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Metal-Dependent Reaction Tuning with Cyclopentylmetal Reagents: Application to the Asymmetric Synthesis of (+)-α-Conhydrine and (*S*)-2-Cyclopentyl-2-phenylglycolic Acid

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Abstract: The reaction profile of the cyclopentyl organometallic reagents with the aliphatic ketones can be tuned to reduction or addition by changing the metal atom. Cyclopentylmagnesium bromide (CPMB) reduces aromatic and aliphatic aldehydes and ketones to the corresponding alcohols without any C–C bond formation and shows good diastereoselectivity in the reduction of the substituted cyclic and polycyclic ketones as well as chiral α-oxygenated aliphatic ketones. However, in the presence of 10 mol% of $ZnCl_2$, the cyclopentylmagnesium halides follow a normal Grignard addition to the ketones to give tertiary alcohols with complete diastereoselectivity. The reductive as well as the addition protocols were used for the asymmetric synthesis of two medicinally important compounds, (+)-α-conhydrine and (*S*)-2-cyclopentyl-2-phenylglycolic acid.

Keywords: aldehydes · asymmetric synthesis · Grignard reaction · ketones · reduction

Introduction

While Grignard and organolithium reagents continue to remain the popular choices for C–C bond formation in organic chemistry,[1,2] their reactions with ketones can follow unusual pathways, such as the reduction of carbonyls to alcohols or the enolization of ketones to give aldol products.[3] The use of alkylmetal reagents with minimum basicity and maximum nucleophilicity[4,5] can enhance the nucleophilicity of the alkylating reagent to achieve the desired addition to the ketones. The reduction of a carbonyl compound by RMgX proceeds by transfer of its α-hydrogen atom to the carbonyl group with simultaneous formation of alkenes from RMgX. With Grignard reagents, prepared especially from a bulky secondary alkyl halide, and where generation of the alkene is sterically favoured, the reduction route can become predominant, and in some cases, overwhelming. Under these conditions, the RMgX can be profitably used as a reducing agent, provided RX is easily available and inexpensive, and the Grignard reagent offers good selectivity in the reduction. At the same time, the use of the latter type of the Grignard reagents for carbon–carbon bond formation remains a challenging task. Herein, we report that the reaction specificity of the organometallic reagents derived from halocyclopentanes can be efficiently tuned by using two different metals. The developed protocols were also used for the syntheses of two biologically active compounds.

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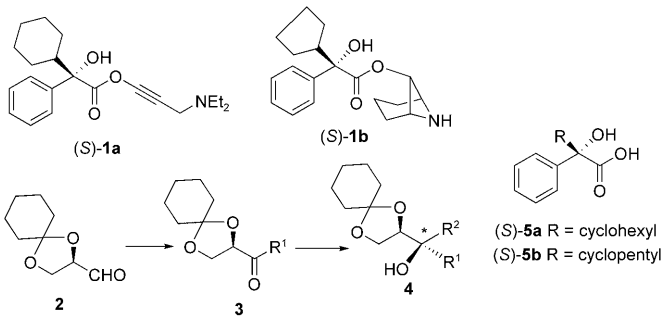
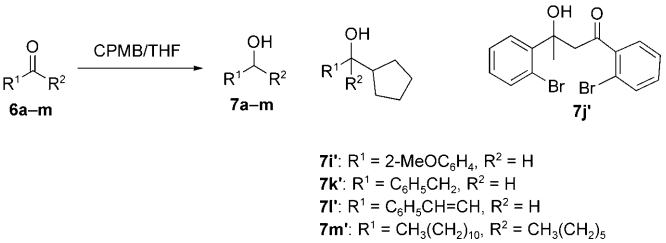
Results and Discussion

The initial motivation for the present work stems from our interest in developing efficient asymmetric syntheses of the esters of tertiary hydroxy acids of compounds such as oxybutynin (**1a**) and **1b**, which are potent muscarinic antagonists for the treatment of centric and peripheral choline dysfunctions.[6] Tertiary hydroxy acids and their derivatives are also important intermediates in the asymmetric synthesis of a variety of medicinal agents[7] and natural products.[8] Hence, we have recently developed[9a] an efficient method for the asymmetric construction of the tertiary carbinol skeleton **4** by the addition of different Grignard reagents to the ketones **3**, amenable from the glyceraldehyde derivative **2** (Scheme 1). The method was subsequently used[9b] for the synthesis of the acid segment **5a** of oxybutynin. It was envisaged that extension of a similar strategy might provide **5b**, which is required for the synthesis of **1b**. However, our attempted addition of cyclopentylmagnesium bromide (CPMB) to aldehyde **2** furnished the reduced alcohol with-



Scheme 1. Asymmetric construction of the tertiary carbinol skeleton **4** for the synthesis of the acid segment **5a** of oxybutynin. R^1, R^2 = alkyl/aryl.

out any trace of the cyclopentyl addition product. This result prompted us to explore the potential of CPMB as a reducing agent for a variety of aldehydes and ketones (Scheme 2).



Scheme 2. The use of CPMB as a reducing agent for a series of aromatic and aliphatic aldehydes and ketones.

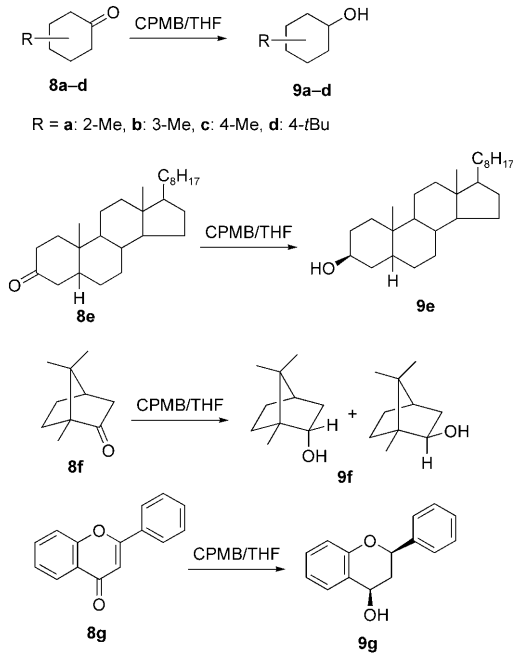
Reactions with acyclic aldehydes/ketones: The studies were carried out with a series of aromatic and aliphatic aldehydes/ketones **6a–m** (Scheme 2) and a 1 M solution of CPMB in THF, and the results are summarized in Table 1. The reaction proceeded uneventfully with aromatic substrates **6a–h** to furnish the corresponding alcohols **7a–h** in excellent yields (91–96%, Table 1, entries 1–8). However, *ortho*-methoxy ketone **6i** furnished the reduced product **7i** (66%) along with the Grignard addition product **7i′** (25%) (Table 1, entry 9). With *ortho*-bromo ketone **6j**, besides the expected reduced product **7j**, a minor amount (4–7%) of the aldol product **7j′** (Table 1, entry 10) was also obtained. Presumably, the *ortho*-methoxy group in **6i** assisted the Grignard addition through chelation. Likewise, the bromo group in **6j** assisted enolization of the $COCH_3$ group leading to the aldol product. Overall, for the unsubstituted, and *m*- and *p*-substituted aryl carbonyl compounds including the bulky ketone, such as **6h**, CPMB was found to be an excellent reducing agent without leading to any C–C bond formation. The presence of an *ortho*-substituent with the capacity to coordinate with CPMB, however, produced some of the normal Grignard addition/aldol compounds as well. With the aliphatic substrates **6k–m**, the reduced products **7k–m** along with different amounts of the cyclopentyl addition products **7k′–m′** were formed (Table 1, entries 11–13). Notably, CPMB did not reduce the olefin group in **6l**, thus showing complete chemoselectivity in the reduction or the addition steps (Table 1, entry 12).

Table 1. Reduction of acyclic aldehydes and ketones by CPMB.

Entry	Substrate	R^1	R^2	Product(s)	Yield [%][a]
1	**6a**	C_6H_5	H	**7a**	95
2	**6b**	4-$MeOC_6H_4$	H	**7b**	91
3	**6c**	4-BrC_6H_4	H	**7c**	91
4	**6d**	3,4-methylene-dioxy-C_6H_3	H	**7d**	95
5	**6e**	C_6H_5	Me	**7e**	93
6	**6f**	4-$MeOC_6H_4$	Me	**7f**	96
7	**6g**	4-BrC_6H_4	Me	**7g**	94
8	**6h**	C_6H_5	Ph	**7h**	95
9	**6i**[b]	2-$MeOC_6H_4$	Me	**7i/7i′**	66/25
10	**6j**[b]	2-BrC_6H_4	Me	**7j/7j′**	78/4–7
11	**6k**[b]	$PhCH_2$	H	**7k/7k′**	41/37
12	**6l**[b]	PhCH=CH	H	**7l/7l′**	26/44
13	**6m**[b]	$CH_3(CH_2)_{10}$	$CH_3(CH_2)_5$	**7m/7m′**	74/15

[a] Yields of isolated products; [b] **6i** and **6k–m** also gave some Grignard addition products, and a minor quantity of aldol product was formed with **6j**.

Next we turned our attention to the reduction of cyclic substituted ketones by CPMB, as this reaction would provide important information on its ability to carry out diastereoselective reduction. For this purpose, ketones **8a–g** (Scheme 3) were used as the substrates (Table 2).



Scheme 3. Reduction of cyclic substituted ketones by CPMB.

Reduction of cyclic ketones: The reduction of a carbonyl function involves the formation of two new bonds: one between a hydride from the reagent and the carbonyl carbon atom, and a second between the metal of the reagent and

Table 2. Reduction of cyclic substituted ketones by CPMB.

Entry	Substrate	Product	Yield [%][a]	*cis*/*trans*
1	2-methylcyclohexanone (**8a**)	**9a**	89	68:32
2	3-methylcyclohexanone (**8b**)	**9b**	91	100:0
3	4-methylcyclohexanone (**8c**)	**9c**	91	0:100
4	4-*tert*-butylcyclohexanone (**8d**)	**9d**	95	0:100
5	cholestanone (**8e**)	**9e**	93	0:100 (β-alcohol)
6	camphor (**8f**)	**9f**	90	22:78
7	flavanone (**8g**)[b]	**9g**	60	92:8

[a] Yields of isolated products; [b] the cyclopentyl addition product (ca. 25%) was also obtained.

the carbonyl oxygen atom. If hydride transfer is more important in the transition state, then steric approach control predominates. However, when metal–oxygen bond formation is more important, product development control is the major factor. With substituted cyclohexanones, this situation would lead to axial or the thermodynamically more stable equatorial alcohols, respectively. However, although apparently an equatorial approach of a bulky reducing agent is considered sterically more favourable, it would also result in a transition state containing an alkoxide ion. The difference between the free energies of the two isomers in such a series is very small (1–3 kcal mol^{-1}), and the product distribution ratio is governed by an even smaller difference ($\leq$ 1 kcal mol^{-1}) in the activation energies of the transition states. Further, besides the steric bulk of the reducing agent,[10a] its ionic character also plays an important role in controlling the above two processes.[10b] The increased covalent character of the reagent such as CPMB would assist greater hydrogen bridging,[10c] which would increase the electrophilic character of the metal, favouring the attack of its carbonyl oxygen atom in the early transition state. In this process, the intermediate stages of the reduction are governed by the steric requirements of the products, and products with an equatorial hydroxy group would result.

In 2-methylcyclohexanone (**8a**), the methyl group is placed equatorially to minimize steric congestion. For its reduction, CPMB would coordinate with the carbonyl group preferentially from the equatorial side because of the absence of steric repulsion between the 2,6-axial hydrogen atoms of the cyclohexane ring and the cyclopentyl group.[11a] Consequently, the subsequent hydrogen transfer to the carbonyl group would result in the predominant formation of *cis*-2-methylcyclohexanol. With CPMB, alcohol **9a** was obtained in 68:32 ratio of *cis* and *trans* isomers.

With 3-methylcyclohexanone (**8b**), the thermodynamically more stable *cis* (diequatorial) isomer was formed exclusively, as evident from the CH(OH) resonances at $\delta = 3.9$–4.0 ppm in ^{1}H NMR spectrum.[11b] This conformer is far more stable than the corresponding diaxial conformer by 3.65 kcal mol^{-1} owing to the steric effect of the methyl group.[11c] With 4-methyl and 4-*tert*-butylcyclohexanone (**8c** and **8d**), the respective alkyl groups are placed too remotely from the carbonyl site to offer any steric restriction, and the approach of the reducing agent from either side of the carbonyl group is equally favourable. Thus, the predominant product of their reduction with CPMB would produce the thermodynamically more stable *trans* alcohols **9c** and **9d**, respectively, as was observed with CPMB.

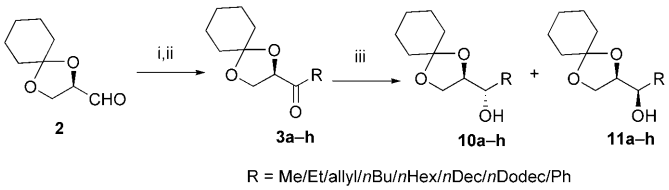
The reducing agent can approach the unhindered ketone group of cholestan-3-one (**8e**) from either an axial or equatorial direction.[11e] In the transition state, however, the bulky alkoxide group cannot occupy a pseudoaxial position, since it would be sterically hindered by the axial hydrogen atoms on C1 and C5. Further, the solvent-induced stabilization of the ion is also hindered in such a position.[11f] Thus, the preferred transition state would be that with the alkoxide group in a pseudoequatorial position, producing predominantly the β-cholestan-3-ol (**9e**). In consonance with this idea, CPMB also exclusively produced β-cholestan-3-ol, as evident from the resonances of the CH(OH) proton at $\delta) = 3.57$ ppm in the ^{1}H NMR spectrum.

Camphor (**8f**), however, presents an interesting case, as one of its bridgehead *gem* dimethyl groups is placed almost above the ketone group. Thus, the course of its reduction is dictated by the 7,7-dimethyl substituents in its rigid bicyclic system, leading to a predominantly *endo* attack. However, the resultant pseudo-*exo* transition state would also be considerably hindered by the bridgehead methyl group. The net result would be the production of a mixture of *exo* (isoborneol) and *endo* (borneol) products. We obtained a mixture of isoborneol/borneol in 78:22 ratio, as revealed from integration of the signal for the carbinol CH proton at $\delta \approx 4.0$ (borneol) and 3.6 ppm (isoborneol) in the ^{1}H NMR spectrum.

4-Flavanone (**8g**) structurally resembles **8b**, although it exists as a skewed chair conformer, somewhat flattened by the C5=C6 double bond and the oxygen atom at the 4 position. Its phenyl substituent at C3 is in a pseudoequatorial position, as revealed from the NMR spectrum. The presence of the fused benzene ring would facilitate an axial approach of CPMB towards its ketone function because of the lack of a 1,3-diaxial interaction, resulting in the formation of an equatorial alcohol. This was also borne out by the fact that reduction of **8g** with CPMB produced the *cis* product **9g** only.[11g]

We have also carried out the reduction of **8a–g** with $NaBH_4$ to confirm our results by comparison of the physical and spectral data of the resultant alcohols (data not shown). CPMB produced better results in most of the cases and provided the alcohols **9a–g** with higher purity, as is evident from their clean ^{1}H NMR spectra.

These above results prompted us to explore the potential of CPMB for diastereoselective reduction (Scheme 4) of chiral ketones **3a–h**, which were used by us earlier for the synthesis of chiral tertiary alcohols.[9a] The reduction strategy was particularly important since the resultant 3-alkylglycerols have been extensively used by us for the synthesis of various bioactive compounds.[12a–j]



Scheme 4. Diastereoselective reduction with CPMB. PCC = pyridinium chlorochromate. i) RMgX/THF or Et_2O; ii) PCC/NaOAc/CH_2Cl_2; iii) CPMB/THF.

Diastereoselective reduction of α-oxygenated chiral ketones with CPMB: For this study, ketones **3a–h**, prepared by using reported procedures,[9a,13] were subjected to reaction with CPMB (Table 3). Irrespective of their alkyl chain length and presence of unsaturation or an aryl group, all the substrates were reduced by CPMB to give mixtures of the *anti*- and *syn*-alkylglycerols **10a–h** and **11a–h** (Table 3, entries 1–8) without the formation of any noticeable Grignard addition product. In all the cases, the reduction proceeded with good *syn* selectivity as revealed from their NMR data.[13] Amongst the substrates, higher *syn* selectivity was obtained with those possessing small chain alkyl groups (**3a–e**). It is worth noting that the addition of RMgX to **2** proceeds with predominant *anti* selectivity.[12] Thus, the present reductive protocol is complementary to the direct Grignard addition route and provides better diastereoselectivity. The diastereomeric products, other than **10h/11h**, were easily separated by conventional column chromatography. The relative ratio of the diastereomeric carbinols **10h/11h** could be easily ascertained by integration of the PhC*H*(OH) resonances in the ^{1}H NMR spectra, which appeared as two doublets at $\delta = 4.51$ (major, *syn*) and 4.93 ppm (minor, *anti*). The result assumes significance given that reaction of PhMgBr with **2** gave an approximately 1:1 mixture of *syn* and *anti* products (data not shown).

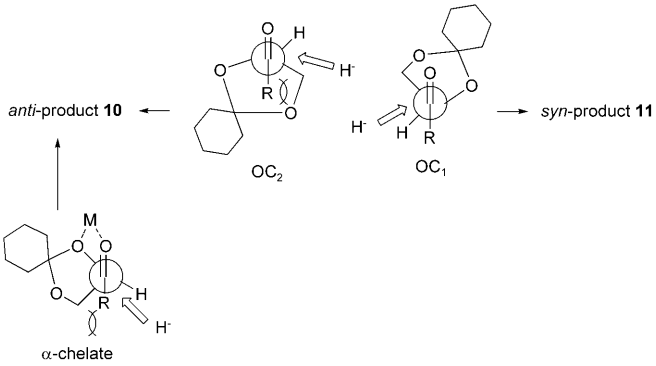
Table 3. Diastereomeric reduction of the chiral ketones **3a–h**.

Entry	Substrate	R	**6/7**[a]	Yield [%][b]
1	**3a**	Me	0:100	91
2	**3b**	Et	20:80	73
3	**3c**	allyl	10:90	80
4	**3d**	*n*Bu	17:83	92
5	**3e**	*n*Hex	16:84	91
6	**3f**	*n*Dec	21:79	90
7	**3g**	*n*Dodec	21:79	91
8	**3h**	Ph	22:78[c]	90

[a] Based on yields of isolated products; [b] total yield of the diastereomers; [c] determined from the ^{1}H NMR spectrum.

Although long known, the reducing action of Grignard reagents has been used only sporadically in preparative organic synthesis.[14a–c] The present results established CPMB as a promising agent for the reduction of both aromatic and aliphatic aldehydes and ketones, as well as diastereoselective reduction of substituted cyclic and α-oxygenated chiral ketones. Earlier, K-selectride was found to offer exclusive *syn* selectivity in the reduction of the substrates **3a–g**.[13] CPMB showed slightly less diastereoselectivity than K-selectride in the reduction of **3a–g**. However, features such as low cost, ease of preparation and the nonhazardous nature of CPMB offer distinct advantages for its use in asymmetric reduction. Evidently, the formation of cyclopentene during the process is the driving force for the reducing action of CPMB. Compared with the sp^3-hybridized cyclopentyl system, cyclopentene is devoid of sterically unfavourable hydrogen–hydrogen eclipsing interactions. This is not the case with cyclohexylmagnesium bromide, which furnishes the normal Grignard addition products with ketones such as **3h**.[9b]

The high *syn* selectivity offered by CPMB in the reduction of **3a–h** suggested that the hydride transfer takes place primarily by the Felkin–Anh model.[15a,b] Between the two possible open-chain Felkin–Anh conformers (Scheme 5), OC_1 has the minimum gauche interaction and hence is thermodynamically more stable than OC_2.[16] Consequently, the reduction takes place through the OC_1 conformation leading to the *syn*-alcohols preferentially. The possibility of a α-chelation controlled reaction leading to the *anti* alcohols would be less probable, considering the bulk of the cyclohexyl and cyclopentyl groups in the substrates and reagent, respectively. With K-selectride, the chelate-controlled reaction could be excluded completely in view of the greater bulk of the reducing agent as well as the presence of K^+ as the counterion. This explains the exclusive diastereoselectivity observed with K-selectride.[13] Given that CPMB is a less bulky Mg-based reducing agent, the reduction might also proceed partially through the chelate-controlled pathway, furnishing the *anti*-alcohols as the minor products (see below).

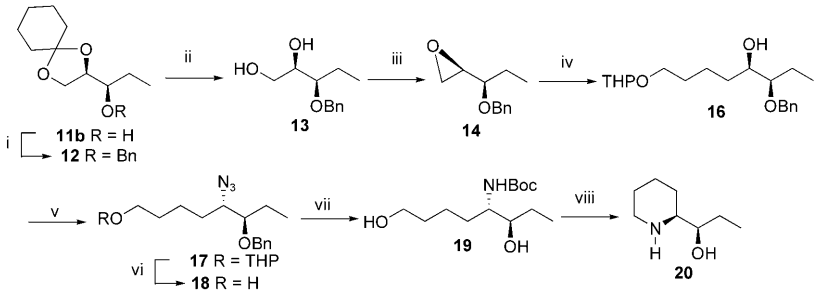


Scheme 5. Felkin–Anh model for the *syn* selectivity of CPMB in the reduction of **3a–h**.

Asymmetric synthesis of (+)-α-conhydrine (20): The 1-hydroxyalkyl substituted piperidine alkaloid, conhydrine (**20**), was considered a suitable target for a first application of the above methodology to natural product synthesis. This structural framework is frequently encountered in natural alkaloids.[17] Conhydrine is a hemlock alkaloid, which is isolated from the seeds and leaves of the poisonous plant *Conium maculatum*, whose extracts were used in ancient Greece for

the execution of criminals.[18] A large number of auxiliary-supported or chiral pool asymmetric syntheses of the unnatural β-conhydrine[19a–h] and (−)-α-conhydrine[20a–e] have been documented.

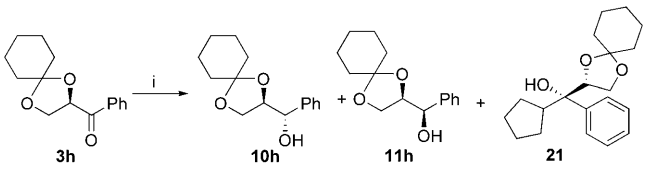
For the synthesis of **20** (Scheme 6), alcohol **11b** was benzylated to **12**, which on treatment with $CuCl_2 \cdot 2H_2O$ in MeOH gave diol **13**. Monotosylation of its primary hydroxy function followed by treatment with base afforded epoxide **14**. Its reaction with the Grignard reagent prepared from bromide **15** in the presence of $CuBr \cdot Me_2S$ proceeded smoothly to furnish **16**. Its invertive azidation with diphenylphosphoryl azide (DPPA) in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine afforded **17**, which on depyranylation gave **18**. This compound was converted into protected amine **19** by a one-pot catalytic hydrogenation in the presence of Boc_2O (Boc = *tert*-butyloxycarbonyl).[21] Its mesylation, and subsequent acidic removal of the Boc group by trifluoroacetic acid (TFA) afforded **20**.



Scheme 6. Synthesis of **20**. THP = tetrahydropyranyl, PPTS = pyridinium *p*-toluenesulfonate, Ms = methanesulfonyl. i) BnBr/NaH/THF/Δ (86%); ii) $CuCl_2 \cdot 2H_2O$/MeOH/Δ (92%); iii) *p*TsCl/py, K_2CO_3/MeOH (75%); iv) $THPO(CH_2)_3Br$ (**15**)/Mg/THF/$CuBr \cdot Me_2S$ (78%); v) DPPA/Ph_3P/DEAD/THF (84%); vi) MeOH/PPTS (92%); vii) H_2/10% Pd-C/EtOAc, Boc_2O (91%); viii) MsCl/Et_3N/−78 °C, TFA/CH_2Cl_2 (67%).

Asymmetric synthesis of (*S*)-2-cyclopentyl-2-phenylglycolic acid (5b): The designated tertiary hydroxy acid **5b** is the key chiral segment of the muscarinic receptor antagonist **1b**,[6a–e] which shows better efficacy than the widely used drug oxybutynin.[6f] Like oxybutynin, (*S*)-**1b** displays a better therapeutic profile than (±)-**1b**, highlighting the importance of chiral drugs.[22]

The synthesis required the addition of a cyclopentyl group to ketone **3h**, for which CPMB was inadequate. It was envisaged that the required task could be accomplished with a cyclopentylmetal reagent containing a soft metal atom. The results of our studies (Scheme 7) in that direction are summarized in Table 4. Although cyclopentylmagnesium chloride (CPMC) was ineffective, cyclopentyllithium (CPLi) furnished the reduced product **10h+11h** (55%) along with the desired alkyl addition product **21** (25%) (Table 4, entries 1 and 2). In light of this result, we attempted the reaction with $(CP)_3MgLi$,[23] prepared in situ from a 1:2 mixture of CPMC and CPLi. $(CP)_3MgLi$ furnished **21** (50%) as the major product along with **10h+11h** (35%) (Table 4, entry 3).



Scheme 7. Addition of a cyclopentyl group to ketone **3h**. i) CPMC or CPLi or CP_3MgLi or CPMC + 10 mol% $ZnCl_2$.

Finally, our attempt with CPMC in the presence of 10 mol% of $ZnCl_2$ gave a satisfactory result, furnishing **21** (80%) and **10h+11h** (15%) (Table 4, entry 4). Presumably, the reaction proceeded via the trialkylzinc(II) ate complex,[24] generated in situ from CPMC and $ZnCl_2$. It was gratifying to note that **21** was formed as a single diastereomer, as revealed from its ^1H and ^{13}C NMR spectra. To the best of our knowledge, this is the first report of absolute diastereocontrol using this reagent.

In the earlier reports,[23,24] the organometallic reagents, prepared from other alkyl/aryl halides and softer metals, were shown to carry out alkyl addition to the ketone function without reducing it. In contrast, our results revealed that the reducing action of the cyclopentylmetal reagents can at best be controlled by varying the reaction conditions but not excluded completely. The unique property of these reagents is also evident from the fact that by following the reported procedure,[24] when we attempted the reaction by stirring a mixture of CPMC and $ZnCl_2$ for 10 min followed by addition of **3h**, only the reduced product was obtained. This result suggested that unlike the other RMgX compounds, reaction of CPMC (or CPMB) with $ZnCl_2$ was very slow, confirming the uniqueness of the latter reagents. The problem was overcome by stirring CPMC and $ZnCl_2$ for 2 h before the addition of **3h**.

The results of Tables 3 and 4 revealed that, other than CPMB and CPMC, the cyclopentylmetal reagents did not

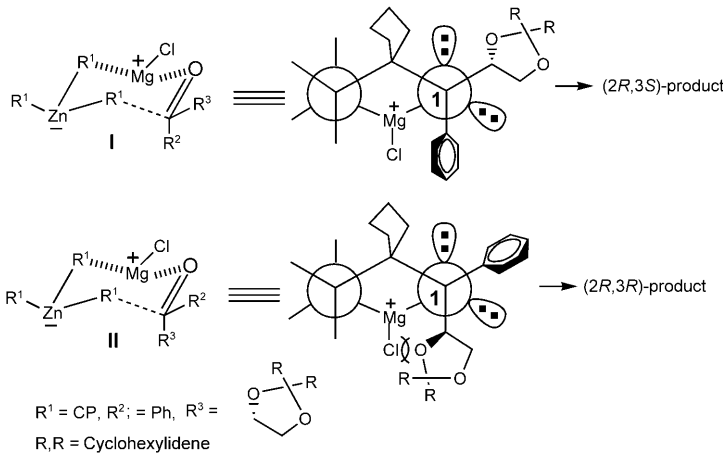
Table 4. Reaction courses of different cyclopentylmetal reagents to **3h**.

Entry	Reagent	*T* [°C]	Yield of **10h+11h** [%][a]	**10h**/**11h**[b]	Yield of **21** [%][c]
1	CPMC	25	90	20:80	0
2	CPLi	−40	55	44:56	25
3	CPMC (1 equiv) + CPLi (2 equiv)	−78	35	45:55	50
4	CPMC + $ZnCl_2$ (10 mol%)	0	15	44:56	80

[a] Total yield of the diastereomers; [b] determined from the ^1H NMR spectrum; [c] based on yields of isolated products.

show any diastereoselectivity in the reduction of **3h**. The presence of a softer metal (Li or Zn) in the other reagents is expected to enable some chelation-controlled reduction, furnishing both *anti*- and *syn*-alcohols **10h** and **11h**.

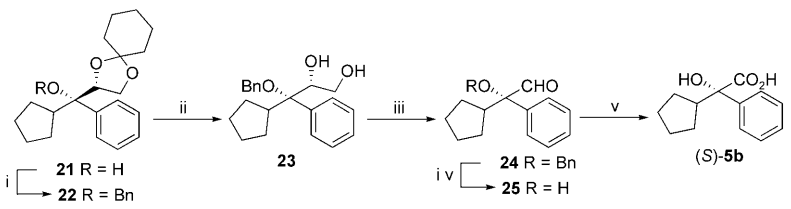
On the basis of our previous results[9a] on the addition of Grignard reagents to chiral ketones, we assigned a 2*R*,3*S* configuration for **21**. This assignment was subsequently confirmed by converting it into the known compound (*S*)-**5b**. The diastereoselectivity of the addition of the trialkylzincate(II) complex can be explained with the help of the possible six-membered transition states (**I** and **II**; Scheme 8).[24]



Scheme 8. Possible six-membered transition states for the addition of trialkylzincate(II) to chiral ketones.

Between these, **I** with R^3 (cyclohexanedioxy group) in the equatorial position is more favoured. The other transition state **II** suffers from extensive diaxial steric interaction between the Cl and R^3 groups. In view of this situation, the reaction proceeds via **I** to furnish (2*R*,3*S*)-**21**.

For the synthesis of **5b** (Scheme 9), alcohol **21** was benzylated[25] to give **22**, which on treatment 3% methanolic HCl gave diol **23**. Cleavage of its diol function with $NaIO_4$ furnished **24**. Its debenzylation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to **25**, followed by oxidation with $NaClO_2$ gave the target acid (*S*)-**5b**. The physical, spectral and optical data of our synthetic sample compared very well with the reported values,[6a–d] confirming its *S* stereochemistry. The enantiomeric excess of (*S*)-**5b** was determined by HPLC (Chiracel OD-H column, mobile phase 95% hexane/5% isopropyl alcohol).



Scheme 9. Synthesis of **5b**. i) NaH/BnBr/Bu_4NI/THF/Δ (96%); ii) 3% HCl/MeOH (87%); iii) $NaIO_4$/MeCN·H_2O (92%); iv) DDQ/CH_2Cl_2 (80%); v) $NaClO_2$/TEMPO/MeCN (77%).

Conclusion

Overall, we have disclosed that by careful choice of metal, the reaction profile of the organometallic reagents derived from halocyclopentanes can be tuned. The cyclopentyl Grignard reagents CPMB or CPMC act exclusively as reducing agents that can be used for the diastereoselective reduction of cyclic/polycyclic as well as chiral α-oxygenated ketones. The reagent can be prepared in any organic chemistry laboratory by using readily available and inexpensive chemicals. It is nonhazardous, stable at room temperature, easily disposable and is a promising substitute for more expensive and exotic reagents such as K-selectride especially for asymmetric reduction of the ketones such as **3a–h**. In the presence of only 10 mol% $ZnCl_2$, however, CPMC furnishes the corresponding tricyclopentylzincate(II), which adds to the ketone to furnish the tertiary alcohols. Using both these protocols, we formulated highly enantiocontrolled syntheses of α-conhydrine and the core acid unit (*S*)-**5b** of a medicinally important compound.

Experimental Section

IR spectra were recorded as films with a JASCO model A-202 spectrophotometer. ^1H (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ with a Bruker AC-200 instrument. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. All organic extracts were dried over anhydrous Na_2SO_4. The chiral ketones **3a–g**[13] and **3h**[9b] were synthesized by following our own reported procedures.

General method for the reaction of CPMB with various carbonyl compounds: To a stirred solution of the aldehyde/ketone (2.0 mmol) in THF (10 mL) was added CPMB (3.0 mmol, 1 M solution in THF) dropwise at room temperature. After stirring the mixture for around 3 h (monitored by TLC), the reaction was quenched with aqueous 10% NH_4Cl, and the mixture was filtered and concentrated in vacuo. The residue was dissolved in Et_2O, and the organic layer was washed with water and brine and dried. Solvent removal in vacuo and column chromatography of the residue afforded the respective alcohols.

1-Cyclopentyl-1-(2′-methoxyphenyl)ethan-1-ol (7i′): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 1.38$–1.68 (m containing a s at $\delta = 1.50$, 11H), 2.54–2.61 (m, 1H), 3.86 (s, 3H), 6.87–6.97 (m, 2H), 7.17–7.33 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta = 25.4$, 25.9, 27.4, 27.5, 31.7, 49.1, 55.4, 76.7, 111.4, 120.7, 127.1, 127.7, 135.7, 156.7 ppm; IR (film): $\tilde{\nu} = 3551$, 3060, 1568 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{20}O_2$: C 76.33, H 9.15; found: C 76.48, H 9.22.

2,4-Di(2′-bromophenyl)-4-oxobutan-2-ol (7j′): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 1.25$ (s, 3H), 1.78 (s, 1H), 3.44 (d, $J = 18.0$ Hz, 1H), 4.47 (d, $J = 18.0$ Hz, 1H), 6.95–7.18 (m, 2H), 7.25–7.62 (m, 5H), 7.94 ppm (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta = 30.8$, 49.6, 73.2, 120.7, 126.2, 129.2, 129.5, 131.3, 131.8, 132.0, 135.4, 146.5, 199.9 ppm; IR (film): $\tilde{\nu} = 3485$, 1675 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{14}Br_2O_2$: C 48.27, H 3.54, Br 40.14; found: C 47.12, H 3.38, Br 39.95.

1-Cyclopentyl-2-phenylethan-1-ol (7k′): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 1.26$–1.96 (m, 10H), 2.55–2.66 (m, 1H), 2.89–2.95 (m, 1H), 3.58–3.67 (m, 1H), 7.25–7.31 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta = 25.7$, 25.9, 28.6, 29.4, 42.8, 45.6, 76.6, 126.3, 128.5, 129.5,

139.0 ppm; IR (film): $\tilde{\nu}=3365\ cm^{-1}$; elemental analysis calcd (%) for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 81.93, H 9.68.

3-Phenylprop-2*E*-en-1-ol (7l): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.76$ (broad, 1H), 4.32 (d, $J=5.6$ Hz, 1H), 6.23 (dt, $J=16.0$, 5.6 Hz, 1H), 6.61 (d, $J=16.0$ Hz, 1H), 7.23–7.40 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=63.6$, 126.5, 127.7, 128.6, 131.0, 136.7 ppm; IR (film): $\tilde{\nu}=3356$, 1603, 971 cm^{-1}.

1-Cyclopentyl-3-phenylprop-2*E*-en-1-ol (7l′): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.25$–1.88 (m, 8H), 2.00–2.12 (m, 1H), 4.07 (t, $J=6.8$ Hz, 1H), 6.23 (dd, $J=15.8$, 6.8 Hz, 1H), 6.57 (d, $J=15.8$ Hz, 1H), 7.23–7.40 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=25.6$, 26.1, 28.9, 29.8, 43.2, 71.7, 125.6, 126.3, 128.1, 128.4, 129.6, 130.4, 136.8 ppm; IR (film): $\tilde{\nu}=3360$, 1598, 967 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{18}O$: C 83.12, H 8.97; found: C 83.27, H 8.81.

Octadecan-7-ol (7m): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.87$ (dist. t, $J=7.0$ Hz, 6H), 1.25 (s, 26H), 1.41–1.50 (m, 4H), 3.52–3.59 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=13.9$, 22.5, 25.5, 29.3, 29.5, 31.8, 37.3, 71.7 ppm; IR (film): $\tilde{\nu}=3595\ cm^{-1}$; elemental analysis calcd (%) for $C_{18}H_{38}O$: C 79.92, H 14.16; found: C 80.08, H 14.15.

7-Cyclopentyloctadecan-7-ol (7m′): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.85$ (dist. t, $J=6.8$ Hz, 6H), 1.25 (brs, 30H), 1.37–1.55 (m, 9H), 1.88–1.94 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=$ 14.1, 22.7, 23.7, 25.6, 26.1, 29.3, 29.6, 30.0, 30.4, 31.9, 37.7, 47.5, 75.2 ppm; IR (film): $\tilde{\nu}=3445\ cm^{-1}$; elemental analysis calcd (%) for $C_{23}H_{46}O$: C 81.58, H 16.79; found: C 81.42, H 13.89.

2-Methylcyclohexanol (9a): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.92$ (d, $J=6.8$ Hz, 3H), 0.99 (d, $J=6.4$ Hz, 3H), 1.19–1.41 (m, 4H), 1.58–1.70 (m, 5H), 1.93 (brs, 1H), 3.06–3.11 and 3.73–3.80 ppm (2× m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=16.8$, 18.5, 20.6, 24.4, 25.1, 25.6, 28.7, 32.4, 33.6, 35.4, 35.8, 40.2, 71.1, 76.4 ppm; IR (film): $\tilde{\nu}=$ 3431 cm^{-1}.

3-Methylcyclohexanol (9b): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.88$ (d, $J=7.2$ Hz, 3H), 1.10–1.41 (m, 4H), 1.54–1.71 (m, 3H), 1.89–1.94 (m, 2H), 3.54 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=22.2$, 24.1, 31.3, 33.9, 35.1, 44.4, 70.4 ppm; IR (film): $\tilde{\nu}=3356\ cm^{-1}$.

4-Methylcyclohexanol (9c): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.89$ (d, $J=6.4$ Hz, 3H), 1.13–1.40 (m, 4H), 1.64–1.71 (m, 3H), 1.87–1.93 (m, 2H), 3.51 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=21.8$, 31.7, 33.3, 35.5, 70.8 ppm; IR (film): $\tilde{\nu}=3349\ cm^{-1}$.

4-*tert*-Butylcyclohexanol (9d): colourless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.82$ (s, 9H), 0.87–1.22 (m, 5H), 1.73–1.78 (m, 2H), 1.95–2.01 (m, 2H), 2.19 (brs, 1H), 3.49 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=25.5$, 27.5, 32.1, 35.7, 47.0, 70.8 ppm; IR (film): $\tilde{\nu}=3413\ cm^{-1}$.

5α-Cholestan-3-ol (9e): white solid; m.p. 140 °C (lit.[10b] 141–147 °C); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.63$ (s, 3H), 0.85 (d, $J=6.8$ Hz, 3H), 0.93 (d, $J=6.8$ Hz, 6H), 1.07–1.45 (m containing a s at δ 1.42, 24H), 1.50–1.92 (m, 10H), 2.26 (s, 1H), 3.42–3.63 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=11.8$, 12.0, 18.4, 20.9, 22.3, 22.5, 23.6, 23.9, 27.7, 27.9, 28.4, 29.4, 31.1, 31.8, 35.2, 35.5, 35.9, 36.7, 37.8, 39.2, 39.7, 42.3, 44.6, 54.1, 55.9, 56.2, 71.0 ppm; IR (film): $\tilde{\nu}=3607\ cm^{-1}$.

Isoborneol/borneol (9f): white solid; m.p. 195 °C; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.80$ and 0.84 (2× s, 3H), 0.88 (s, 3H), 0.92 (s, 3H), 1.28–1.39 (m, 3H), 1.60–1.76 (m, 2H), 1.86 (s, 1H), 2.03–2.08 (m, 1H), 2.27–2.36 (m, 1H), 3.43–3.61 (isoborneol) and 3.95–3.97 ppm (borneol) (two m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=11.3$, 13.3, 18.6, 20.0, 20.4, 25.8, 27.2, 28.2, 29.6, 33.8, 38.9, 40.3, 45.0, 46.3, 48.9, 49.4, 77.3, 79.8 ppm; IR (film): $\tilde{\nu}=3466\ cm^{-1}$.

Flavan-4-ol (9g): white solid; m.p. 102 °C (lit.[11g] 99 °C); ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta=1.67$ (s, 1H), 2.15–2.23 (m, 1H), 2.51- 2.62 (m, 1H), 5.08–5.16 (m, 1H), 5.20 (dd, $J=11.4$, 1.4 Hz, 1H), 6.88–7.03 (m, 2H), 7.18–7.25 (m, 1H), 7.35–7.53 ppm (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta=39.9$, 65.7, 77.1, 116.7, 121.0, 125.7, 126.1, 127.0, 128.2, 128.7, 129.1, 140.5, 154.5 ppm; IR (film): $\tilde{\nu}=3299\ cm^{-1}$.

(1*S*/*R*,2*R*)-2,3-Cyclohexylidenedioxy-1-phenylpropan-1-ol (10h/11h): colourless oil; $[\alpha]_D^{22}=+11.00$ ($c=0.604$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.22$–1.30 (m, 4H), 1.52–1.69 (m, 6H), 2.06 (brs, 1H), 3.67–3.78 (m, 2H), 3.82–3.95 and 4.16–4.31 (two m, 1H), 4.50 and 4.93 ppm (2× d, 72:28, $J=7.2$ and 4.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=$ 23.7, 24.0, 25.1, 34.7, 34.9, 36.1, 36.5, 64.4, 65.5, 72.9, 75.9, 79.1, 79.8, 110.1, 110.6, 126.1, 127.0, 127.6, 128.2, 128.5, 139.8, 140.1 ppm; IR (film): $\tilde{\nu}=3625$, 1589 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{22}O_2$ (246.16): C 78.01, H 9.00; found: C 77.79, H 8.88.

(2*R*,3*R*)-3-Benzyloxy-1,2-cyclohexylidenedioxypentane (12): To a stirred suspension of pentane-washed NaH (0.864 g, 18.00 mmol, 50% suspension in oil) in THF (30 mL) was added **11b** (3.0 g, 15.00 mmol) in THF (20 mL) at room temperature over a period of 30 min. After reflux of the mixture for 1 h, BnBr (3.70 g, 21.64 mol) in THF (20 mL) was added, and the mixture was heated at reflux for an additional 1 h, then brought to room temperature. The mixture was poured into ice-cold water, the organic layer was separated, and the aqueous portion was extracted with diethyl ether. The combined organic extracts were washed with water and brine and dried. Solvent removal in vacuo gave a residue, which was purified by column chromatography (silica gel, 0–10% EtOAc/hexane) to afford **12** (3.74 g, 86%): colourless oil; $[\alpha]_D^{22}=+29.52$ ($c=1.03$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.95$ (t, $J=6.8$ Hz, 3H), 1.26–1.48 (m, 4H), 1.53–1.76 (m, 8H), 3.27–3.40 (m, 1H), 3.56–3.69 (m, 1H), 3.82–3.98 (m, 1H), 4.15–4.22 (m, 1H), 4.56–4.85 (m, 2H), 7.17–7.40 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=9.3$, 23.9, 24.0, 25.2, 35.0, 36.3, 66.1, 72.6, 77.7, 80.3, 109.5, 127.6, 127.8, 128.3, 138.7 ppm; IR (film): $\tilde{\nu}=3088$, 1102 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{26}O_3$ (290.19): C 74.45, H 9.02; found: C 74.63, H 8.86.

(2*R*,3*R*)-3-Benzyloxypentan-1,2-diol (13): A mixture of **13** (3.70 g, 12.76 mmol) and $CuCl_2{\cdot}H_2O$ (20 mol%) in MeOH (30 mL) was stirred at approximately 50 °C until **12** disappeared (as monitored by TLC, ca. 4 h). The mixture was concentrated in vacuo, treated with water (25 mL) and extracted with EtOAc (3×25 mL). The combined organic extracts were washed with water (2×10 mL) and brine (1×5 mL), dried and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, 0–5% MeOH/$CHCl_3$) to obtain pure **13** (2.46 g, 92%): colourless oil; $[\alpha]_D^{22}=+29.12$ ($c=1.36$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.95$ (t, $J=6.8$ Hz, 3H), 1.49–1.68 (m, 2H), 1.71–1.94 (brs, 2H), 3.42–3.52 (m, 1H), 3.67–3.80 (m, 3H), 4.58 (q, $J=11.6$ Hz, 2H), 7.33 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=10.2$, 21.6, 65.6, 70.9, 75.7, 81.2, 127.6, 128.0, 128.3, 138.9 ppm; IR (film): $\tilde{\nu}=3406$, 1067 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{18}O_3$ (210.13): C 68.54, H 8.63; found: C 68.48, H 8.48.

(2*R*,3*R*)-3-Benzyloxy1-1,2-epoxypentane (14): To a cooled (−5 °C) and stirred solution of **13** (2.4 g, 11.43 mmol) and pyridine (1.1 mL, 13.71 mmol) in CH_2Cl_2 (20 mL) was added *p*-toluenesulfonyl chloride (TsCl, 2.18 g, 11.43 mmol). The mixture was stirred at −5 °C for 3.5 h and at 0 °C overnight, then poured into water and extracted with $CHCl_3$. The organic extract was washed with water and brine, dried and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 0–10% EtOAc/hexane) to afford the pure monotosylate (3.72 g, 89%): colourless oil; $[\alpha]_D^{22}=+2.64$ ($c=1.06$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.85$ (t, $J=6.4$ Hz, 3H), 1.47–1.74 (m, 2H), 1.80 (broad, 1H), 2.41 (s, 3H), 3.39–3.51 (m, 1H), 3.72–3.85 (m, 2H), 3.98–4.12 (m, 1H), 4.15–4.22 (m, 1H), 4.36–4.68 (m, 1H), 7.24–7.32 (m, 7H), 7.78 ppm (d, $J=8.2$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=9.8$, 21.6, 22.6, 69.6, 70.9, 72.3, 79.4, 127.9, 128.4, 129.8, 129.9, 132.6, 138.0, 145.0 ppm; IR (film): $\tilde{\nu}=3454$, 1599, 1372, 1178 cm^{-1}.

To a stirred suspension of anhydrous K_2CO_3 (2.11 g, 15.29 mmol) in MeOH (30 mL) was added the above tosylate (3.72 g, 10.22 mmol). The mixture was stirred for 2 h and then filtered. The residue was washed with diethyl ether (2×10 mL), and the combined filtrates were concentrated in vacuo. The residue was taken up in Et_2O (40 mL) and washed with water and brine, dried and concentrated in vacuo to obtain the crude product, which was purified by column chromatography (silica gel, 0–5% Et_2O/hexane) to furnish **14** (1.64 g, 75% from **13**): colourless oil; $[\alpha]_D^{22}=+12.04$ ($c=1.16$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta=$ 0.97 (t, $J=7.2$ Hz, 3H), 1.54–1.73 (m, 2H), 2.72–2.77 (m, 2H), 2.80–2.94 (m, 1H), 3.15–3.23 (m, 1H), 4.62 (q, $J=12.0$ Hz, 2H), 7.32 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=10.2$, 21.8, 41.7, 57.7, 65.4, 80.4, 127.6,

128.0, 128.3, 138.9 ppm; IR (film): $\tilde{\nu}=3062$, 1108 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{16}O_2$ (192.12): C 74.97, H 8.39; found: C 75.14, H 8.54.

(5*R*,6*R*)-1-Tetrahydropyranyloxy-6-benzyloxyoctan-5-ol (16): To a cooled (−10 °C) and stirred solution of the Grignard reagent prepared from the bromide **15** (2.23 g, 10.0 mmol) and Mg (0.288 g, 12.0 mmol) in THF (40 mL) was added $CuBr{\cdot}Me_2S$ (5 mol %) followed by **14** (1.60 g, 8.33 mmol) in THF (15 mL). The mixture was stirred at the same temperature for 6 h and then at 0 °C for 12 h. The reaction was quenched with aqueous saturated NH_4Cl (ca. 2 mL), and the organic extract was separated and dried. Solvent removal followed by column chromatography (silica gel, 0–15 % EtOAc/hexane) furnished **16** (2.18 g, 78 %): colourless oil; $[\alpha]_D^{22}=+10.93$ ($c=1.08$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.95$ (t, $J=6.4$ Hz, 3H), 1.26–1.77 (m, 14H), 2.04 (br s, 1H), 3.37–3.48 (m, 3H), 3.54–3.62 (m, 1H), 3.72–3.86 (m, 2H), 4.49–4.71 (m, 3H), 7.34 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=9.0$, 19.6, 22.4, 25.5, 29.7, 30.7, 31.7, 62.3, 67.6, 71.8, 72.0, 72.3, 72.6, 80.9, 98.8, 127.9, 128.0, 128.4, 138.1 ppm; IR (film): $\tilde{\nu}=3423$, 1454, 1031 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{32}O_4$ (336.23): C 71.39, H 9.59; found: C 71.48, H 9.64.

(5*S*,6*R*)-1-Tetrahydropyranyloxy-5-azido-6-benzyloxyoctane (17): To a solution of **16** (2.18 g, 6.49 mmol) and triphenylphosphine (1.88 g, 7.18 mmol) in dry THF (30 mL) at 0 °C was added DEAD (1.04 g, 7.18 mmol) dropwise followed by DPPA (1.98 g, 7.18 mmol). The mixture was stirred at 0 °C for 30 min and at room temperature for 3 h. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water and brine and dried. Solvent removal in vacuo followed by column chromatography (silica gel, 0–10 % EtOAc/hexane) of the residue gave **17** (1.97 g, 84 %): colourless oil; $[\alpha]_D^{25}=+6.61$ ($c=1.00$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.91$ (t, $J=6.8$ Hz, 3H), 1.24–1.85 (m, 14H), 3.25–3.74 (m, 4H), 3.80–3.88 (m, 2H), 4.48–4.62 (m, 3H), 7.33 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=$ 9.6, 19.4, 23.5, 25.4, 27.0, 29.6, 30.7, 31.2, 51.2, 62.3, 67.2, 67.5, 72.5, 82.4, 98.8, 127.4, 127.6, 128.0, 128.3, 128.6, 138.3 ppm; IR (film): $\tilde{\nu}=2099$, 1454, 1181 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{31}N_3O_3$ (361.24): C 66.45, H 8.64, N 11.62; found: C 66.48, H 8.78, N 11.41.

(5*S*,6*R*)-5-Azido-6-benzyloxyoctan-1-ol (18): A solution of **17** (1.90 g, 5.26 mmol) and pyridinium *p*-toluenesulfonate (0.1 g) in MeOH (25 mL) was heated at reflux for 3 h. Most of the solvent was removed in vacuo, and the residue was diluted with H_2O and extracted with EtOAc. The organic extract was washed with H_2O and brine and dried. Solvent removal in vacuo followed by column chromatography (silica gel, 0–15 % EtOAc/hexane) of the residue gave **18** (1.34 g, 92 %): colourless oil; $[\alpha]_D^{25}=+7.17$ ($c=1.30$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.96$ (t, $J=6.8$ Hz, 3H), 1.26–1.32 (m, 4H), 1.67–1.79 (m, 4H), 3.31–3.61 (m, 4H), 4.62 (q, $J=12.0$ Hz, 2H), 7.40 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=9.6$, 23.3, 29.4, 29.7, 51.6, 63.1, 72.5, 80.1, 127.9, 128.5, 137.8 ppm; IR (film): $\tilde{\nu}=3448$, 2102 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{23}O_2N_3$ (277.18): C 64.95, H 8.36, N 15.15; found: C 65.14, H 8.40, N 15.06.

(5*S*,6*R*)-5-*tert*-Butoxycarbonylaminoctan-1,6-diol (19): To a suspension of 10 % Pd-C (50 mg) saturated with H_2 in EtOAc (20 mL) was added **18** (0.500 g, 1.81 mmol) and Boc_2O (0.5 mL, 2.17 mmol), and the mixture stirred for 24 h. The mixture was passed through a small pad of celite, and the eluent concentrated in vacuo to obtain a residue, which on column chromatography (silica gel, 0–30 % EtOAc/hexane) gave **19** (0.430 g, 91 %): colourless oil; $[\alpha]_D^{25}=+9.12$ ($c=0.81$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.96$ (t, $J=6.8$ Hz, 3H), 1.25–1.37 (m containing a s at δ 1.34, 13H), 1.71–1.87 (m, 4H), 3.54–3.72 (m, 3H), 3.81–3.86 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=10.1$, 19.4, 23.2, 29.5, 29.7, 60.2, 63.8, 72.5, 78.1, 155.6 ppm; IR (film): $\tilde{\nu}=3512$ cm^{-1}.

(+)-α-Conhydrine (20): To a cooled (−78 °C) and stirred solution of **19** (0.420 g, 1.60 mmol) in CH_2Cl_2 (10 mL) was injected methanesulfonyl chloride (0.15 mL, 1.92 mmol) followed by triethylamine (0.270 mL, 1.92 mmol). The mixture was stirred for 1 h at the same temperature, and then aqueous ammonium chloride (3 mL) was added. The mixture was washed with brine, dried and concentrated in vacuo, and the residue passed through a small pad of silica gel.

To a cooled (0 °C) and stirred solution of the above product in dry CH_2Cl_2 (5 mL) was added TFA (0.3 mL, 0.143 mmol). The reaction mixture was stirred at room temperature for 18 h, aqueous saturated $NaHCO_3$ was added, and the mixture was extracted three times with $CHCl_3$. The combined organic extracts were washed with brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0–10 % $CH_3OH/CHCl_3$) to give **20** (0.055 g, 67 %). viscous liquid; $[\alpha]_D^{22}=+8.33$ ($c=0.81$, EtOH), (lit. [18e] $[\alpha]_D^{25}=+8.0$ ($c=$ 1.7, EtOH)); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=0.96$ (t, $J=7.0$ Hz, 3H), 1.36–1.47 (m, 6H), 1.55–1.63 (m, 2H), 2.44 (br s, 2H), 2.86–2.89 (m, 1H), 3.06–3.17 (m, 1H), 3.14–3.19 (m, 1H), 3.44–3.49 (m, 1H), 3.52–3.64 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=13.8$, 19.4, 24.8, 25.7, 25.4, 56.3, 67.2, 70.0 ppm; IR (film): $\tilde{\nu}=3507$ cm^{-1}.

Procedure for reaction of 3h with CPLi: To a stirred solution of the CPLi [prepared from chlorocyclopentane (0.658 g, 6.33 mmol) and Li (0.044 mg, 6.33 mmol)] in THF (20 mL) was added **3h** (0.519 g, 2.11 mmol) in THF (10 mL) at −40 °C. After stirring the mixture for 4 h at the same temperature, the reaction was quenched with aqueous saturated NH_4Cl. The organic layer was separated, the aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine and dried. Removal of the solvent in vacuo and column chromatography (silica gel, 0–15 % EtOAc/hexane) of the residue furnished pure **10h**/**11h** and **21**.

Procedure for reaction of 3h with $(CP)_3MgLi$: To a cooled (−78 °C) solution of CPLi (10.0 mmol, 1 M in THF) was added CPMC (5.0 mmol, 1 M in THF) under argon. After stirring the solution at the same temperature for 1 h, **3h** (0.684 g, 2.78 mmol) in THF (10 mL) was added. The mixture was stirred at −78 °C for 5 h and treated with aqueous saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, 0–15 % EtOAc/hexane) to furnish the pure products.

(1*S*,2*R*)-1-Cyclopentyl-1-phenyl-2,3-cyclohexylideneglycerol (21): To a stirred solution of CPMC (1.0 M in THF, 11 mL, 11 mmol) was added $ZnCl_2$ (0.149 g, 10 mol %) at room temperature under argon. After stirring the mixture for 2 h, the solution was cooled to 0 °C, and **3h** (2.03 g, 8.25 mmol) was added. The mixture was stirred for 4 h at 0 °C, quenched with aqueous saturated NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0–15 % EtOAc/hexane) to give **21** (2.09 g, 80 %) along with **10**/**11h** (0.307 g, 15 %). **21**: colourless oil; $[\alpha]_D^{25}=+5.88$ ($c=1.99$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.15$–1.68 (m, 17H), 1.68–1.91 (m, 1H), 2.23 (br s, 1H), 2.27–2.50 (m, 1H), 3.78 (t, $J=7.2$ Hz, 1H), 4.03 (t, $J=7.2$ Hz, 1H), 4.51 (t, $J=7.2$ Hz, 1H), 7.16–7.38 (m, 3H), 7.38–7.55 ppm (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=23.8$, 23.9, 24.8, 25.2, 26.4, 27.0, 35.0, 35.7, 47.1, 65.1, 76.9, 79.6, 109.3, 126.6, 126.7, 127.5, 142.9 ppm; IR (film): $\tilde{\nu}=3408$, 3060, 1588, 1480 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{28}O_3$ (316.20): C 75.91, H 8.92; found: C 75.82, H 8.78.

(1*S*,2*R*)-1-Benzyloxy-1-cyclopentyl-1-phenyl-2,3-cyclohaxanedioxypropane (22): To a stirred suspension of pentane-washed NaH (0.091 g, 3.79 mmol) in THF (10 mL) was added **21** (1.0 g, 3.16 mmol) in THF (30 mL) and the mixture was heated at reflux for 2 h. The mixture was brought to room temperature, benzyl bromide (0.648 g, 3.79 mmol) and Bu_4NI (0.12 g) were added, and the mixture was heated at reflux further for 12 h. The reaction was quenched with aqueous saturated NH_4Cl, the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated to obtain a residue, which on column chromatography (silica gel, 0–10 % EtOAc/hexane) furnished pure **22** (1.23 g, 96 %): colourless oil; $[\alpha]_D^{24}=+4.46$ ($c=0.81$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.17$–1.75 (m, 17H), 1.75–1.96 (m, 1H), 2.21–2.47 (m, 1H), 3.96–4.24 (m, 1.5H), 4.58 (s, 2H), 4.47–4.93 (m, 1.5H), 7.13–7.57 ppm (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=23.9$, 24.0, 24.8, 25.1, 25.3, 26.8, 27.8, 33.7, 36.0, 49.3, 66.3, 72.1, 78.8, 83.1, 109.1, 126.4, 126.8, 126.9, 127.4, 127.6, 127.8, 128.3, 139.3, 140.0 ppm; IR (film): $\tilde{\nu}=3087$, 1585, 1495 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{34}O_3$ (406.25): C 79.76, H 8.43; found: C 79.61, H 8.45.

(2*R*,3*S*)-3-Benzyloxy-3-cyclopentyl-3-phenylpentane-1,2-diol (23): A solution of **22** (0.812 g, 2 mmol) in MeOH (20 mL) containing 3 % HCl was

stirred at room temperature until completion of the reaction (as monitored by TLC, 5.0 h). After the acid was neutralized with aqueous 10% $NaHCO_3$, the mixture was concentrated in vacuo, and the residue was chromatographed (silica gel, 0–5% MeOH/$CHCl_3$) to furnish pure **23** (0.568 g, 87%): colourless oil; $[\alpha]_D^{26}=+5.79$ ($c=0.69$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.28$–1.64 (m, 6H), 1.64–2.04 (m, 4H), 2.71–2.97 (m, 1H), 3.57–3.76 (m, 1H), 3.81–3.96 (m, 1H), 4.05–4.24 (m, 1H), 4.61 (d, $J=11.8$ Hz, 1H), 4.71 (d, $J=11.8$ Hz, 1H), 7.27–7.46 ppm (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=25.2$, 25.7, 27.2, 28.1, 44.7, 63.0, 66.2, 75.7, 85.6, 126.6, 127.0, 127.3, 127.4, 128.1, 128.2, 128.5, 128.8, 138.4, 139.3 ppm; IR (film): $\tilde{\nu}=3410$, 1581, 1061 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{26}O_3$ (326.19): C 77.27, H 8.03; found: C 77.42, H 8.24.

(*S*)-2-Cyclopentyl-2-phenyl-2-benzyloxyacetaldehyde (24): To a cooled (0°C) and stirred solution of **23** (0.499 g, 1.53 mmol) in CH_3CN-H_2O (6:4, 15 mL) was added $NaIO_4$ (0.492 g, 2.3 mmol). The mixture was stirred for 2.0 h at the same temperature and then filtered. The filtrate was concentrated in vacuo to obtain a residue, which was taken up in diethyl ether (15 mL). The ether layer was washed successively with water, aqueous 10% $NaHSO_3$, water, aqueous 10% $Na_2S_2O_3$, water and brine. After drying, the extract was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 0–10% EtOAc/hexane) to give **24** (0.414 g, 92%): colourless oil; $[\alpha]_D^{22}=+3.8$ ($c=0.66$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.36$–1.80 (m, 8H), 2.48–2.74 (m, 1H), 4.47 (d, $J=12.0$ Hz, 1H), 4.57 (d, $J=12.0$, 1H), 7.26–7.54 (m, 10H), 9.98 ppm (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=25.1$, 25.2, 26.6, 27.3, 47.2, 67.1, 87.7, 126.9, 127.5, 127.6, 127.8, 128.3, 128.4, 136.8, 138.6. 202.6 ppm; IR (film): $\tilde{\nu}=2854$, 1723 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{22}O_2$ (294.16): C 81.60, H 7.53; found: C 81.41, H 7.32.

(*S*)-2-Cyclopentyl-2-phenyl-2-hydroxyacetaldehyde (25): To a stirred solution of **24** (0.40 g, 1.36 mmol) in CH_2Cl_2 (10 mL) containing water (0.5 mL) was added DDQ (0.461 g, 2.04 mmol). The mixture was stirred for 5 h at 25°C, and aqueous saturated $NaHCO_3$ was added to the mixture, which was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0–15% EtOAc/hexane) to afford **25** (0.222 g 80%): colourless oil; $[\alpha]_D^{23}=+4.1$ ($c=0.83$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.30$–1.75 (m, 8H), 2.40–2.69 (m, 1H), 7.26–7.41 (m, 5H), 9.92 ppm (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=25.1$, 25.3, 26.5, 27.4, 47.1, 67.0, 126.6, 128.2, 136.1, 138.9, 202.3 ppm; IR (film): $\tilde{\nu}=3475$, 2854, 1723 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{16}O_2$ (204.12): C 76.44, H 7.90; found: C 76.21, H 8.01.

(*S*)-2-Cyclopentyl-2-phenylglycolic acid (5b): To a solution of **25** (0.09 g, 0.44 mmol) in CH_3CN (5 mL) and sodium phosphate (pH 6.5) buffer (2 mL) were added 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) (0.018 g, 0.12 mmol) and $NaClO_2$ (0.56 g, 0.62 mmol), and the mixture was stirred at 55°C for 2 days. The mixture was brought to room temperature, diluted with H_2O (10 mL) and extracted with EtOAc. The organic extract was washed with water and brine, dried and concentrated in vacuo. The residue was subjected to preparative TLC (silica gel, 15% EtOAc/hexane) to furnish pure (*S*)-**5b** (0.075 g, 77%): colourless solid; m.p. 114°C, (lit.[6d] 115–116°C); $[\alpha]_D^{22}=+2.2$ ($c=0.27$, MeOH), [lit.[6d] +2.0 (MeOH)]; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta=1.36$–1.83 (m, 8H), 1.83–2.01 (m, 2H), 7.31–7.67 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=25.4$, 25.7, 26.9, 27.3, 46.4, 66.8, 126.9, 128.2, 136.1, 138.9, 180.4 ppm; IR (film): $\tilde{\nu}=3546$, 1708 cm^{-1}.

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