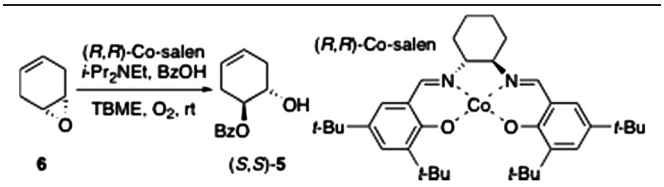
†Electronic supplementary information (ESI) available: Full experimental procedures and copies of $^{1}H/^{13}C$ NMR spectra and CSP-HPLC data. See DOI: 10.1039/c2ob26406d

Table 1 Desymmetrisation of *meso*-epoxide **6**



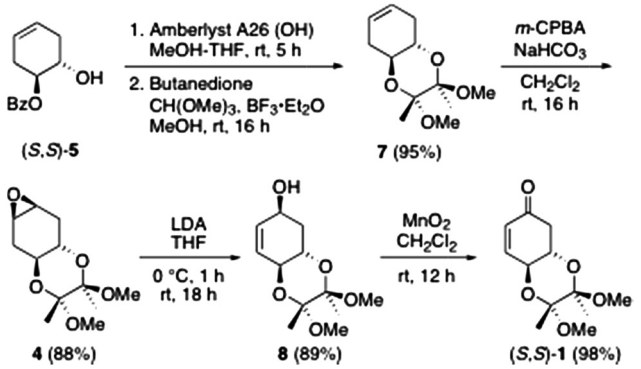
Entry	Mol% (*R*,*R*)-Co-salen	Time (h)	Yield[a] (%)	er[b]
1	5	53	74	83 : 17
2	2.5	90	79	85 : 15
3	2	94	85	85 : 15
4	1	120	70	79 : 21
5	0	140	0	n/a

[a] Yield after purification by chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC on a Chiralpak AS column; major enantiomer is (*S*,*S*)-**5**.

To start with, *meso*-epoxide **6** was prepared by epoxidation of 1,4-cyclohexadiene using *m*-CPBA in $NaHCO_3$-buffered dichloromethane.[13] Purification by distillation gave **6** in 67% yield. Next, the Jacobsen desymmetrisation step was evaluated. Based on precedent,[12] the (*R*,*R*)-Co-salen was selected as we anticipated that this should deliver (*S*,*S*)-**5**. Ultimately, this was proven to be the case by conversion of (*S*,*S*)-**5** into enone (*S*,*S*)-**1** (*vide infra*). Following the literature protocol,[12] the (*R*,*R*)-Co-salen (1–5 mol%) was oxidatively pre-activated by stirring under an oxygen atmosphere in TBME. Then, i-Pr_2NEt, additional TBME solvent and *meso*-epoxide **6** were added and the reaction was stirred for 53–120 h. The results of this study are presented in Table 1. Using 5 mol% (*R*,*R*)-Co-salen for 53 h, benzoate (*S*,*S*)-**5** was isolated in 74% yield and 83 : 17 er (entry 1). A similarly high yield and enantioselectivity were obtained at 2.5, 2.0 and 1.0 mol% loadings of the (*R*,*R*)-Co-salen catalyst, but longer reaction times were required (90–120 h) (entries 2–4). These results are consistent with the lack of a background reaction between benzoic acid and epoxide **6** under these conditions: a reaction in the absence of catalyst yielded no product (entry 5). Based on these results, a reaction using 2 mol% (*R*,*R*)-Co-salen was scaled up. Thus, 16.7 g of **6** delivered 32.4 g (85% yield) of benzoate (*S*,*S*)-**5** in 85 : 15 er. Crucially, recrystallisation from dichloromethane and heptane gave 12.1 g (32%) of (*S*,*S*)-**5** in 98.5 : 1.5 er.

With benzoate (*S*,*S*)-**5** of high er in hand, conversion into the desired enone (*S*,*S*)-**1** was carried out (Scheme 3). Initial attempts at saponification of benzoate (*S*,*S*)-**5** using KOH led to low yields due to problems in isolating the water-soluble diol product. Instead, use of the polymer-supported Amberlyst A26 (OH form) in MeOH cleaved the ester and removed the need for an aqueous work-up. The crude diol thus obtained was then BDA-protected using butanedione, trimethyl orthoformate and $BF_3{\cdot}Et_2O$ to give **7** in 95% yield over the 2 steps. Subsequent epoxidation proceeded uneventfully to give BDA-protected epoxide **4** in 88% yield.

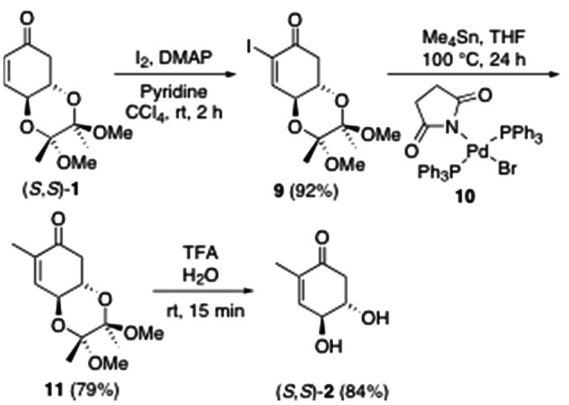
Treatment of epoxide **4** with LDA in THF led to efficient epoxide rearrangement to give allylic alcohol **8** in 89% yield (Scheme 3). The BDA group locks the protected diol in **4** in a *trans*-diequatorial arrangement and the stereospecific preference



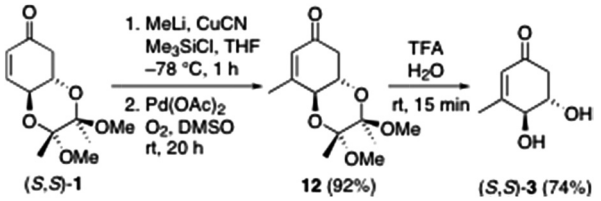
Scheme 3

for removal of an axial proton that is *syn* to the epoxide leads to the generation of a single diastereomeric allylic alcohol.[11] Finally, oxidation using MnO_2 in dichloromethane gave enone (*S*,*S*)-**1** in 98% yield. The absolute stereochemistry of our synthesised enone **1** was established as (*S*,*S*) by comparison of its optical rotation ($[\alpha]_D$ −72.0 (*c* 1.0 in $CHCl_3$)) with that of (*R*,*R*)-**1** ($[\alpha]_D$ +64.4 (*c* 0.39 in $CHCl_3$)) prepared from (−)-quinic acid.[4a] We also confirmed that (*S*,*S*)-**1** was formed in 98.5 : 1.5 er using CSP-HPLC. Our synthesis of the previously unknown enone (*S*,*S*)-**1** proceeds in 6 steps and 14% overall yield.

To demonstrate the synthetic utility of enone (*S*,*S*)-**1**, it was used in the first syntheses of two theobroxide-related natural products, (*S*,*S*)-**2** and (*S*,*S*)-**3** (Fig. 1). α-Methyl-dihydroxyenone (*S*,*S*)-**2** was isolated from the mycelia of *Lasiodiplodia theobromae*, a common pathogenic fungus found in the tropics and subtropics.[7] In terms of biological activity, (*S*,*S*)-**2** showed potato micro-tuber-inducing activity at a concentration of 10^{-3} M which compared well with other theobroxide-related natural products. Our synthesis of (*S*,*S*)-**2** is shown in Scheme 4. First, iodination of enone (*S*,*S*)-**1** was carried out in 92% yield to give iodide **9** which was subjected to Stille coupling with tetramethyltin to produce α-methyl enone **11**. In our hands, use of Pd_2dba_3, $AsPh_3$, CuI and Et_2NH (THF, 100 °C, sealed tube, 24 h)[14] was only moderately successful (32% yield of **11**). In contrast, replacing this cocktail of reagents with NBS palladium precatalyst **10**[15] led to efficient Stille coupling under similar conditions. In this way, α-methyl enone **11** was formed in 79% yield. Then, BDA-deprotection using TFA–water gave naturally occurring



Scheme 4



Scheme 5

(*S*,*S*)-**2** in 84% yield which exhibited $[\alpha]_D$ +141.4 (*c* 0.7 in MeOH) (lit.,[8] $[\alpha]_D$ +128 (*c* 0.21 in MeOH)).

Our attention then turned to structurally related β-methyl enone (*S*,*S*)-**3** (Fig. 1). This enone was also isolated from the pathogenic fungus *Lasiodiplodia theobromae* and showed growth inhibitory effects on seedlings of *Nicotiana tabacum*.[8] Surprisingly, the enone was isolated from *Lasiodiplodia theobromae* as a mixture of enantiomers (~60 : 40 mixture of (*S*,*S*)-**3** and (*R*,*R*)-**3**). The plan was to utilise enone (*S*,*S*)-**1** in a synthesis of the major enantiomer in the naturally occurring mixture. Thus, Me_3SiCl-promoted conjugate addition of lithium dimethylcuprate to enone (*S*,*S*)-**1** gave an intermediate silyl enol ether. Subsequent Saegusa oxidation using catalytic $Pd(OAc)_2$ in the presence of oxygen[16] delivered β-methyl enone **12** in 92% yield (Scheme 5). Then, the BDA group was removed using TFA–water to give (*S*,*S*)-**3** in 74% yield. Our synthesised (*S*,*S*)-**3** exhibited $[\alpha]_D$ +107.0 (*c* 1.0 in MeOH) (lit.,[9] $[\alpha]_D$ +11.3 (*c* 0.01 in MeOH) for a ~60 : 40 mixture of (*S*,*S*)-**3** and (*R*,*R*)-**3** isolated from *Lasiodiplodia theobromae*).

In conclusion, a 6-step, catalytic asymmetric synthesis of butane diacetal-protected (4*S*,5*S*)-dihydroxycyclohexen-1-one (*S*,*S*)-**1** has been developed and utilised in the synthesis of two cyclohexenone natural products isolated from *Lasiodiplodia theobromae*. Enone (*S*,*S*)-**1** can now be considered a useful starting material for future synthetic endeavours.

Acknowledgements

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