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Asymmetric double ring-opening of a C_{2h}-symmetric bis-epoxide: improved enantiomeric excess of the product through enantioselective desymmetrisation and 'proof-reading' steps†

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A new strategy in asymmetric synthesis is described in which the desymmetrisation of a C_{2h}-symmetric molecule is followed by a subsequent enantioselective 'proof-reading' step. The double asymmetric ring-opening of the bis-epoxide (1*R**,3*R**,5*S**,7*S**)-4,8-dioxa-tricyclo[5.1.0.0^{3,5}]octane with azidotrimethylsilane, catalysed by a chiral chromium Salen catalyst, was studied. The reaction involves the initial asymmetric ring-opening of the bis-epoxide to give the intermediate in moderate enantiomeric excess (*ca.* 50% ee); the second ring-opening step yields the required diazido diol, (1*S*,3*S*,4*S*,6*S*)-4,6-diazidocyclohexane-1,3-diol, in 72% yield and 70% ee. The origin of proof reading stems from the diversion of the minor enantiomer of the intermediate to a centrosymmetric by-product, a process which improves the enantiomeric excess of the required product. Using alternative conditions, the reaction was optimised to yield the required product in >98% ee.

Introduction

Reactions which involve two asymmetric steps, such as sequential[1] and parallel[2] kinetic resolutions, can offer significant advantages over their single stepped counterparts. The enantiomeric excess of the products of many desymmetrisation reactions may be improved by kinetic resolution, and careful control of conversion can allow an appropriate balance between the yield and enantiomeric excess of the desymmetrised product to be struck.[3,4] For example, desymmetrisation of the *meso* diacetate **1** using pig liver esterase (PLE) yielded the hydroxy acetate **2** whose enantiomeric excess could be improved by selective hydrolysis of its minor enantiomer (Scheme 1).[3] Such an effect may be considered to 'proof read' the reaction since the second enantioselective step serves to improve on the inherent enantioselectivity of the initial desymmetrisation. Proof-reading effects in desymmetrisation reactions, especially those which also raise issues of diastereoselectivity, have been analysed quantitatively.[4]

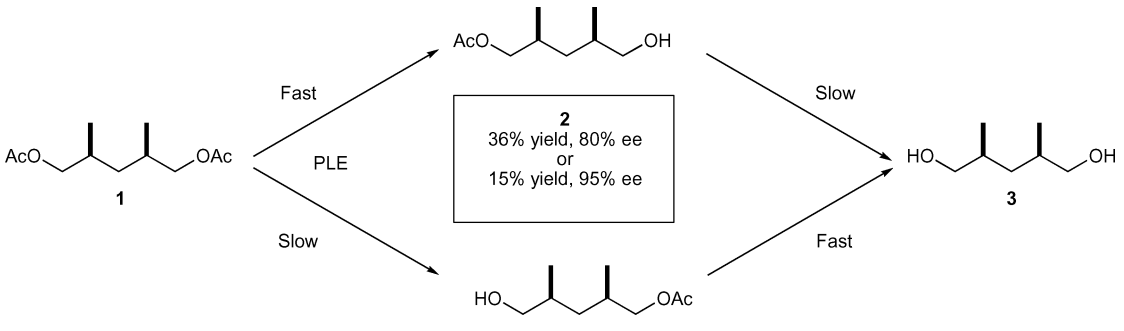
In this paper, we describe the desymmetrisation of a C_{2h}-symmetric bis-epoxide which is also followed by a subsequent proof-reading step. However, in marked contrast to the desymmetrisation of C_s-symmetric molecules such as **1**, the second asymmetric step does not inevitably lead to a *meso* compound. Instead, the final product is still chiral and its enantiomeric excess is influenced by both of the preceding asymmetric steps. In this generic class of desymmetrisation, careful control of conversion is not necessary for the benefits of the proof-reading step to be enjoyed.

† Electronic supplementary information (ESI) available: Experimental procedures and ^{1}H NMR spectra. See http://www.rsc.org/suppdata/ob/b5/b504972e/

Asymmetric double ring-opening of a C_{2h}-symmetric bis-epoxide

In connection with a research programme directed towards novel aminoglycoside analogues, we required the diazido diol **5** (Scheme 2). Although a racemic sample had been previously prepared in high yield,[5] we required an asymmetric synthesis of **5**.[6] The bis-epoxide **4** was, therefore, treated[7] with azidotrimethylsilane and 4 mol% (*R*,*R*)-**7**, and our results are summarised in Table 1. As has been previously observed,[8] the enantiomeric excess of the product, **5**, was optimal at higher reaction concentrations (compare entries 1 and 2). At lower concentrations, the required product **5**, which had 70% ee, was accompanied by significant quantities of the centrosymmetric by-product **6**. It is ironic that the centrosymmetric—and hence achiral[9]—product **6** was only observed when a chiral catalyst was used! With sodium azide in buffered water,[5] only the racemic isomer **5**, the product of *trans*-diaxial opening[10] of the second epoxide, had been observed.

We hypothesised that the formation of the centrosymmetric by-product **6** might have influenced the enantiomeric excess of the required product **5**. The reaction was investigated in more detail under sub-optimal conditions [initial concentration of **4**: 0.5 M in Et_2O] in order that the enantiomeric excesses observed after one and two ring-openings could be easily compared. The concentrations of the starting material **4**, the intermediate and



Scheme 1

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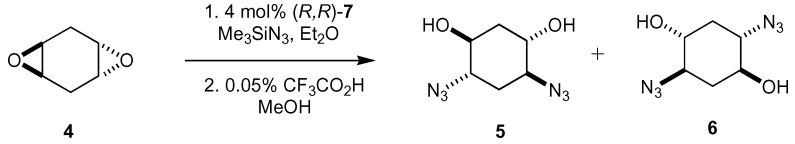


4 5 6

Scheme 2

Table 1 Effect of concentration on asymmetric ring opening of bis-epoxide **4** (see Scheme 2)

	4	**5**		**6**
Entry	Concentration (M; in Et_2O)	Yield[a] (%)	Ee[b] (%)	Yield[a] (%)
1	3.0	49[c]	>98	0
2	0.5	70 (72[d])	70	5 (21[d])

[a] Isolated yield. [b] Determined by chiral analytical HPLC. [c] In a separate experiment, the enantiomeric catalyst (*S*,*S*)-**7** was used; the intermediate was purified by flash chromatography, and the enantiomeric product *ent*-**5** was obtained in 68% overall yield, see Supporting Information†. [d] Yield in parentheses determined by analysis of the crude product by 500 MHz ^{1}H NMR spectroscopy after 72 h. At this point, starting material had been completely consumed.

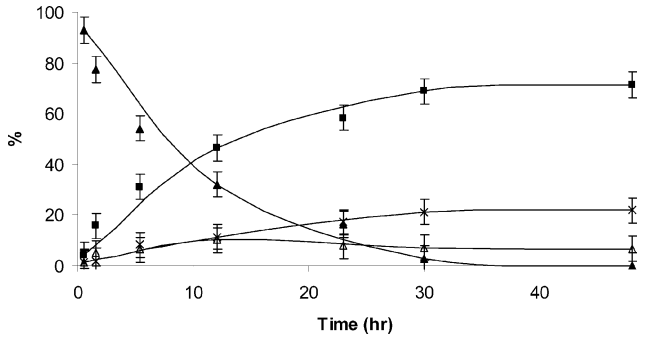
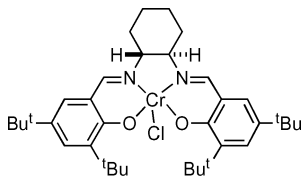


Fig. 1 Relative concentrations of the starting material **4** (solid triangle), the intermediate **12** (open triangle), the required product **5** (solid square), and the centrosymmetric by-product **6** (cross, ×), as a function of time.

the products **5** and **6** were monitored as a function of time by analysis of aliquots by 500 MHz ^{1}H NMR spectroscopy (Fig. 1).

Asymmetric synthesis of the intermediate 12

In order to determine the provenance of the centrosymmetric by-product **6**, an enantiomerically enriched sample of the intermediate **12** was required. Because its concentration was rather low throughout the course of the asymmetric ring-opening of **4** (see Fig. 1), an alternative asymmetric synthesis of **12** was undertaken (Scheme 3). In our hands, treatment of the neat unsaturated epoxide **8** with 7.5 mol% (*R*,*R*)-**7**,[7] and deprotection, gave the azido alcohol **9** in 57% yield and 80% ee.[11] Epoxidation with dimethyldioxirane, generated *in situ* from Oxone™/acetone,[12] gave a 50 : 50 diastereomeric mixture of **10** and **11**, which was separated by preparative HPLC; trimethylsilylation gave the required intermediate **12**.



(*R*,*R*)-**7**

Fate of the intermediate 12

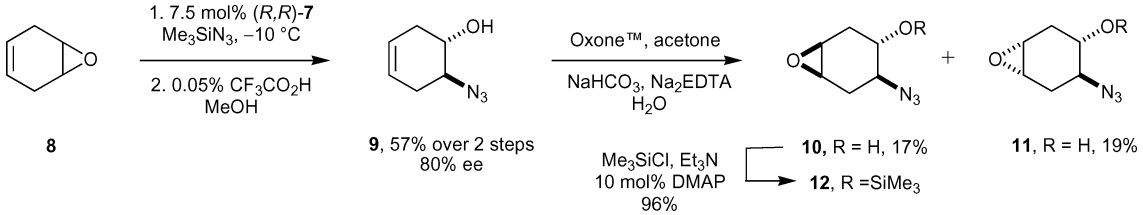
The fate of the major enantiomer of the intermediate was deduced by treating **12** (80% ee; 0.5 M in Et_2O) with azidotrimethylsilane and 4 mol% (*R*,*R*)-**7** (entry 1, Table 2). The 90 : 10 mixture of **12** and *ent*-**12** yielded a 95 : 5 mixture of **5** and **6** in which **5** had 90% ee, *i.e.* a 90 : 5 : 5 mixture of **5**, **6** and *ent*-**5**. Hence, the second asymmetric step *does* improve the enantiomeric excess of the intermediate by diverting about half of the minor enantiomer, *ent*-**12**, to the centrosymmetric by-product **6**. In this case, the enantiomeric excess was improved from 80% ee (in **12**) to 90% ee (in **5**) by reducing the contamination of the major enantiomer of **5** with its antipode.

The most obvious strategy for determining the fate of the minor enantiomer of the intermediate would have been to subject *ent*-**12** to the same reaction conditions. However, a more convenient approach, which yielded exactly the same information, was to subject the same sample of **12** (which had 80% ee) to the reaction catalysed by the enantiomeric catalyst (*S*,*S*)-**7** (entry 2, Table 2). In this way, the fate of the minor enantiomer of the intermediate was deduced unambiguously. With (*S*,*S*)-**7**, a 90 : 10 mixture of **12** and *ent*-**12** yielded a 60 : 40 mixture of **5** and **6** in which **5** had just 60% ee. In other words, (*R*,*R*)-**7** would have converted a 10 : 90 mixture of **12** and *ent*-**12** into a 10 : 40 : 50 mixture of **5**, **6** and *ent*-**5**. Here, the same conclusion is reached independently: with (*R*,*R*)-**7**

Table 2 Fates of enantiomerically enriched samples of the intermediates **12** and *ent*-**12** in ring-openings catalysed by (*R*,*R*)-**7**

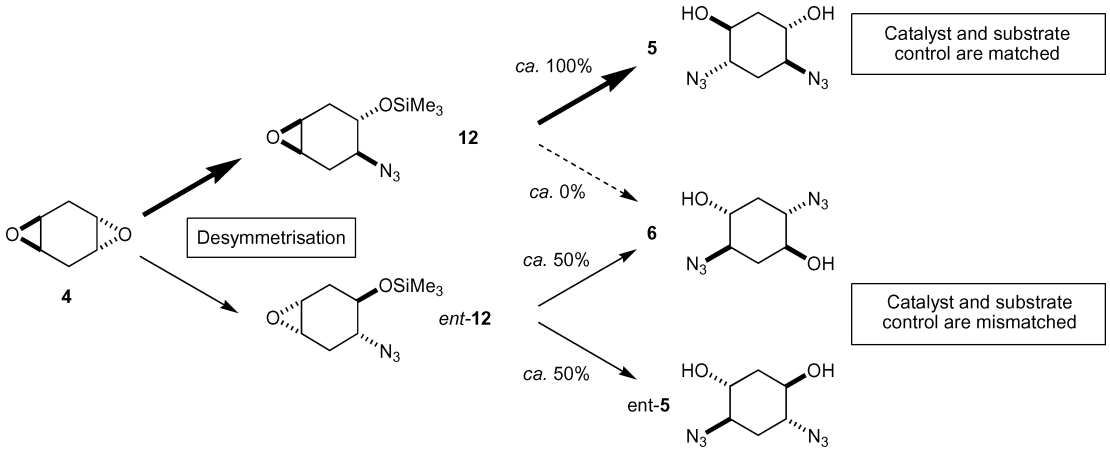
	12		**5** and **6**		
Entry	Ee[a](%)	**12** : *ent*-**12**	**5** + *ent*-**5** : **6**[b,c]	**5** : **6** : *ent*-**5**[c]	**5**, ee[d] (%)
1	80	90 : 10	95 : 5	90 : 5 : 5	90
2[e]	−80[d]	10 : 90	60 : 40	10 : 40 : 50	60

[a] Determined by analysis of a sample of **5** by chiral HPLC, prepared by treatment of **10** with NaN_3 in buffered water and deprotection. [b] Determined by analysis of the crude reaction mixture by 500 MHz ^{1}H NMR spectroscopy. [c] The errors in the ratios of products are ±5%, and are rounded accordingly. [d] Determined by chiral analytical HPLC. [e] The fate of the minor enantiomer of **12** was inferred from the reaction of its enantiomer (which had 80% ee) catalysed by the enantiomeric catalyst (*S*,*S*)-**7**.



8 9, 57% over 2 steps 80% ee 10, R = H, 17% 11, R = H, 19%

Scheme 3



Scheme 4

as the catalyst, about half of *ent*-**12** would be diverted to the centrosymmetric by-product **6**.

The proof-reading effect stems from 'matched' and 'mismatched' influences of the substrate and the catalyst (Scheme 4). After the initial desymmetrisation induced by (*R*,*R*)-**7**, an enantiomerically enriched intermediate **12** is obtained. For the major enantiomer of the intermediate, **12**, catalyst control-inducing opening at the *R*-configured end of the epoxide[7]—and substrate control—the preference for *trans*-diaxial opening[10]—are matched, leading to essentially only the major enantiomer of the product **5**. In contrast, substrate and catalyst control are mismatched for the minor enantiomer of the intermediate, *ent*-**12**, resulting in some diversion to the alternative centrosymmetric product, **6**. As a result, the enantiomeric excess of the required product **5** is higher than that of the intermediate **12**.

Effect of proof-reading on the desymmetrisation of the C_{2h}-symmetric bis-epoxide

The proof-reading effect must also influence the enantiomeric excess of the product **5** prepared by double asymmetric ring-opening of the C_{2h}-symmetric epoxide **4**. With 0.5 M **4** in ether, the required product **5** was obtained in 70% ee (see Table 1). Presumably, the initial desymmetrisation process gave the intermediate **12** in about 50% ee, which was improved by selective diversion of the minor enantiomer to the centrosymmetric by-product.

For single step desymmetrisations, relatively large differences between the activation energies of the competing pathways ($\Delta\Delta G^{\ddagger}$) are required to achieve rather modest improvements in high enantiomeric excesses: for example, an improvement of about 0.4 kcal mol^{-1} in $\Delta\Delta G^{\ddagger}$ is required to increase the enantiomeric excess of a product from 92% ee to 96% ee. The proof-reading mechanism described here can yield similar improvements without requiring an intrinsically more enantioselective reaction. Although the relative importance of catalyst and substrate control may be different under the more concentrated, optimised conditions (3.0 M in ether), it is likely the observed high enantiomeric excess (>98% ee) of the product **5** derives in part from the proof-reading mechanism available.

Summary

In summary, we have described a novel desymmetrisation strategy which benefits from the cooperation of two enantioselective steps. The proof-reading enjoyed increased the enantiomeric excess of the required product **5** considerably. Furthermore, because the required product was produced in the second of the enantioselective steps, careful monitoring of the conversion of the reaction was not necessary.

Experimental

(1*S*,3*S*,4*S*,6*S*)-4,6-Diazidocyclohexane-1,3-diol[5] 5

Azidotrimethylsilane (15.5 mL, 117.2 mmol) was added dropwise to a stirred solution of the diepoxide[13] **4** (6.25 g, 55.8 mmol) and (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butyl-salicylidene)-1,2-cyclohexane-diaminochromium(III) chloride (4 mol%, 705 mg, 1.12 mmol) in ether (19 mL) and stirred for 96 h. The reaction mixture was then concentrated under reduced pressure to give a crude product, which was purified by flash chromatography eluting with petrol–EtOAc 9 : 1 (+1% Et_3N) to give the diazide as a yellow oil. The TMS-protected diol was dissolved in 0.05% TFA in MeOH (80 mL) and stirred for 16 h, evaporated under reduced pressure to give a crude product, which was purified by flash chromatography eluting with 8 : 2 petrol–EtOAc to give product which was recrystallised from CH_2Cl_2–MeOH as the *diol* (4.44 g, 49%) as colourless prisms, mp 98–99 °C (from MeOH–CH_2Cl_2, lit.[5] 96 °C for the racemate); R_f 0.25 (7 : 3, petrol–EtOAc); $[\alpha]_D^{20}$ +5.6 (*c* 1.0 in CH_2Cl_2); Found: C, 36.6; H, 5.20; N, 42.3%; $C_6H_{10}N_6O_2$ requires C, 36.4; H, 5.10; N, 42.4%); ν_{max}/cm^{-1} (thin film) 3368, 2923, and 2087; δ_H (300 MHz; d_4-MeOD) 3.71 (2H, q, *J* 5.8, 1-H and 3-H), 3.45 (2H, q, *J* 5.8, 4-H and 6-H), 1.80 (2H, t, *J* 5.8, 2-CH_2) and 1.73 (2H, t, *J* 5.8, 5-CH_2); δ_C (75 MHz; d_4-MeOD) 69.8, 63.4, 36.9 and 30.5; *m*/*z* (ES^-) 197 (100%, M − H).

The unrecrystallised sample was shown to have >98% ee by chiral analytical HPLC (Chiracel OD column, 4.6 × 250 mm, detecting at 225 nm; 95 : 5 hexane–isopropanol; retention times 32 and 35 min).

In a separate experiment, the enantiomeric catalyst (*S*,*S*)-**7** was used; the intermediate was purified by flash chromatography, and the enantiomeric product *ent*-**5** (which had >98% ee) was obtained in 68% overall yield, see Supporting Information.†

(1*R**,2*R**,4*S**,5*S**)-2,5-Diazidocyclohexane-1,4-diol 6 and NMR reaction monitoring

Azidotrimethylsilane (9.42 mL, 71.4 mmol) was added dropwise to stirred solution of the diepoxide **4** (2 g, 17.85 mmol) and (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butyl-salicylidene)-1,2-cyclohexane-diaminochromium(III) chloride (4 mol%, 451 mg, 0.714 mmol) in ether (36 mL). Samples were taken at regular intervals and petrol–EtOAc–Et_3N (50 : 48 : 2) was added to these which were concentration under reduced pressure, filtered through a pipette of silica eluting with petrol–EtOAc–Et_3N (50 : 48 : 2, care was taken as to only remove the catalyst from the crude reaction mixture), evaporated under reduced pressure to give a crude product which was examined by 500 MHz ^{1}H NMR spectroscopy. After 96 h, the reaction mixture was filtered through a short pad of silica as above, and the crude residue treated with 0.05% TFA in MeOH (50 mL) for

30 min. The reaction mixture was concentrated under reduced pressure to give a crude product, which was recrystallised (twice) from crude (CH_2Cl_2–MeOH) and the mother liquor purified by flash chromatography eluting with 7 : 3 petrol–EtOAc to give the *centrosymmetric diol* **6** (183 mg 5%) as colourless plates, mp 158–160 °C (from CH_2Cl_2–MeOH); R_f 0.2 (7 : 3 petrol–EtOAc) (Found: C, 36.8; H, 5.05; N, 42.3%; $C_6H_{10}N_6O_2$ requires C, 36.4; H, 5.10; N, 42.4%); ν_{max}/cm^{-1} (thin film) 3376, 2939, 2906 and 2105; δ_H (300 MHz; d_4-MeOD) 3.51 (2H, ddd, *J* 12.5, 9.5 and 4.5, 1-H and 4-H), 3.27 (2H, ddd, *J* 12.5, 9.5 and 4.5, 2-H and 5-H), 2.03 (2H, app dt, *J* 12.5 and 4.5, 3-H_A and 6-H_A) and 1.22 (2H, app q, *J* 12.5, 3-H_B and 6-H_B); δ_C (75 MHz, d_4-MeOD) 73.0, 65.3 and 37.7; *m*/*z* (ES^-) 197 (100%, (M − H); (Found: [M − H] 197.0789; $C_6H_{10}N_6O_2$ requires *M* − *H*, 197.0792).

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