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Epoxide rearrangements using dilithiated aminoalcohols as chiral bases

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Abstract—Dilithiated norephedrine and ephedrine have been utilised in the enantioselective rearrangement of cyclic epoxides to allylic alcohols, with dilithiated norephedrine generally giving the best enantioselectivity. Dilithiated ephedrine offered better levels of substrate conversion, but with lower enantioselectivity. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The discovery of new processes for effecting asymmetric transformations still represents one of the major goals of organic chemistry. Of the stoichiometric methods available[1] for asymmetric synthesis, those employing chiral reagents are potentially superior to auxiliary based methods, as transformations can be effected in a single step without the need for the attachment and removal of auxiliary groups. One of the most powerful of these methods, the use of chiral lithium amide bases offers a further advantage in that it is possible to conveniently recycle the base and thus increase its effectiveness and cost efficiency.

Inspection of the available literature on chiral lithium amide bases illustrates that over the last 20 years they have developed into a frequently used methodology, particularly for enolisations of prochiral ketones and rearrangement reactions. The first review of this area by Simpkins[2] covered the literature from 1980 to 1991 and cited 44 references on the use of chiral lithium amide bases. A second comprehensive review by O'Brien[3] covered the period from 1991 to 1997 and cited a further 120 references. It is worth noting that since 1998 these two reviews have been cited nearly 200 times and based on this evidence, there appears to be a continued growth in the interest in this area of chemistry. Some of the most exciting recent developments are the use of catalytic systems that employ chiral lithium amide bases[4] and also the use of magnesium amides[5] in enantioselective deprotonation, both of which will no doubt generate more interest in this fascinating area of chemistry.

In 1993 we reported[6] our findings which related to the enantioselective rearrangement of epoxides utilising dilithiated aminoalcohols. We had proposed that these chiral bases would be suitable based on work performed by Mulzer[7] and on a rationale which arose from consideration of the LIDAKOR bases (lithium amide bases used in conjunction with potassium *tert*-butoxide) developed by Schlosser.[8] We have continued to investigate this area and wish to report our findings in more detail.

2. Results and discussion

During our original experiments[6] we found that the best

Table 1. Rearrangement of epoxides **1a/b** using norephedrine and ephedrine

Entry	Substrate	R	Base[a]	Equivalents	Yield (%)	Ratio[b] **2/3**	ee[b] (%)
1	**1a**	Bn	**4** (−NED)	3	91	93:07	86
2	**1a**	Bn	**5** (+NED)	3	92	10:90	80 (78)
3	**1b**	TBS	**4** (−NED)	3.5	70	79:21	58
4	**1b**	TBS	**5** (+NED)	3.5	77	15:85	70 (65)
5	**1b**	TBS	**6** (−EPH)	4	90	70:30	40
6	**1b**	TBS	**7** (+EPH)	4	90	39:61	22

[a] Conditions: base in THF/hexane at −78°C warmed to rt over 16 h.
[b] Determined from the ^{1}H NMR of the (*R*)-*O*-acetyl mandelate esters. Figures in brackets refer to values determined by optical rotation measurements.

Keywords: enantiospecificity; rearrangements; epoxides; basicity.
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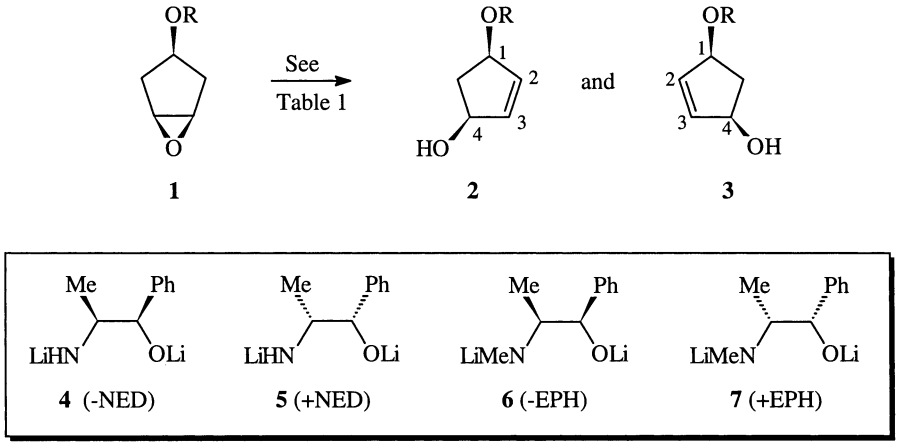
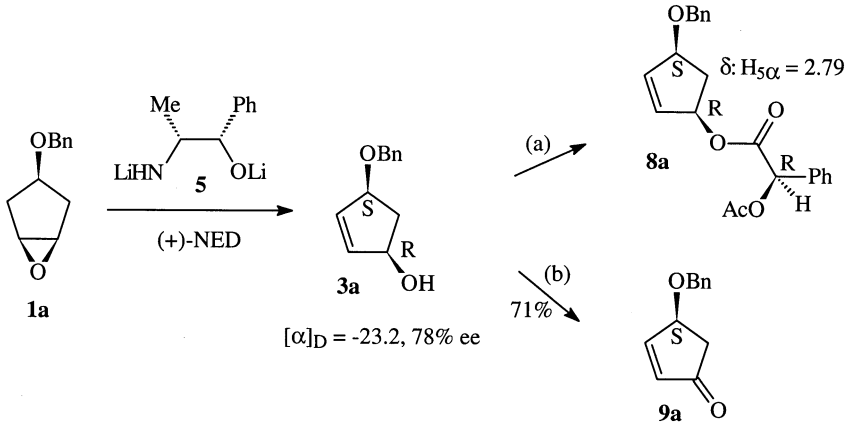


Scheme 1.



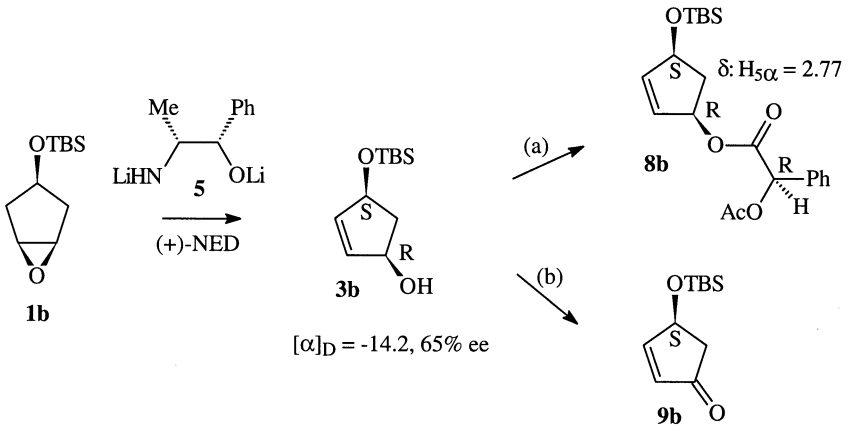
Scheme 2. (a) (*R*)-*O*-acetyl mandelic acid, DMAP, DCCI, DCM, rt, 18 h; quantitative conversion (^{1}H NMR). (b) 2 equiv. PCC, DCM, rt, 1–2 h.

chiral bases for effecting the rearrangement of the *cis*-epoxide **1a** (R=Bn) into the allylic alcohols **2a** or **3a** (R=Bn) were the dilithiated (1*R*,2*S*)-norephedrine **4** (−NED) (Table 1, entry 1) or (1*S*,2*R*)-norephedrine **5** (+NED) (Table 1, entry 2). We found that the optimum conditions for this transformation were when 3 equiv. of base were employed and the reaction was conducted at −78°C and allowed to warm to rt over 16 h (Scheme 1).

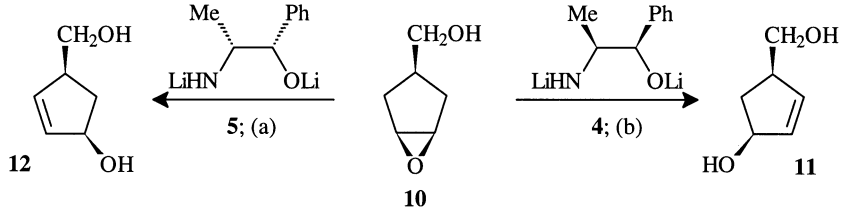
After the publication of our original communication some concern was raised[†] over the assignment of the absolute stereochemistry of the products isolated from the rearrangement of these epoxides. The method we had adopted was based upon work published by Leonard and involved the preparation of (*R*)-*O*-acetyl mandelate derivatives of the alcohols **3**.[9] In order to confirm the assignment of these products we treated a sample of the allylic alcohol **3a** obtained from the rearrangement of **1a** using dilithiated (1*S*,2*R*)-norephedrine **5** with (*R*)-*O*-acetyl mandelic acid to prepare the mandelate derivative **8a** which gave as the major signal a resonance at δ=2.79 ppm for the H-5α proton; by comparison of the relative intensity of this signal with that of the minor diastereoisomer (δ=2.68 ppm) we were able to determine the enantiomeric excess (Scheme 2). The $[\alpha]_D^{20}$ measurement for this alcohol was determined as −23.2 (α=−0.174, c=0.75, $CHCl_3$) which corresponds to an optical purity of 78% based on a reported $[\alpha]^{25}_D$ of −29.9 at 100% ee[10] for the (1*S*,4*R*)-alcohol **3a**. Final confirmation that the compound has this absolute configuration was shown when **3a** was oxidised to the (*S*)-enone **9a** which has an $[\alpha]_D^{20}$ (−45.5, c=0.9, $CHCl_3$) which is of the opposite sign to that reported for the (*R*)-enone ($[\alpha]_D^{16}$=+42, c=0.9, $CHCl_3$).[11] We can thus confirm that the stereoselectivity of the reaction for +NED is selective for the formation of the (1*S*,4*R*)-alcohol **3a** as detailed in Table 1 (entries 1 and 2) and thus the predominant sense of asymmetric induction indicated in our original communication[6] should be reversed.

With the work on the epoxide substrate **1a** in hand, we proceeded to investigate the rearrangement of the corresponding *cis-tert*-butyldimethylsilyloxycyclopentene epoxide **1b** and found that the reaction was less facile than for the benzyl substituted analogue. However when the substrate **1b** was treated with 3.5 equiv. of the dilithiated aminoalcohols **4** or **5** (Table 1, entries 3 and 4), the reaction proceeded to the corresponding allylic alcohols **2a** and **2b** in reasonable yield over the same time-scale and with the same sense of asymmetric induction as in the previous case. In addition, we found that allowing the reaction to proceed for a longer period of time or using more equivalents of base did

[†] Inconsistencies in the sense of asymmetric induction were brought to our attention by Dr D. M. Hodgson.[14,16]



Scheme 3. (a) (*R*)-*O*-acetyl mandelic acid, DMAP, DCCI, DCM, 0°C–rt, 18 h; quantitative conversion (^{1}H NMR). (b) 2 equiv. PCC, DCM, rt, 1–2 h.



Scheme 4. (a) **5** (3 equiv.) THF:PhH (1:1) 0°C–rt 24 h; 57%, 95% ee. (b) **4** (3 equiv.) THF:PhH (1:1) 0°C–rt 24 h; 66%, 95% ee.

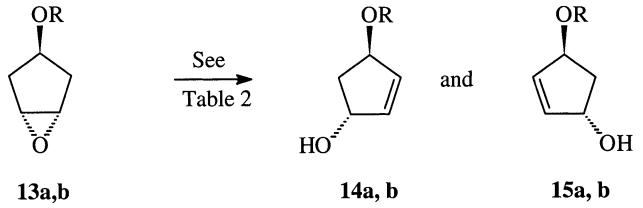
not have a significant effect upon the yield of the reaction or indeed the levels of enantioselectivity. We also investigated the use of the stronger bases and found that if the dilithiated salts of (1*R*,2*S*)-ephedrine **6** (−EPH) or (1*S*,2*R*)-ephedrine **7** (+EPH) were utilised (Table 1, entries 5 and 6) the reactions proceeded in better yield, however the ees were diminished.

With the problems encountered in the determination of absolute configuration of the benzyl substituted series we decided to re-investigate the assignment procedure for the TBS-substituted alcohols. Thus treatment of **1b** (R=TBS) with the dilithiated salt of +NED led to an alcohol which had an $[\alpha]_D^{20}=-14.2$ ($\alpha=-0.074$, $c=0.52$, $CHCl_3$) which corresponds to an optical purity of 65% based on a literature reported[12] value of $[\alpha]_D^{20}=-22$ ($c=0.52$, 100% ee, $CHCl_3$) for the (1*S*,4*R*)-alcohol **3b**. Derivatisation of this alcohol with the previously employed (*R*)-*O*-acetyl mandelic acid gave **8b** which had as the major signal a resonance at $\delta=2.77$ for the H-5α proton, gave an ee of 70%. Interestingly this observation, that the (1*S*,4*R*)-(*R*)-*O*-acetyl mandelate derivative **8b** has a resonance at $\delta=2.77$, contradicts the data reported by Leonard and Hendrie.[9] Final proof of the absolute configuration was obtained when this alcohol was oxidised to the enone **9b**, which gave an $[\alpha]_D^{20}=-38.9$ ($\alpha=-0.389$, $c=1.0$, MeOH) which is of the opposite sign to that reported for the (*R*)-enone ($[\alpha]_D^{20}=+66.6$, $c=1.0$, MeOH)[13] (Scheme 3).

It is possible that steric factors are producing the differences in reactivity and enantioselectivity between the benzyl and *tert*-butyldimethylsilyl protected epoxides, indeed work performed by Hodgson et al.[14] offers some additional support to this premise. They observed that treatment of *meso*-epoxide **10** with the dilithiated salts of either −NED **4**, or +NED **5** led to formation of alcohols **11** or **12**, respectively in exceptionally high ees (>95% ee) (Scheme 4). However it was also observed that trityl- and benzyl-protected derivatives of **10** failed to undergo this rearrangement under similar conditions. This observation indicates that the presence of an internal co-ordination site in close proximity to the point of deprotonation is required to give effective transformation and that introduction of a protecting group precludes both the formation of an anion for direct base co-ordination and may hinder any potential chelation with the oxygen function. When applying these criteria to our systems it is apparent that the benzyl protected epoxide **1a** may offer less steric resistance to the formation of a highly ordered transition state than does the *tert*-butyldimethylsilyl group in compound **1b**.[‡]

In order to investigate this reaction further we prepared the *trans*-epoxides **13a**, **b** and extended our studies to this system. Somewhat disappointingly neither of these epoxides were cleanly converted into the allylic alcohols **14** and **15** under the previously employed conditions (Scheme 5). It was felt that this was possibly due to low basicity on the part of the dilithiated norephedrines and also that the lack of a secondary co-ordination site adjacent to the epoxide might have a significant role to play in this failure to react. We then turned our attention to the use of dilithiated (1*R*,2*S*)-ephedrine **6** (−EPH) and found that treatment of the epoxide **13a** (R=Bn) with four equivalents of this base led to the formation of the allylic alcohols **14a** and **15a** in

[‡] Asami has reported that the rearrangement of the TBDMS derivative of **10** proceeds in poor yield (28%, 72% ee), when compared to the corresponding TBDMS protected *trans*-isomer (74% yield, 83% ee); it was proposed that steric factors were the cause of this difference in reactivity.[15]



Scheme 5.

53% yield (81% based on recovered starting material). The optical yield of this reaction was calculated by oxidation of a sample of the alcohol ($[\alpha]_D^{20}$ of −25.4, c=0.55, $CHCl_3$) to the corresponding (*S*)-enone **9a** ((*R*)-enone $[\alpha]_D^{16}$=+42, c=0.9, $CHCl_3$)[11] which with an $[\alpha]_D^{16}$ of −13.9 (c=0.55, $CHCl_3$) gave an optical purity for the (−)-alcohol **15a** of 34%.

Similarly treatment of the epoxide **13b** (R=TBS) with four equivalents of (1*R*,2*S*)-ephedrine **6** (−EPH) led to the formation of the allylic alcohols **14b** and **15b** in a lower yield of 38% (62% based on recovered starting material), with an optical purity of 36% (($[\alpha]^{25}_D$=−42, c=1.0, $CHCl_3$, lit. $[\alpha]^{25}_D$=−65, c=0.9, $CHCl_3$ at 55% ee).[10] (Table 2). Again it was observed that extending the reaction time or the number of equivalents of base had no significant enhancing effect on either the ee or the yield of the product. Overall the ees for these transformations were low and again probably reflect the differences in structure of the two substrates, in that the *trans*-epoxides lack a secondary co-ordination site for the bases.

3. Conclusions

The overall conclusions from both this work and the available literature are that steric factors acting on both the base and substrate play a considerable role in the efficiency and enantioselectivity of these epoxide rearrangements. In addition a duality of mechanism is also possible in these reactions and care must be taken to investigate the detailed mechanism of any of these processes before arriving at any firm mechanistic conclusions.[16] We are at present involved in the development of these and structurally related bases and their application to further synthetic methodology and it is hoped that with further experimentation, more specific guidelines as to the choice of base or substrate protection criteria will become clear. In addition, the commercially availability of these and other[17] readily available dilithiated bases and their ease of use and re-isolation will add to the significance of these applications.

4. Experimental

4.1. General

Column chromatography was carried out on Kieselgel (230–400 mesh) with the eluant specified. TLC was conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) glass plates. All reactions were conducted in oven-dried apparatus under an atmosphere of argon. Light petroleum refers to the fraction boiling in the range 35–60°C. Dichloromethane, diethyl ether, benzene and THF were dried and distilled before use. Chemical shifts are reported as δ values relative to TMS as an internal standard. ^{1}H NMR spectra were recorded in deuterochloroform on a Bruker AC250 spectrometer. IR were recorded as thin films or as chloroform solutions on a Perkin–Elmer 1600 series instrument. Mass spectra were recorded on a VG Masslab Model 12/253 spectrometer using CI (ammonia) or EI. All compounds were oils unless otherwise stated. Optical rotations were determined on a POLAAR 2001 instrument.

Compounds **1b** and **13b** were prepared by literature methods;[9] allylic alcohols **2/3b**, and **14b/15b** displayed spectral data consistent with that reported previously.[10b]

4.1.1. 4-Benzyloxycyclopentene. Sodium hydride (0.79 g, 19.0 mmol) was added to a cooled (0°C), stirred solution of cyclopenten-4-ol[18] (1.23 g, 14.6 mmol) in THF (50 mL). After effervescence had ceased, benzyl bromide (3.25 g, 19.0 mmol) was added dropwise over 5 min and the resulting mixture was allowed to warm to rt over 4 h. Excess sodium hydride was quenched with methanol (6 mL) and the mixture diluted with water (100 mL), the two layers separated and the aqueous layer extracted with ether (3×25 mL). The combined organic extracts were washed with water (50 mL), dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. Flash chromatography (80:20 petrol/EtOAc; R_f=0.65) gave 4-benzyloxycyclopentene (2.37 g, 95%) as a colourless oil.

δ_H 7.35 (5H, m, Ph), 5.72 (2H, s, H-3, H-4), 4.52 (2H, s, Ph-CH_2), 4.31 (1H, m, H-1), 2.6 (2H, dd, J=15.3, 7.3 Hz, H-2α or H-2β, H-5α or H-5β), 2.45 (2H, dd, J=15.3, 7.3 Hz, H-2α or H-2β, H-5α or H-5β). δ_C 138.5 (C), 128.82 (CH), 128.58 (CH), 127.2 (CH), 78.5 (CH_2), 71.9 (CH), 70.6 (CH_2), 39.1 (CH_2). ν_{max} (liquid film) 3062, 2903 (C–H), 1454 (C=C), 1072 (C–O). m/z (EI); 174 (10%, $[M]^+$). HRMS (CI NH_3) found 174.1045. $C_{12}H_{14}O$ ($[M]^+$) requires: 174.1045.

4.1.2. *cis*-(1a) and *trans*-4-Benzyloxycyclopentan-1,2-epoxide (13a). *m*-Chloroperoxybenzoic acid (9.40 g, 2 equiv., 50–60% purity) was added in one portion to a

Table 2. Rearrangement of epoxides **13a/b** using ephedrine

Entry	Substrate	R	Base[a]	Equivalents	Yield[b]	Ratio[c] **14/15**	OP[c]
1	**13a**	Bn	**6** (−EPH)	4	53 (81)	33:67	34
2	**13b**	TBS	**7** (−EPH)	4	38 (62)	32:68	36

[a] Conditions: base, THF, hexane, −78°C warmed to rt over 16 h.
[b] Yields in brackets represent yields based on recovered starting material.
[c] OP=optical purity, see text.

stirred, cooled (0°C) solution of 4-benzoxycyclopentene (2.37 g, 13.63 mmol) in dichloromethane (10 mL). The mixture was stirred to rt. overnight. Excess *m*-Chloroperoxybenzoic acid was reduced by addition of saturated sodium metabisulphite solution until a negative starch-iodide test was observed; the mixture was then neutralised with calcium hydroxide (2 g) and filtered through celite. After drying over magnesium sulfate and filtration, the filtrate was evaporated under reduced pressure and the crude product was re-dissolved in diethyl ether to precipitate any remaining impurities; filtration, evaporation under reduced pressure and chromatography (75:25 petrol/diethyl ether) gave the *cis*-epoxide **1a** (1.067 g, 45%, R_f=0.13) and the *trans*-product **13a** (1.047 g, 44%, R_f=0.60).

Data for ***1a***: colourless oil δ_H 7.35 (5H, m, Ph), 4.57 (1H, s, Ph-CH_2), 4.07 (1H, t, *J*=7.3 Hz, CH), 3.54 (2H, s, 2×CH), 2.23 (2H, d, *J*=15.3 Hz, 2×CH), 1.97 (2H, dd, *J*=7.3, 15.3 Hz, 2×CH). δ_C 138.3 (C), 128.1 (CH), 127.5 (CH), 127.2 (CH), 77.2 (CH), 70.6 (CH), 57.4 (CH_2), 34.8 (CH_2). ν_{max} (liquid film) 3028, 2924 (C–H), 1496, 1095. *m/z* (CI, NH_3) 191 (90% $[M+H]^+$). HRMS (CI, NH_3): found 191.1072. $C_{12}H_{14}O_2$ ($[M+H]^+$) requires 191.1072.

Data for ***17a***: colourless oil. δ_H 7.35 (5H, m, Ph), 4.56 (2H, s, Ph-CH_2), 3.89 (1H, app quintet *J*=7.0, CH), 3.52 (2H, s, 2×CH), 2.53 (2H, dd, *J*=7.0, 14.0 Hz, 2×CH), 1.73 (2H, dd, *J*=7.0, 14.0 Hz, 2×CH). δ_C=138.3 (C), 128.5 (CH), 127.8 (CH), 75.8 (CH), 72.0 (CH), 55.9 (CH_2), 34.4 (CH_2). ν_{max} (liquid film)?3030, 2922 (C–H), 1494, 1112 (C–O). *m/z* (CI, NH_3) 208 (40%, $[M+NH_4]^+$). HRMS (CI, NH_3): found 208.1338. $C_{12}H_{18}O_2N$, ($[M+NH_4]^+$) requires 208.1338.

4.2. General method for epoxide rearrangements using dilithiated bases

n-Butyl lithium (6–8 equiv. of 1.5–2.1 M hexane solution) was added to a solution of the requisite base (3–4 equiv.) in THF (1 mL per 0.5 mmol of base) at (0°C) under nitrogen; the solution was then stirred for 10 min and cooled to −78–100°C. The epoxide (1 equiv.) dissolved in THF (1 mL per 0.5 mmol) was then added via syringe and the reaction allowed to warm to rt over 16 h. The reaction was quenched by the addition of HCl (2 M, excess) and the reaction diluted with water (ca. 50 mL), extracted with diethyl ether (ca. 2×50 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The products were purified by flash column chromatography (ether/petrol).

4.2.1. Data for (1*R*,4*S*)/(1*S*,4*R*)-*cis*-1-Benzyloxycyclopent-2-en-4-ol 2a/3a (R=Bn). Colourless oils $[\alpha]_D^{20}$(**3a**)=−23.2 (*c*=0.75, $CHCl_3$, 78% optical purity).[10] δ_H=7.30 (5H, m, Ph), 6.06 (2H, m, 2×CH), 4.57 (1H, dd, *J*=4.0, 7.0, CH), 4.63 (1H, d, *J*=15.3 Hz, PhCH), 4.49 (1H, d, *J*=15.3 Hz, PhCH), 4.45 (1H, dd, *J*=4.0, 7.0 Hz, CH), 2.67 (1H, app dt, *J*=14.0, 7.0 Hz, CH), 1.72 (1H, br s, OH), 1.43 (1H, app dt, *J*=14.0, 4.0 CH). δ_C 138.30 (C), 137.22 (CH) 134.13 (CH), 128.43, (2×ArH), 127.84 (2×ArH), 127.69 (ArH), 81.49 (CH_2), 75.01 (CH), 71.07 (CH), 40.94 (CH_2). ν_{max} (liquid film) 3350 (O–H), 2953, 2856 (C–H), 1448 (C=C). *m/z* (CI, NH_3) 208 (100%, $[M+NH_4]^+$). HRMS (CI, NH_3): found 208.1338. $C_{12}H_{18}O_2N$, ($[M+NH_4]^+$) requires 208.1338.

4.2.2. Data for (1*S*,4*S*)/(1*R*,4*R*)-*trans*-1-Benzyloxycyclopent-2-en-4-ol 14a/15a (R=Bn). Colourless oils. $[\alpha]_D^{20}$(**15a**)=−25.4 (*c*=0.55, $CHCl_3$, 34% optical purity) δ_H=7.38–7.20 (5H, m, Ph), 6.12 (1H, dd, *J*=6.5, 1.0 Hz, CH) 6.08 (1H, dd, *J*=6.5, 1.0 Hz, CH), 5.05 (1H, m, CH), 4.82 (1H, m, CH), 4.56 (1H, d, *J*=11.5 Hz, PhCH), 4.40 (1H, d, *J*=11.5 Hz, PhCH), 2.23 (1H, ddd, *J*=14.5, 7.0, 4.0 Hz, CH), 2.00 (1H, ddd, *J*=14.5, 6.5, 3.0 Hz, CH) 1.65 (1H, br s, OH). δ_C 138.33 (C), 137.87 (CH) 134.89 (CH), 128.41, (2×ArH), 127.79 (2×ArH), 127.66 (ArH), 83.05 (CH_2), 76.10 (CH), 71.15 (CH), 40.97 (CH_2). ν_{max} (liquid film)?3394 (O–H), 3030 (3060) 2932, 2862 (C–H), 1453 (C=C). *m/z* (CI, NH_3) 208 (100%, $[M+NH_4]^+$). HRMS (CI, NH_3): found 208.1338. $C_{12}H_{18}O_2N$, ($[M+NH_4]^+$) requires 208.1338.

4.3. General method for determining enantiomeric excesses

A solution of dicyclohexylcarbodiimide (1.5 equiv.) in dichloromethane (ca. 1 mL) was added dropwise to a stirred solution of (*R*)-*O*-acetyl mandelic acid (1.5 equiv.), the protected *cis*-2-cyclopenten-4-ol (1 equiv.) and DMAP (cat) dissolved in dichloromethane (ca. 1 mL per 0.5 mmol substrate) at 0°C and the reaction stirred at rt for 18 h. The white precipitate of dicyclohexyl urea was removed by filtration and the filtrate washed successively with water (5 mL) and copper(II) sulphate solution (5 mL, saturated), dried (magnesium sulfate) and evaporated under reduced pressure. The crude compound was used directly for determination of enantiomeric excess after ensuring that a complete reaction had occurred

^{1}H signals for the H-5α proton at δ=2.79 ppm correspond to the mandelate derivative (**8a**) of the benzylated alcohol **3a** and δ=2.68 ppm for the alcohol **2a**.

^{1}H signals for the H-5α proton at δ=2.77 ppm correspond to the mandelate derivative (**8b**)of the *tert*-butyldimethysilylated alcohol **3b** and δ=2.65 ppm for the alcohol **2b**.

4.4. General method for pyridinium chlorochromate oxidations

Pyridinium chlorochromate (2 equiv.) was added in one portion to a stirred solution of the required alcohol (0.1–0.3 mmol) dissolved in dry dichloromethane (ca. 2 mL). After stirring to completion, ca. 1–2 h (TLC) the reaction was diluted with ether (5 mL), filtered through a pad of silica gel, which was washed with excess ether (ca. 50 mL). After evaporation of the filtrate the products were purified by flash column chromatography (diethyl ether/petrol).

4.4.1. (4*S*)-4-Benzyloxycyclopent-2-en-1-one (9a). 71%. R_f=0.30 (50% diethyl ether in petrol). $[\alpha]_D^{20}$=−45.5, *c*=0.9, $CHCl_3$ ((*R*)-enone is reported as $[\alpha]_D^{16}$=+42, *c*=0.9, $CHCl_3$[11]).

4.4.2. (4*S*)-4-*tert*-Butyldimethylsilyloxycyclopent-2-en-1-one (9b). 55% R_f=0.20 (25% diethyl ether in petrol).

$[\alpha]_D^{20}=-38.9$, $c=1.0$, MeOH ((*R*)-enone is reported as $[\alpha]_D^{20}+66.6$, $c=1.0$, MeOH[13]).

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