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Synthesis of the first per(3-deoxy)-cyclooligosaccharide: hepta(*manno*-3-deoxy-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin

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Abstract

Reduction of hepta(*manno*-2,3-anhydro-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin with lithium triethylborohydride gives hepta(*manno*-3-deoxy-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin. This compound plus the hepta(2-*O*-methyl)- and hepta(2-*O*-benzyl)-derivatives all have the $^4C_1$ conformation. Capillary GC columns manufactured with hepta(*manno*-2,3-anhydro-, hepta(*manno*-3-deoxy-2-*O*-methyl- and hepta(*manno*-2-*O*-benzyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin stationary phases were evaluated for enantio-discrimination with 39 non-polar racemic analytes. The GC column coated with the benzyl derivative showed enantioselectivity comparable to, and in some cases superior to, a commercial per(methyl)-β-cyclodextrin column. The other columns showed little or no enantio-discrimination. A thermodynamics study established a linear enthalpy–entropy compensation effect for two series of analytes on the commercial permethyl-β-cyclodextrin column, but not for the column coated with the benzyl derivative.

1. Introduction

Despite the enormous effort devoted to the chemistry of cyclodextrins (CDs), derivatives in which the stereochemistry has been modified are exceedingly rare. The vast majority have the D-*gluco*-configuration and $^4C_1$-conformation of naturally occurring cyclodextrins.[1,2] There have been three main approaches to CDs with novel stereochemistry. The de novo synthesis of CDs from 'amacrocyclic' precursors[3] has yielded *manno*-stereoisomers of α-, β- and γ-CDs[4] amongst others,[5] but the synthetic routes are long and the yields extremely low (<0.5%). Shorter sequences are possible by cleaving commercial cyclodextrins, chemically modifying the differentiated ends and then recyclising, but this approach at best can only give a modified disaccharide moiety.[6]

The singular or multiple modification of commercially available CDs has the potential to deliver short sequences to novel compounds if adequate selectivity can be achieved, but it is experimentally very

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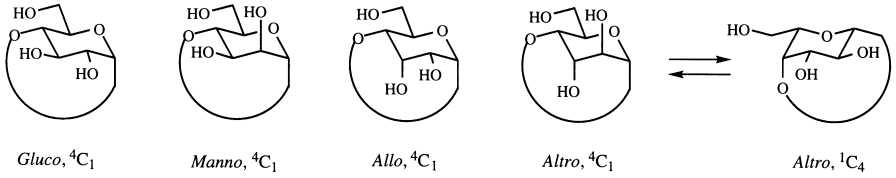
demanding.[7] For example per(3,6-anhydro)-α- and β-cyclodextrins ($^1C_4$) have been prepared in just two steps by selective 6-*O*-tosylation and intramolecular nucleophilic displacement.[8]

During the course of a study of novel cyclodextrin, chiral stationary phases (CSPs) for capillary column gas chromatography,[9] we examined the prospects for modifying the stereochemistry of the 2- and 3-hydroxy groups of cyclodextrins. There are four possible configurations at the C-2/C-3 centres: *gluco*, *manno*, *allo* and *altro* (Scheme 1). In *gluco*-cyclodextrins the hydroxyl groups at C-2 and C-3, protrude approximately parallel to the C_7 axis and extend the length of the chiral cavity on the secondary ('top') face, which is generally believed to be most important for guest binding. Both the *allo* and *altro* stereoisomers have axial substituents at C-3 which occupy the central cavity in the $^4C_1$ conformation. *altro*-Monosaccharides undergo facile interconversion between $^4C_1$ and $^1C_4$ conformers. *manno*-Configuration cyclodextrins in the $^4C_1$ conformation have a more sparse periphery on the secondary face (relative to the *gluco*-compounds), with the C-3 substituents approximately parallel to the C_7 axis and the C-2 substituents perpendicular to the C_7 axis.[10] These observations are also broadly applicable to α- and γ-cyclodextrins, but are not applicable to higher homologues which have quite different stereochemical properties.



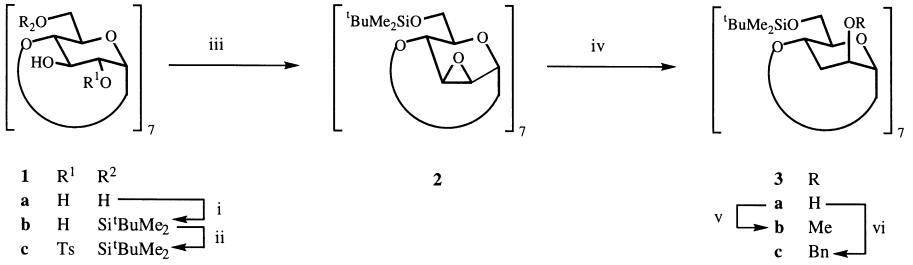
Scheme 1. Generalised conformations for cyclodextrins, viewed from the secondary ('top') face

Hepta(*manno*-2,3-anhydro-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin **2**, prepared by D'Souza[11,12] and Coleman,[13] offered the opportunity to test these possibilities. Surprisingly, there are only two reports of its reactions with nucleophiles; epoxide cleavage with water and ammonia gave β-cycloaltrin[14] and 3-amino-3-deoxy-β-cycloaltrin, respectively.[15] As with related monosaccharide *manno*-epoxides[16] and β-cyclodextrin *manno*-monoepoxide[17–19] nucleophilic attack occurs at C-3 to give products of *trans*-diaxial ring opening. The ^{1}H NMR spectrum of these compounds only showed a single set of resonances with $^3J_{1,2}$=4.5 and 5.6 Hz, respectively. These coupling constants are intermediate between those expected for equatorial, equatorial coupling (1.8 Hz) in the $^4C_1$ conformer and the axial, axial coupling (8.2 Hz) expected for the $^1C_4$ conformer.[20] The conclusion that this indicates an equilibrium between the two conformers is supported by the X-ray crystal structure of α-cycloaltrin (prepared in the same way as β-cycloaltrin) which has alternating rings in $^4C_1$ and $^1C_4$ conformations.[21] With this information in hand, we elected to reduce the hepta(*manno*-epoxide) **2** to the hepta(*manno*-3-deoxy-alcohol) **3** with the expectation that the $^4C_1$ conformation would be retained. If the structure of *gluco*-cyclodextrins **1** can be drawn (in a cartoon) as a cup, then the structure of the hepta(*manno*-3-deoxy-alcohol) **3** would have the aspect ratio of a traditional rimmed soup bowl. Many per(6-deoxy)-CDs[22,23] have been prepared, but as far as we are aware the only other examples of deoxy-CDs in the refereed literature[24] are mono-2-deoxy-α- and β-cyclodextrins.[6] A large number of deoxy-cyclodextrins have been claimed in a patent, but no characterisation data was presented.[25]

2. Discussion

Carefully dried β-cyclodextrin **1a** was silylated as described previously[26,27] and the hepta(silyl ether) **1b** so formed was tosylated selectively at the 2-position (Scheme 2). Coleman was only able to identify

and assign two protons on the pyranoside ring (H-1 and H-2), in the ^{1}H NMR spectrum of the hepta(tosylate) **1c**.[28] With the benefit of a higher field instrument (^{1}H, 400 MHz) and a *J*-COSY spectrum, the couplings could be traced unambiguously between H-1, H-2 and H-3. The assignment of H-3 was further confirmed by coupling to HO-3, which in a single spectrum appeared as a sharp doublet (*J* 3.0 Hz). In all other spectra, a broad multiplet was observed at a virtually identical chemical shift (δ 3.1). The assignment of the other signals was made on the basis of the other cross-peaks, but some signals overlapped and there was no redundant information. H-3 (δ 3.84) and H-6 (δ 3.88) are coupled to a two proton four line multiplet (δ 3.62), which appears to be the superimposition of a triplet due to H-4 (*J* 9.4 Hz) and a sharp doublet due to H-6′ (*J* 10.2 Hz). The latter value differs slightly from that seen in H-6 (^2J 11.6 Hz) due to the overlap with H-4. The multiplet at δ 3.62 is also coupled to a very broad doublet signal at δ 3.6 (*J* 9.1 Hz, H-5), which is due to a strong coupling to H-4, a small coupling to H-6 (*J* 2.9 Hz) and a very small coupling to H-6′. The coupling constants deduced for $^3J_{\text{H-5,H-6}}$ and $^3J_{\text{H-5,H-6'}}$ are consistent with the common *gg* orientation for the methylene-silyl ether moiety.



Scheme 2. Synthesis of per(3-deoxy)-cyclomannins. Reagents and conditions: (i) ^{t}BuMe$_2$SiCl (1.15 equiv.), imidazole, DMF, rt, 3 h (92% yield); (ii) *p*TsCl (2.8 equiv.), pyr., DMAP, 50°C, 25 h (63% yield); (iii) NaH, THF, 4 h (44% yield); (iv) LiEt$_3$BH (1 M, in THF, 5.1 equiv.), rt, 2 h, LiEt$_3$BH (1 M, in THF, 2.6 equiv.), reflux, 48 h (40% yield); (v) NaH, MeI, THF, rt, 12 h (90% yield); (vi) NaH, BnBr, THF, rt, 48 h (59% yield). All products were purified by column chromatography over silica gel. Equivalents are relative to moles of functional groups.

Treatment of the hepta(tosylate) **1c** with sodium hydride in THF effected cyclisation to the hepta(epoxide) **2**. This was sufficiently stable that it could be purified by silica gel chromatography and stored for months in the freezer. In contrast, D'Souza reported that this compound was unstable at room temperature and decomposed to the silylated cyclodextrin **1b**, although presumably, this would require an unprecedented nucleophilic attack by water at C-2. We also attempted the direct conversion of the hepta(silyl ether) **1b** to the hepta(epoxide) **2** using sodium hydride and benzenesulfonyl chloride, but were not able to isolate a clean product. The ^{1}H NMR spectrum of the hepta(epoxide) **2** was virtually identical to that reported previously, except that the signal for H-5 (δ 3.50), which was reported to be a multiplet appeared as a broad doublet (*J* 8.7 Hz) for the reasons noted above for the hepta(tosylate) **1c**.

Development of a method for the reduction of the hepta(epoxide) **2** required considerable experimentation. Reduction with excess diisobutylaluminium hydride in toluene gave a complex mixture as did lithium aluminium hydride. Although in the latter case (in retrospect) traces of the desired hepta(alcohol) **3** were evident in the ^{1}H NMR spectrum. Eventually, it was discovered that addition of two portions of commercial Super-Hydride® (1 M) in THF to the hepta(epoxide) **2**, followed by reflux for 48 hours gave a 40% yield of the hepta(alcohol) **3a**, after repeated column chromatography. This material was clearly homogenous as judged by TLC, ^{13}C NMR and mass spectra, however, the ^{1}H NMR spectrum showed line broadening of circa 1.5–2 Hz and the signals were poorly dispersed. In view of this and the unsuitability of the hepta(alcohol) **3a** for use as a GC-CSP we prepared the hepta(2-*O*-methyl) **3b** and hepta(2-*O*-benzyl) **3c** ethers under standard conditions. The hepta(2-*O*-methyl) **3b** ether was intended for comparison against commercial permethyl-CDs and per(6-*O*-*t*-butyldimethylsilyl-2,3-di-*O*-methyl)-

CDs, whereas the larger benzyl groups of the hepta(2-*O*-benzyl) **3c** ether should help to fill the sparse secondary periphery due to the absence of the 3-substituent and be comparable with other recently reported benzylated CD CSPs.[29] Both derivatives showed some line broadening, although this was somewhat less for the hepta(2-*O*-benzyl) **3c** ether and hence most efforts were devoted to the assignment of the NMR spectra of this compound.

The ^{1}H NMR signals for the anomeric protons of the three hepta(3-deoxy)-compounds **3a**,**b**,**c** appeared as a barely resolved doublet of 2.8 Hz, a broad singlet and a barely resolved doublet of 2.4 Hz, respectively, with similar chemical shifts (δ 4.62, 4.73 and 4.84, respectively). These values are consistent with equatorial, equatorial coupling, and hence the $^{4}C_{1}$ conformation. The $^{3}J_{\text{H-1,H-2}}$ coupling could not be confirmed in the signal for H-2, because this appeared as a broad multiplet, because of the line broadening and second order effects due to the similar chemical shifts of the two H-3s. No coupling constants could be extracted from 2H-3, H-4 or H-5 either due to multiple coupling and insufficient resolution or signal overlap. All of the H-6 signals showed the expected large geminal couplings (10.7–11.2 Hz) and small or zero vicinal couplings to H-5, consequently the methylene-silyl ether moiety is predominantly in the *gg* orientation as deduced for the *gluco*-compounds **1a**–**c** and the hepta(epoxide) **2**.

In the ^{13}C NMR spectrum the signal for C-2 of the hepta(alcohol) **3a** appears at δ 68.0, and is shifted downfield in the corresponding hepta(2-*O*-methyl) **3b** (δ 77.7) and hepta(2-*O*-benzyl) **3c** ethers (δ 76.1). In contrast the corresponding signals for C-1 and C-3 (**3a** δ 100.5, 32.9) are shifted slightly upfield (**3b** δ 99.3, 31.2; **3c** δ 99.2, 31.4).[18] The chemical shifts for C-5 and C-6 are virtually identical in all three compounds.

All compounds were characterised by combustion analysis and FAB-MS using a *m*-nitrobenzyl alcohol matrix. No partially functionalised CDs, dimers or multiply charged ions, were observed albeit that in some cases the ion abundances were low relative to matrix ions. The hepta(tosylate) **1c**, the hepta(epoxide) **2** and the hepta(methyl ether) **3b** gave M+Na peaks as is commonly observed for CDs, however the hepta(2-*O*-benzyl) ether **3c** gave a M+H+Na ion and the hepta(alcohol) **3a** gave an ion which can be rationalised as $M-CH_4+Na$.

The spectroscopic data establishes that the hepta(deoxy)-CDs **3a**,**b**,**c** have the $^{4}C_{1}$ conformation with the methylene-silyl ether moiety predominantly in the *gg* orientation. An impression of the structure of the hepta(2-*O*-benzyl) ether **3c** is shown in Fig. 1. The orientation of the benzyl groups is arbitrary.

3. Capillary column GC

The virtues of using capillary GC to measure enantio-discrimination are not widely appreciated. A typical 30 metre capillary column only contains about 3 milligrams of stationary phase of which less than 1 milligram is the enantio-discriminating component. Hence the amount required is rather less than that employed in NMR and, moreover, given that the CSP is stable, any number of analytes can be tested without having to separate the guest from the host.

Capillary columns (12 m, 0.25 mm id, 0.20 μm phase thickness) were manufactured using the static method, with OV-1701 as the diluent (diluent:CD ratio of 85:15) and dichloromethane as the solvent. The columns are designated as follows (CM=cyclomannin): commercial J & W per(methyl)-CD, permethyl-CD; hepta(epoxide) **2**, h(E)-CM; hepta(2-*O*-methyl) **3b** ether, h(Me)-CM; and hepta(2-*O*-benzyl) **3c** ether, h(Bn)-CD.

Most GC runs were isothermal and most analytes were run at four temperatures in the range 30–100°C. Racemic analytes (Scheme 3) which were particularly difficult to separate were also run with the

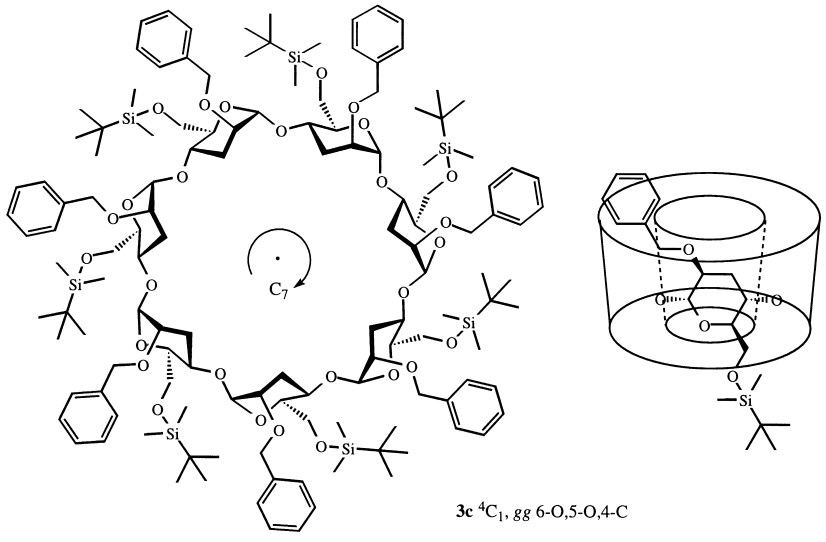
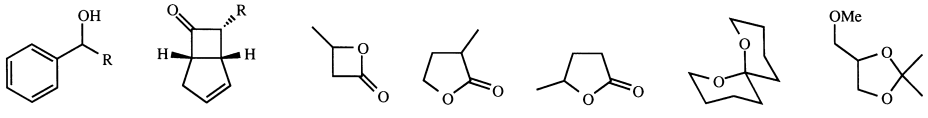


Figure 1. Structure of the hepta(2-*O*-benzyl) ether **3c** viewed from the secondary face

temperature programme 40°C (5 min)×5°C/min, 100°C (40 min). These are marked P in Table 1. In a few cases, the same analyte was run at slightly different temperatures on the two columns.



11
a R = Me
b R = Et
c R = ^{n}Pr
d R = ^{n}Bu

***rac*-12**
a R = H
b R = Me
c R = Et
d R = ^{n}Pr

13

14

15
a R = Me
b R = ^{n}Pn

26

27

Scheme 3. Analytes

This work was performed as part of a study of CSPs which are enantioselective at low temperature. To reduce otherwise long retention times, we used comparatively short (12 m) and narrow columns (0.25 mm id). A mass spectrometer was used as the detector and naturally the ion source is at a low vacuum. The use of narrow columns reduces the length of column which is subjected to an appreciable vacuum and hence increases the usable length of the column. The 12 metre columns used in the current work have a resolution equivalent to 65% of that of a 30 metre column.

We were aware of our limitations for manufacturing capillary columns with an even coating of stationary phase. Consequently it was assumed that the separation factor was solely a function of the enantio-discrimination of the CSP and that peak shape was a function of this and any inadequacies in the quality of column coating. Hence our analysis of the enantio-discrimination is based on separation factors (α) rather than efficiency (theoretical plates). In virtually all cases, peak width increased as the retention time increased for both the permethyl-CD column and the columns manufactured in house. This effect is commonly observed and was particularly noticeable with the higher members of the homologous series of analytes.

The h(E)-CM column showed little or no enantio-discrimination, and the retention times were generally shorter than the other columns e.g. bicyclic ketones **12a**–**d**, t_R (40°C) 4.00, 7.25, 14.28, and 33.14 min, respectively (cf. Table 1). The possibility that decomposition of the CSP was occurring was

Table 1
Retention times (minutes) and separation factors (α) for racemic analytes on permethyl-CD and h(Bn)-CM columns

Racemic analytes	Temp.	Permethyl-CD			h(Bn)-CM		
	°C	t_{R1}	t_{R2}	α	t_{R1}	t_{R2}	α
Limonene **4**	40	7.17	7.43	1.04	8.22	8.62	1.05
α-Pinene **5**	40	**3.90**	**4.28**	**1.11**	3.85		1.00
α-Ionone **6**	80	**22.58**	**24.63**	**1.09**	31.19	32.85	1.05
α-Terpineol **7**	70/60	15.48		1.00	**26.82**	**29.12**	**1.09**
Linalool **8**	60	11.83	12.13	1.03	11.57	11.93	1.03
Carvone **9**	70	14.12		1.00	32.62		1.00
β-Citronellol **10**	80	9.85		1.00	12.15		1.00
1-Phenylethanol **11a**	70	10.25	11.90	**1.16**	10.05	10.98	1.10
1-Phenyl-1-propanol **11b**	70	21.13	23.82	**1.13**	19.43	20.37	1.05
1-Phenyl-1-butanol **11c**	70	38.20		1.00	**34.82**	**36.69**	**1.06**
1-Phenyl-1-pentanol **11d**	70	76.05	78.91	1.04	**69.27**	**74.30**	**1.07**
Bicyclo[3.2.0]hept-2-ene-6-one **12a**	40	9.80	11.22	1.15	9.10	10.52	1.16
7-*endo*-Methyl-bicyclo [3.2.0]hept-2-ene-6-one **12b**	40	18.97	23.17	1.22	16.15	19.52	1.21
7-*endo*-Ethyl-bicyclo [3.2.0]hept-2-ene-6-one **12c**	40	**36.37**	**46.35**	**1.27**	31.12	36.34	1.17
7-*endo*-Propyl-bicyclo [3.2.0]hept-2-ene-6-one **12d**	40	**76.57**	**89.66**	**1.17**	67.84	73.86	1.09
β-Butyrolactone (β-methyl-β-propiolactone) **13**	30	2.93		1.00	4.67		1.00
α-Methyl-γ-butyrolactone **14**	40	12.23		1.00	16.73	17.37	**1.04**
γ-Valerolactone **15a**	40	13.88		1.00	18.72	19.30	**1.03**
γ-Nonanoic lactone **15b**	80	33.82	35.30	1.04	41.89	43.30	1.03
3-Buten-2-ol **16**	30	**1.72**	**1.83**	**1.08**	1.67		1.00
1-Penten-3-ol **17**	30	1.75		1.00	2.02		1.00
trans-3-Penten-2-ol **18**	30	**1.83**	**2.00**	**1.11**	2.53	2.70	1.08
2-Methyl-1-butanol **19**	30	3.75	3.92	1.05	3.83	3.98	1.04
1-Hexen-3-ol **20**	30	**5.05**	**5.22**	**1.04**	4.77		1.00
2-Ethyl-1-hexanol **21**	60	8.87	9.50	1.07	7.75	8.12	1.05
3-Pentyn-2-ol **22**	30	**2.20**	**2.32**	**1.06**	2.37		1.00
3-Hexyn-2-ol **23**	30	8.55	10.05	1.18	8.48	9.87	1.17
2-Heptanol **24a**	40	8.47		1.00	7.40		1.00
2-Octanol **24b**	40	20.38	21.07	1.03	17.28		1.00
2-Nonanol **24c**	40	**48.85**	**51.59**	**1.06**	41.49		1.00
2-Decanol **24d**	P	59.39		1.00	59.05		1.00
2-Undecanol **24e**	P	62.59		1.00	63.14		1.00
2-Dodecanol **24f**	P	67.02		1.00	68.72		1.00
Styrene oxide **25**	40	**10.68**	**11.57**	**1.09**	20.82	21.58	1.04
1,7-Dioxaspiro[5.5]undecane **26**	60	7.40	7.77	1.05	**8.78**	**9.57**	**1.09**
1,2-*O*-Isopropylidene-3-*O*-methyl glycerol **27**	30	8.38	9.57	1.15	7.80	8.95	1.15
N-TFA-2-aminoheptane **28**	50	36.72		1.00	42.30		1.00
N-TFA-2-amino-1-butanol **29**	60	24.67		1.00	34.55		1.00
N-TFA-α-methylbenzylamine **30**	70/80	36.24		1.00	24.48		1.00
DL-Valine methyl ester **31**	40	9.67	10.53	1.09	10.52		1.00

considered, however the lowest possible oven temperatures were used and the retention times of analytes measured at the beginning of the study were identical to those at the end of the study.

The h(Me)-CM column also had little or no enantio-discrimination, although separation of 1-phenylpropanol **11b** was just about achieved (α=1.02, at 60°C, t_R=10.13 and 10.35 min). As with the h(E)-CM column, retention times were comparable to or shorter than the other columns, e.g. bicyclic ketones **12a**–**d**, t_R (40°C) 5.97, 11.27, 23.03, and 57.74 min, respectively (cf. Table 1).

Despairing of achieving any useful results with these 3-deoxy-*manno* derivatives, we finally turned to the H(Bn)-CM column and were rewarded with some excellent results. Table 1 summarises the results obtained at the lowest usable temperatures with this column and the permethyl-CD column. When one column is clearly superior to the other, the data is shown in bold.

3.1. Terpenes, **4–10**

The performance of the two columns with the terpenes **4**–**10** are largely comparable. Although the permethyl-CD column has a better α-factor with α-ionone **6**, the peak for the later eluting enantiomer showed trailing, whereas with the h(Bn)-CM column both peaks had a satisfactory shape and that of the later eluting enantiomer was marginally sharper. The retention time differences between the columns for the ketones are remarkable. The α-ionone enantiomers **6** elute on average some 8.5 min later from the h(Bn)-CM column than from the permethyl-CD dextrin column, whereas with carvone **9** the retention time is 130% greater, albeit that there is no enantio-discrimination on either column.

3.2. Phenylalkanols, **11a–d**

The 1-phenylalkanols are standard test analytes for testing CSPs. The (*R*)- and (*S*)-enantiomers of phenylethanol **11a**, phenylpropanol **11b**, and phenylbutanol **11c** are commercial products and (*S*)-phenylpentanol **11d** was prepared by yeast reduction of valerophenone **32**. Work up and column chromatography gave the desired enantiomer in 8% yield (66% ee by optical rotation, 45% ee by CSP GC) which was comparable with the literature values (5–37% yield, 71–55% ee by optical rotation).[30]

On all the CD columns we have examined which are capable of separating the enantiomers of the 1-phenylalkanols **11a**–**d**, the (*R*)-enantiomer of the ethanol **11a** and propanol **11b** homologues, and the (*S*)-enantiomers of the butanol **11c** and pentanol **11d** elute first. This can be rationalised as a preference for the phenyl group binding into the cavity of the CD for the (*S*)-enantiomers of the lower homologues[31] and the alkyl chain of the (*R*)-enantiomers of the higher homologues. Whatever the explanation, 1-phenyl-butanol **11c** is generally the most difficult to separate. The permethyl-CD column was incapable of resolving the enantiomers of the butanol homologue **11c**, whereas they were cleanly separated by the h(Bn)-CM column. The enantiomers of phenylpentanol **11d** were separated by the permethyl-CD column, but the peaks trailed so badly that the peaks were barely distinguishable whereas on the h(Bn)-CM column, the peak shape was much better and the Δt was over 5 min. Further aspects of the separation of phenylalkanols on these columns are discussed in the section on thermodynamics.

The explanation for the reversal in enantioselection in the phenyl-alcohol **11a**–**d** homologous series is wholly reasonable, however the assignments of the absolute configurations of the higher homologues are not based on unambiguous methods. The absolute configurations of phenylethanol **11a**[32] and phenyl-propanol **11b**[33] were established by syntheses which can be traced to D-glyceraldehyde, whereas those of phenylbutanol **11c**[34] and phenylpentanol **11d** were initially assigned on the basis of Freudenberg's 'rule of shift',[35] i.e. configurationally related compounds show similar shifts in rotation upon derivatisation. The configurations assigned are consistent with those predicted by Brewster's groups increment calculations,[36] Horeau partial esterification,[37] and yeast reduction of the corresponding ketones rationalised using Prelog's rule.[38] The absolute configuration of phenylpentanol **11d** is a matter of considerable importance because it is the product of innumerable reactions in which butyl anions are added to benzaldehyde in the presence of a chiral auxiliary. Sensing that a revision of this absolute stereochemistry would prompt reformation of a large body of asymmetric chemistry, we sought a crystalline derivative with a centre of known stereochemistry whose structure could be determined unambiguously by X-

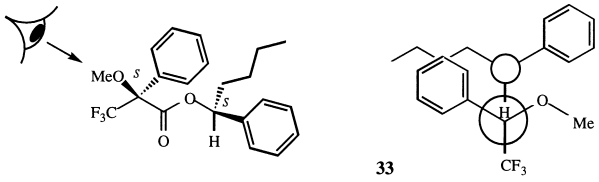


Figure 2.

ray crystallography. The putative (*S*)-1-phenyl-1-pentanol **11d**, produced by yeast reduction, was reacted with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl) in the presence of DMAP. Work up and repeated column chromatography gave the Mosher's ester as a yellowish liquid (58% yield). Crystallisation was attempted using hexane, benzene, ether, petroleum ether and mixtures thereof, but no crystals could be obtained. Even resort to sonocrystallisation was unsuccessful.[39]

With this lack of success we also resorted to an indirect method. In the preferred conformation of MPTA esters of secondary alcohols the trifluoromethyl group, the ester carbonyl and the alkanol hydrogen are synperiplanar (Fig. 2).[40] If the carbonyl group is modelled as a *tau* bond,[41] this is a fully staggered conformation. The absolute configurations of diastereomeric MTPA esters can usually be assigned from ^{1}H NMR spectra, by assuming that the phenyl group of the acyl moiety shields the hydrogens of groups which are in the *syn* orientation (typically $\Delta\delta$ 0.05–0.13 ppm).[42] In the current case, the requisite heavily coupled methylene groups in the two enantiomers could not be distinguished. However the signal for the methoxy group of the major diastereoisomer (δ 3.43) was 0.09 ppm upfield from that of the minor diastereoisomer (δ 3.52).[43,44] This can be attributed to a comparable shielding effect by the phenyl ring of the alkyl moiety of the ester. Given that the predominant conformation of the (*S*)-MTPA-ester in solution is that shown in Fig. 2, only the (*S*)-enantiomer of phenylpentanol **11d** has the methoxy group *syn* to the phenyl ring. This correlation has been noted previously for certain groups of compounds[45] and in a forthcoming publication we will show that this is a general and useful observation.[46]

3.3. Bicyclo[3.2.0]hept-2-ene-6-ones, ***12a–d***

The enantiomers of the bicyclic ketones **12a**–**d** were easily distinguished by both columns, the α-factors for these compounds were the highest obtained in this study and no pair of enantiomers had a difference in retention time of less than 1 min. The Δt for the *endo*-propyl-homologue **12d** was almost 14 min on the permethyl-CD column and over 6 min on the h(Bn)-CM column, albeit the peaks had extensive trails at this temperature. Further aspects of the separation of the bicyclo[3.2.0]hept-2-ene-6-ones on these columns are discussed in the section on thermodynamics.

3.4. Lactones, ***13–15***

The h(Bn)-CM column was clearly superior to the permethyl-CD column for the lactones **13**–**16**. Neither column was capable of separating β-butyrolactone **13**, but all the other examples **14**, **15a**,**b** were separated by the h(Bn)-CM column albeit with low, but usable separation factors.

3.5. Alcohols, ***16–24***

Both columns had comparable performance with each of the analytes in this group, although in all cases the permethyl-CD column was slightly superior. The separation factors are moderate to low, but

this is mitigated by the short retention times. These compounds are amongst the most volatile used in the study and the lack of separation is probably due to insufficient residence time in the liquid phase. The homologous series of 2-alkanols **24a**–**f** was poorly separated with either column and no improvement was achieved by using a temperature programmed run. Most CD-CSPs give poor results with these analytes.

3.6. *Sundries,* ***25***–***31***

The enantiomers of styrene oxide **25** were almost equally separated on the permethyl-CD (Δt=0.89 min) and h(Bn)-CM columns (Δt=0.76 min), but the retention times on the h(Bn)-CM column were almost twice as long. This presumably reflects the greater solubility of styrene oxide in the benzylated CSP. 1,7-Dioxaspiro[5.5]undecane **26** is the female released sexual attraction pheromone of the olive fly, *Bactrocera oleae*.[47] The enantiomeric excesses of this compound and hydroxylated derivatives have been determined by GC on a CD-CSP[48] and the modes of binding to CDs investigated by NMR.[49] The separation factor and the peak shape were better on the h(Bn)-CM column (α 1.09) than on the permethyl-CD column (α 1.04), although the retention time was slightly longer. Both columns gave almost identical and excellent separations (α 1.15) of the enantiomers of 1,2-*O*-isopropylidene-3-*O*-methyl glycerol **27**, but none of the trifluoroacetylated amines **28**–**30** were separated. DL-Valine methyl ester **31** was only separated with the permethyl-CD column.

The thermal stability of the hepta(2-*O*-benzyl) ether **3c** was assessed by thermogravimetric analysis. Weight loss commenced slowly at 260°C and the majority of the weight was lost between 325 and 380°C. This indicates that the maximum temperature for the column should be conservatively set to 180–200°C, which is somewhat less than commercial permethyl-CD columns (260/280°C). One possible interpretation is that the axial benzyloxy substituents undergo thermal elimination more rapidly than the equatorial methoxy groups present in the permethyl-CD columns.

4. Thermodynamics study

The h(Bn)-CM column is the first cyclodextrin column which does not have *gluco*-stereochemistry and moreover benzyl-substituted cyclodextrins are also comparatively rare. It appeared that it would be worthwhile to undertake a thermodynamic study in order to discover if the mode of discrimination was fundamentally different to that of other cyclodextrin-CSPs. We considered it plausible that the shallower cavity plus the more flexible and polarisable rim of the hepta(2-*O*-benzyl) ether **3c** would result in looser and more disordered binding of analytes relative to permethyl-CD. Consequently enthalpic effects should play a larger role than entropic effects. As in the prior study, data was acquired for both the new column and a commercial permethyl-CD column. Two homologous series, the phenyl alkanols **11a**–**d** and the 7-alkyl-bicyclo[3.2.0]hept-2-en-6-ones **12a**–**d**, were investigated so that trends such as enthalpy–entropy compensation could be distinguished.

Data for the calculation of thermodynamics parameters were acquired by measuring retention times for each homologous series at a number of temperatures. As in the prior work, mixtures of homologues were analysed concurrently, so as to minimise errors in the measurement of retention times. The range of temperatures used was dictated by the need to obtain reproducible retention times without excessive peak broadening and also to avoid excessively short retention times which are less reproducible. The results presented in Tables 2 and 3 were calculated using the method of Klug et al.[50] which yields $\Delta\Delta H$ and $\Delta\Delta G_{Thm}$ ($\Delta\Delta G$ at the harmonic mean temperature of the experiments). These parameters were then used

Table 2
Thermodynamic study of 1-phenyl-1-alkanols **11a–d** permethyl-CD (T_m 348.16 K, T_{hm} 347.80 K, T_c 411 K)

Permethyl-CD (T_m 348.16 K, T_{hm} 347.80 K, T_c 411 K)				
Temperature	Phenylethanol **11a** (α *R/S*)	Phenylpropanol **11b** (α *R/S*)	Phenylbutanol **11c** (α *S/R*)	Phenylpentanol **11d** (α *S/R*)
60°C	1.208 ± 0.003	1.162 ± 0.004	-	1.042 ± 0.001
70°C	1.169 ± 0.003	1.131 ± 0.002	-	1.038 ± 0.000
80°C	1.149 ± 0.000	1.108 ± 0.001	-	1.031 ± 0.000
90°C	1.118 ± 0.004	1.082 ± 0.002	-	1.028 ± 0.000
ΔΔS J K^{-1} mol^{-1}	5.983 ± 0.034	5.839 ± 0.013	-	1.086 ± 0.008
ΔΔH kJ mol^{-1}	2.511 ± 0.186	2.359 ± 0.069	-	0.476 ± 0.049
ΔΔH/ΔΔS K (°C)	420 ± 33 (147)	404 ± 13 (131)	-	439 ± 48 (166)
$\Delta\Delta G_{T_{hm}}$ kJ mol^{-1}	0.4305	0.3286	-	0.09873
h(Bn)-CM (T_m 343.16 K, T_{hm} 342.97 K, T_c 389 K)				
60°C	1.121 ± 0.000	1.057 ± 0.000	1.057 ± 0.000	1.085 ± 0.000
70°C	1.098 ± 0.000	1.048 ± 0.001	1.053 ± 0.002	1.074 ± 0.002
80°C	1.078 ± 0.001	1.037 ± 0.001	1.048 ± 0.001	1.065 ± 0.004
ΔΔS J K^{-1} mol^{-1}	4.736 ± 0.004	2.307 ± 0.008	0.784 ± 0.004	2.033 ± 0.004
ΔΔH kJ mol^{-1}	1.920 ± 0.034	0.936 ± 0.072	0.421 ± 0.034	0.915 ± 0.034
ΔΔH/ΔΔS K (°C)	405 ± 8 (132)	406 ± 33 (133)	537 ± 46 (264)	450 ± 18 (177)
$\Delta\Delta G_{T_{hm}}$ kJ mol^{-1}	0.2726	0.1336	0.1484	0.2082

to calculate ΔΔS in the usual way. Plots of lnα vs 1/T plots were also made as a check and because they are easier to interpret visually.

As expected, the α-factors decrease with increases in temperature for all the analytes on all the columns. On the permethyl-CD column the phenylethanol **11a** and phenylpropanol **11b** enantiomers had comparable values for both ΔΔS and ΔΔH as indicated by parallel lines on the lnα vs 1/T plot but phenylpentanol **11d** showed much smaller values for both. On the h(Bn)-CM column the phenylpropanol **11b** and phenylpentanol **11c** enantiomers had comparable values for both ΔΔS and ΔΔH, although because of the change in order of elution this represents opposing effects for pairs of enantiomers.

Generally, the absolute values of ΔΔH, ΔΔS are larger on the permethyl-CD column than on the h(Bn)-CM column. Phenylpentanol **11d** and phenylbutanol **11c** are the exceptions to this generalisation. Unfortunately, the span of the α-factors for phenylbutanol **11c** on the h(Bn)-CM column is only 0.009 and hence any calculations are ill-conditioned and unreliable. For example, the values of ΔΔH/ΔΔS (based on the maximum uncertainties in the measurement of the retention times) cover a range of almost 100°C. Nevertheless the poor quality of the thermodynamic data, does not detract from the practically useful result that only the h(Bn)-CM column was able to separate the enantiomers of phenylbutanol **11c**. The large error for bicyclo[3.2.0]hept-2-en-6-one **12a** on the h(Bn)-CM column is largely a consequence of the measurement at 70°C (and the short retention time) and the probable error in ΔΔH/ΔΔS is likely to be circa ±20°C.

The values of ΔΔH and ΔΔS in Tables 2 and 3 have a fairly constant ratio which is conveniently expressed as ΔΔH/ΔΔS. This ratio is also the temperature at which no separation of enantiomers occurs (see Experimental for explanation). Apparently constant ratios between enthalpy and entropy are frequently observed from equilibrium (or kinetic) measurements. This phenomenon is variously known as enthalpy–entropy compensation, the isokinetic effect (for rate studies) or just the compensation effect.[51,52] However demonstration of this effect by plotting ΔΔH against ΔΔS is misleading because the

Table 3
Thermodynamic study of bicyclo[3.2.0]hept-2-en-6-ones **12a–d** permethyl-CD (T_m 333.16 K, T_{hm} 332.56 K, T_c 413 K)

Temperature	**12a** (α)	**12b** (α)	**12c** (α)	**12d** (α)
40°C	1.151 ± 0.002	1.228 ± 0.003	1.278 ± 0.000	1.172 ± 0.000
50°C	1.129 ± 0.001	1.197 ± 0.002	1.235 ± 0.001	1.148 ± 0.003
60°C	1.112 ± 0.000	1.164 ± 0.001	1.196 ± 0.001	1.123 ± 0.003
70°C	1.093 ± 0.000	1.140 ± 0.003	1.164 ± 0.000	1.102 ± 0.002
80°C	1.078 ± 0.001	1.122 ± 0.004	1.134 ± 0.004	1.085 ± 0.001
$\Delta\Delta S$ J K^{-1} mol^{-1}	3.442 ± 0.007	4.780 ± 0.025	6.382 ± 0.012	4.418 ± 0.010
$\Delta\Delta H$ kJ mol^{-1}	1.504 ± 0.025	2.115 ± 0.088	2.747 ± 0.041	1.797 ± 0.036
$\Delta\Delta H/\Delta\Delta S$ K (°C)	437 ± 8 (164)	443 ± 21 (169)	431 ± 7 (157)	430 ± 10 (156)
$\Delta\Delta G_{T_{hm}}$ kJ mol^{-1}	0.3078	0.4530	0.5280	0.3421
h(Bn)-CM (T_m 328.16 K, T_{hm} 327.78 K, T_c 498 K)				
40°C	1.162 ± 0.004	1.212 ± 0.004	1.171 ± 0.000	1.092 ± 0.003
50°C	1.144 ± 0.003	1.184 ± 0.001	1.147 ± 0.001	1.077 ± 0.002
60°C	1.128 ± 0.003	1.162 ± 0.004	1.128 ± 0.005	1.066 ± 0.005
70°C	1.120 ± 0.006	1.142 ± 0.006	1.108 ± 0.002	1.057 ± 0.001
$\Delta\Delta S$ J K^{-1} mol^{-1}	2.136 ± 0.022	3.739 ± 0.012	3.619 ± 0.007	2.198 ± 0.012
$\Delta\Delta H$ kJ mol^{-1}	1.117 ± 0.104	1.765 ± 0.055	1.633 ± 0.033	0.9679 ± 0.058
$\Delta\Delta H/\Delta\Delta S$ K (°C)	523 ± 54 (250)	472 ± 16 (199)	451 ± 10 (178)	440 ± 29 (167)
$\Delta\Delta G_{T_{hm}}$ kJ mol^{-1}	0.3748	0.4656	0.3744	0.2035

major axis of the error ellipse runs is coincident with the regression line of the data when these parameters are determined from van't Hoff (or Arrhenius) plots. If the experimental temperature range is too small the error ellipse approximates to a straight line (major axis>>>minor axis).[53] Consequently, as the errors in the data increase, the coefficient of regression of the line increases because the data is spread over a wider span. This problem may be largely avoided by plotting $\Delta\Delta H$ vs $\Delta\Delta G_{Thm}$ which enables the compensation temperature (T_c) to be calculated from the gradient of the regression line (Fig. 3).[50,54]

The plot for the phenylalkanols on the permethyl-CD column (Fig. 3A) is compromised by the limited number of data points and clustering of the values for **11a** and **11b**. The values for phenylpentanol **11d** are plotted as positive differences, although they are actually negative differences. This originates from the change in elution order of the enantiomers (**11a**, **11b**, α *R/S*; **11c**, **11d** α *S/R*). Plotting the values for phenylpentanol **11d** as negatives increases the relative clustering of the the two higher data points and unduly weights the regression line relative to the significance of the experimental value. This is also a feature of the phenylalkanols on the h(Bn)-CM column (Fig. 3B) and it is noteworthy that both $\Delta\Delta H$ and $\Delta\Delta S$ decrease in sequence with 'ascent' of the phenylalkanol homologous series **11a–d** on both columns. The data for the bicyclo[3.2.0]hept-2-en-6-ones **12a–d** on permethyl-CD has the highest span for the separation factors and temperature (Table 3) and consequently the thermodynamic parameters have the lowest errors in the current study. Fig. 3C shows a high quality regression line for well dispersed values. The bicyclo[3.2.0]hept-2-en-6-ones **12a–d** on the h(Bn)-CM column gave a poor regression line (Fig. 3D), largely as a consequence of the data for the parent unsubstituted compound **12a** and the poor dispersion of the data points.

Overall, the results provide evidence for the operation of an enthalpy–entropy compensation effect for the the permethyl-CD column, but not on the h(Bn)-CM column. This is most clearly seen for the bicyclo[3.2.0]hept-2-en-6-ones **12a–d** on permethyl-CD and to a much lesser extent for the phenylalkanols **11a**, **11b**, **11d** on the same column, because of limitations of the data. Both the gradients and

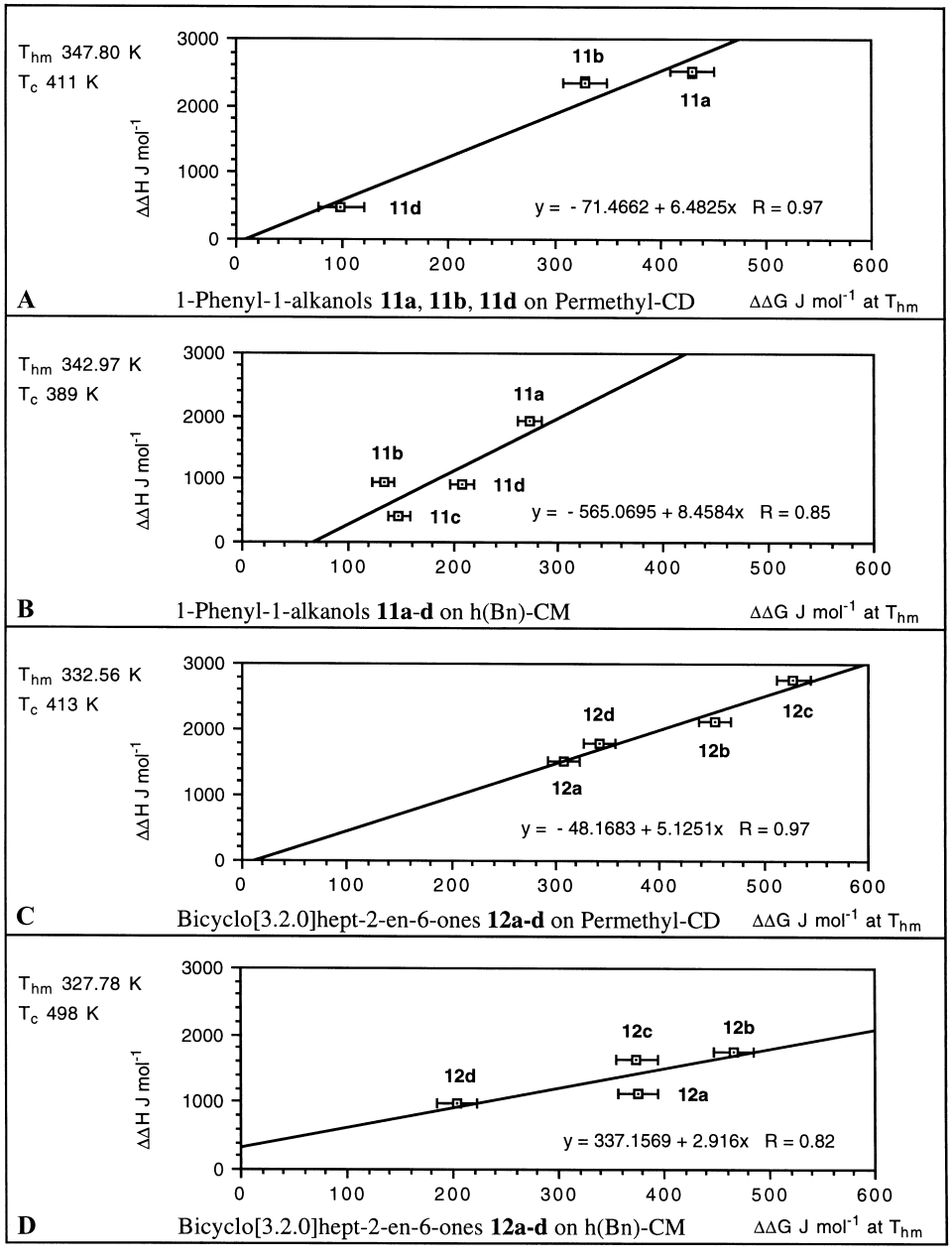


Figure 3. $\Delta\Delta H$ vs $\Delta\Delta G_{Thm}$ for 1-phenyl-1-alkanols **11a–d** and bicyclo[3.2.0]hept-2-en-6-ones **12a–d**

intercepts for these data sets are similar (although the T_{hm} are slightly different) and the compensation temperatures (T_c 411 and 413 K, respectively), are virtually identical. When the two data sets are combined (Fig. 4, T 332.56K) the regression line has marginally smaller residuals than either data set alone. In contrast, the results for the h(Bn)-CM column show poorer quality correlations, albeit based on poorer quality data (due to shorter spans for α and temperature range, Fig. 3B and 3D). When the two data sets were combined (T 342.97 K) and replotted in the same way as for the two permethyl-CD data sets, the residuals were poorer (R=0.72). The results do not wholly exclude an enthalpy–entropy

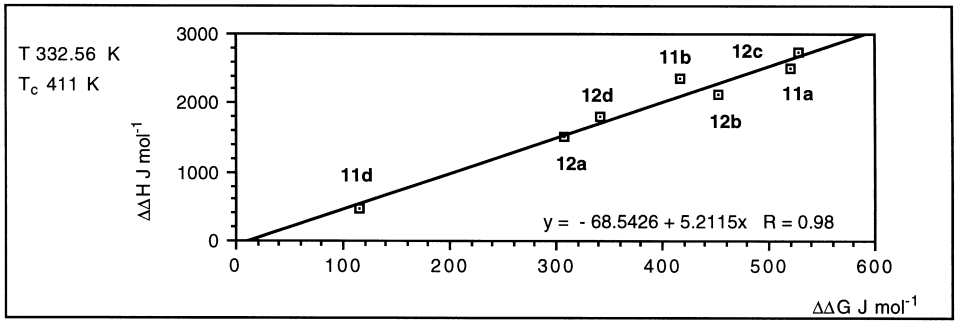


Figure 4. $\Delta\Delta H$ vs $\Delta\Delta G_{Thm}$ for 1-phenyl-1-alkanols **11a**, **11b**, **11d** and bicyclo[3.2.0]hept-2-en-6-ones **12a**–**d** on permethyl-CD

compensation effect for the individual homologous series of analytes on this column, but do not provide sufficient good quality evidence to support it.

Armstrong has studied the thermodynamics of the separation of trifluoroacetylated alcohols and amines with a capillary column coated with 2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl-β-cyclodextrin. Analytes were divided into two groups, those with $\Delta\Delta S$ and $\Delta\Delta H$ greater than 18.0 J K^{-1} mol^{-1} and 7.5 kJ mol^{-1}, respectively (Group I), and those with parameters below these values (Group II). Comparable values were adduced for a homologous γ-cyclodextrin column. It was postulated that the group I analytes are resolved by differential inclusion of the enantiomers within the cavity of the cyclodextrin, whereas the group II analytes are resolved by a looser association possibly with the exterior of the cyclodextrin.[55] This rationale parallels our postulated mechanisms for resolution by permethyl-CD and hepta(2-*O*-benzyl) ether **3c**. Accordingly, if the thermodynamic parameters for the analytes on the permethyl-CD column have larger absolute values than those for the h(Bn)-CM column, it supports the postulated mechanistic differrence. As noted above, pairwise comparison of $\Delta\Delta S$ and $\Delta\Delta H$ for individual analytes on the two columns support this proposal (Tables 2 and 3). All the analytes have larger values of $\Delta\Delta S$ and $\Delta\Delta H$ on the permethyl-CD column than on the h(Bn)-CM column, except for phenylbutanol **11c** and phenylpentanol **11d**. This is further supported by the list of values ranked by descending $\Delta\Delta S$ (Table 4) in which the top of the Table is dominated by separations on the permethyl-CD column. However there is no clean break in the sequence. Four minor breaks in the ranges can be distinguished but they are probably not significant.

It has been suggested that smaller absolute values for $\Delta\Delta H$ and $\Delta\Delta S$ are found for analytes with greater conformational mobility.[56] In the current case increased conformational mobility should parallel ascent of the homologous series. Inspection of Table 4 shows that this trend is followed at best, erratically. For example, although four of the five highest ranked entries are due to the first or second member of the homologous series, the highest and lowest ranked entries are from the third member of homologous series.

In summary, the ratio between the difference in the enthalpy and entropy of binding for the pairs of enantiomers appears to indicate that energetically favourable binding requires tight binding. In the case of the two series of analytes **11a**–**d**, **12a**–**d** on the permethyl-CD column this ratio is constant, whereas for the h(Bn)-column a range of similar values were observed. This is consistant with a range of different modes of enantio-discrimination.

Table 4
Thermodynamic parameters ranked according to ΔΔS

$\Delta\Delta S$ J K^{-1} mol^{-1}	$\Delta\Delta H$ J mol^{-1}	$\Delta\Delta G_{T_{hm}}$ J mol^{-1}	Column, analyte
6.382	2747	528.o	Permethyl-CD, **12c**
5.983	2511	430.5	Permethyl-CD, **11a**
5.839	2359	328.6	Permethyl-CD, **11b**
4.780	2115	453.0	Permethyl-CD, **12b**
4.736	1920	272.6	h(Bn)-CM, **11a**
4.418	1797	342.1	Permethyl-CD, **12d**
3.739	1765	465.6	h(Bn)-CM, **12b**
3.619	1633	374.4	h(Bn)-CM, **12c**
3.442	1504	307.8	Permethyl-CD, **12a**
2.307	936	133.6	h(Bn)-CM, **11b**
2.198	968	203.5	h(Bn)-CM, **12d**
2.136	1117	374.8	h(Bn)-CM, **12a**
2.033	915	208.2	h(Bn)-CM, **11d**
1.086	476	98.73	Permethyl-CD **11d**
0.784	421	148.4	h(Bn)-CM, **11c**

5. Conclusions

In summary, this data set indicates that neither the *gluco*-configuration at C-2 and C-3, nor a fully substituted secondary rim is required for enantio-discrimination by cyclic-oligosaccharides when used as GC-CSPs. However methyl substitution alone in the 3-deoxy-*manno*-series is insufficient to confer enantio-discrimination.

6. Experimental

6.1. General conditions, equipment and software

Purified or dried solvents were freshly distilled under an argon or nitrogen atmosphere from a suitable drying agent.

All reactions were monitored by thin layer chromatography (TLC), which was run on 0.2 mm Merck aluminium backed precoated silica gel plates (60 F_{254}) with UV light or ethanolic phosphomolybdic acid (3%) and heat as developing agents. Merck silica gel 60 (70–230 mesh) was used for flash column chromatography.

NMR spectra were recorded on a Bruker Advance DPX-400 spectrometer with UXNMR software at 400 MHz for protons and 100 MHz for carbon-13. Chemical shifts are relative to tetramethylsilane as an internal standard or the spectrometer reference for the solvent. All integrations for cyclodextrins are reported as monomeric sugar units and hence the true ratios are seven times those reported. Coupling constants patterns were analysed using the computer program Multiplet (release NMRUC51, D. R. Kelly, unpublished work) and are quoted in hertz (Hz). They are reported to 0.1 Hz, but have an uncertainty of ±0.3 Hz, due to the digital resolution of the FID accumulation and Fourier transformation. Spin simulations were performed using RACCOON (P. F. Schatz, University of Wisconsin).

Infra red (IR) spectra were recorded on a Perkin–Elmer 1600 Series FTIR spectrophotometer using

sodium chloride cells. Optical rotations were determined at the sodium D line on an Optical Activity AA-1000 polarimeter at ambient temperatures.

Fast atom bombardment (FAB) mass spectra were recorded at the EPSRC Mass Spectrometry Centre at Swansea. All of the compounds in this report were above the mass limit for FAB-MS PEG referenced high resolution mass spectra at the Swansea facility. Ion cluster patterns were calculated using the computer program HiMass (D. R. Kelly, 1991, unpublished work) and compared visually with the spectra. Ion clusters with normalised intensity differences of less than 5% from that calculated were deemed identical.

GC–MS was run on an HP5890 gas chromatograph linked to a dual pumped (250 l/s, 50 l/s) Trio-1 mass spectrometer with an EI source at 70 eV. Helium head pressure 8 psi. Injector temperature 200°C, split 10:1. All commercial capillary columns used for purity evaluation were J & W (30 m×0.32 mm, 0.25 μm). Column evaluation trials were performed with 12 m columns (see below). Spectra (*m/e* 36–600) were acquired in 0.9 s, followed by an interscan time of 0.1 s, hence retention times have an uncertainty of 0.033 min.

Thermogravimetric analysis (TGA) data were measured on Stanton Redcroft, STA-780 instrument, heating at 10°C/min. Melting points were determined in capillary tubes using a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 240c.

6.2. Synthesis

6.2.1. $6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Hepta-O-(tert-butyldimethylsilyl)-$2^A,2^B,2^C,2^D,2^E,2^F,2^G$-hepta-O-(p-toluenesulfonyl)-β-cyclodextrin, **1b**

4-(*N*,*N*-Dimethylamino)pyridine (6.5 g, 53 mmol) and *p*-toluenesulfonyl chloride (10.5 g, 55 mmol) were added with stirring at room temperature to a mixture of hepta(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **1b** (5.4 g, 2.8 mmol) in dry pyridine (250 ml). The mixture was stirred for 24 h at 50°C. Water (50 ml) was added to the reaction mixture which was concentrated under reduced pressure. The residue was extracted with ethyl acetate (2×250 ml). The extracts were washed with hydrochloric acid (2N, 2×125 ml), saturated sodium hydrogen carbonate (75 ml) and water (2×125 ml), and then dried over sodium sulfate. TLC showed the product at R_f 0.35 ($CHCl_3$:acetone, 95:5). Column chromatography ($CHCl_3$:acetone, 95:5) gave the title compound **1c** as a white powder (5.3 g, 63%). M.p. 172–174°C; *m/z* (FAB^+, NOBA matrix), 8.5%, $M+Na^+$, found 3036, $C_{133}H_{210}O_{49}Si_7S_7Na$: requires 3036. Anal. $C_{133}H_{210}O_{49}Si_7S_7$: requires C, 52.99, H, 7.02; found: C, 52.71, H, 6.84; $[\alpha]_D^{20}$ +62.1 (c 1.11, $CHCl_3$), +57 (c 1.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.3, Ts), 7.30 (2H, d, *J* 8.3, Ts), 5.25 (1H, d, *J* 3.7, H-1), 4.27 (1H, dd, *J* 9.9, 3.7, H-2), 3.88 (1H, dd, *J* 11.6, 2.9, H-6), 3.84 (1H, dd, *J* 9.3, 9.3, H-3), 3.62 (2H, four lines, 'quartet-like intensities', separations 9.4, 8.6, 10.2 Hz, H-4 and H-6′), 3.46 (1H, br d, *J* 9.1, H-5), 3.1 (1H, br or d, *J* 3.0, 3-OH), 2.43 (3H, s, Ts methyl), 0.85 (9H, $C(CH_3)_3$), 0.0 (6H, $Si(CH_3)_2$); δ_H (400 MHz, COSY, $CDCl_3$) 5.25–4.27 (H-1 to H-2), 4.27–3.84 (H-2 to H-3), 3.88 to 3.62 (H-6 to H-6′), 3.84–3.62 (H-3 to H-4), 3.62–3.46 (H-4 to H-5); δ_C (100 MHz, $CDCl_3$) 144.1, 131.9, 128.6, 127.3, 97.8 (C-1), 79.0 (C-2), 78.8 (C-4), 70.6 (C-3), 68.9 (C-5), 60.61 (C-6), 24.8, 20.7, 17.20 [$(CH_3)_3Si$], −2.0 and −2.1 [$(CH_3)_2Si$].

6.2.2. $6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Hepta(O-tert-butyldimethylsilyl)-$2^A,3^A$-$2^B,3^B$-$2^C,3^C$-$2^D,3^D$-$2^E,3^E$-,$2^F,3^F$-$2^G,3^G$-hepta(anhydro)-hepta(manno)-β-cyclodextrin, **2**

To a solution of anhydrous hepta(6-*O*-*tert*-butyldimethylsilyl-2-*O*-tosyl)-β-cyclodextrin **1c** (4.5 g, 1.5 mmol) in dry THF (300 ml) was added sodium hydride (0.9 g, 60% in mineral oil, 23 mmol). The mixture was stirred at 60°C for 4 h. Methanol (300 ml) was added slowly to end the reaction. Hydrochloric acid (2N) was added to pH 7, and the mixture was concentrated under reduced pressure. The residue was

extracted with ethyl acetate (2×400 ml) and then dried over sodium sulfate and concentrated. Column chromatography (ethyl acetate:dichloromethane, 13:87) gave the title compound **2** as a white solid (1.2 g, 44%). M.p. 139–140°C; *m/z* (FAB$^+$, NOBA matrix), 5%, M+Na$^+$, found 1831, $C_{84}H_{154}O_{28}Si_7Na$: requires 1831. Anal. $C_{84}H_{154}O_{28}Si_7$: requires C, 55.78, H, 8.58; found: C, 54.63, H, 8.66. $[\alpha]_D^{20}$ +80.3 (c 1.0, $CHCl_3$), lit. +83.0 (c 1.0 $CHCl_3$);[13] δ_H (400 MHz, $CDCl_3$) 5.17 (1H, s, H-1), 4.11 (1H, d, *J* 9.0, H-4), 3.86 (1H, dd, *J* 11.6, 3.1, H-6′), 3.63 (1H, d, *J* 11.1, H-6), 3.50 (1H, br. d, *J* 8.7, H-5), 3.29 (1H, d, *J* 3.6, H-2), 3.05 (1H, d, *J* 3.5, H-3), 0.84 (9H, $C(CH_3)_3$), 0.0 (6H, $Si(CH_3)_2$); δ_H (400 MHz, COSY, $CDCl_3$) 5.17–3.86 (H-1–H-2), 3.86–3.05 (H-2 to H-3), 3.05–4.11 (H-3 to H-4), 4.11–3.50 (H-4 to H-5), 3.50–3.86 (H-5 to H-6); δ_C (100 MHz, $CDCl_3$) 97.0 (C-1), 69.9 (C-5), 68.8 (C-4), 62.9 (C-6), 53.8 (C-2), 49.5 (C-3), 26.0, 18.6 [$(CH_3)_3Si$], −4.8 and −4.9 [$(CH_3)_2Si$]; δ_H+δ_C ($CDCl_3$), 5.17–97.0 (H-C-1), 4.11–68.8 (H-C-4), 3.83 and 3.63–62.9 (2H-C-6), 3.50–69.9 (H-C-5), 3.29–53.8 (H-C-2), 3.05–49.5 (H-C-3).

*6.2.3. 6^A,6^B,6^C,6^D,6^E,6^F,6^G-Hepta(*O-tert-*butyldimethylsilyl)-3^A,3^B,3^C,3^D,3^E,3^F,3^G-hepta(deoxy)-hepta(*manno*)-β-cyclodextrin,* ***3a***

6.2.3.1. Diisobutylaluminium hydride. Diisobutylaluminium hydride solution (0.7 ml, 1.5 M in toluene) was added slowly at 0°C to a solution of hepta(*manno*-2,3-anhydro-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin **2** (250 mg, 0.14 mmol) in toluene (20 ml) under argon. The solution was stirred at room temperature for 2 h, then refluxed for 24 h at 60°C. Methanol (10 ml) was added slowly to quench the reaction. The mixture was concentrated under reduced pressure and redissolved in dichloromethane. The mixture was extracted with 2N hydrochloric acid (5 ml), saturated sodium hydrogen carbonate (10 ml) and water (10 ml), and then dried over sodium sulfate. Flash silica gel column chromatography (eluent chloroform:methanol, 96:4 to 80:20) gave four fractions. ^{1}H NMR spectra indicated that these were epoxy-alcohols resulting from incomplete reduction. No attempt was made to determine the complete structures.

6.2.3.2. Lithium aluminium hydride. A solution of hepta(*manno*-2,3-anhydro-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin **2** (250 mg, 0.14 mmol) in dry THF (10ml) was added slowly to lithium aluminium hydride (0.38 g, 10 mmol) at room temperature under argon. The solution was stirred for 5 h. Methanol (10 ml) was added slowly to quench the reaction. The mixture was concentrated under reduced pressure and redissolved in dichloromethane. The mixture was extracted with hydrochloric acid (2N, 5 ml), saturated sodium hydrogen carbonate (10 ml) and water (10 ml), and then dried over sodium sulfate. Column chromatography (eluent chloroform:methanol, 96:4 to 80:20) showed partially reduced product, plus traces of the desired product **3a** δ_H (400 MHz, $CDCl_3$) 4.60–4.70 (1H, H-1), 4.0–3.66 (7H, broad peaks, H-2,3,5 and 6), 1.85–2.00 (2H, broad peaks, H-3)

6.2.3.3. Super-Hydride®. Lithium triethylborohydride solution (10 ml, 1.0 M in THF, 10 mmol) was added slowly to cyclo-α-1,4-hepta[-6-*O*-*tert*-butyldimethylsilylmanno-2,3-epoxide] [81] (510 mg, 0.28 mmol) under argon. The solution was stirred at room temperature for 2 h. Lithium triethylborohydride solution (5 ml, 1.0 M in THF, 5 mmol) was added and the reaction refluxed for 48 h at 60°C. Methanol (10 ml) was added slowly to quench the reaction. The mixture was concentrated under reduced pressure and redissolved in dichloromethane. The mixture was extracted with hydrochloric acid (2N, 5 ml), saturated sodium hydrogen carbonate (10 mL) and water (10 ml), and then dried over sodium sulfate. Repeated flash silica gel column chromatography (eluent chloroform:methanol, gradient 96:4 to 80:20) gave the title compound **3a** as a white solid (0.200 g, 40%). M.p. 152–153°C; *m/z* (FAB$^+$, NOBA matrix), 4%,

M−CH_4+Na^+, found 1829, $C_{83}H_{164}O_{28}Si_7Na$: requires 1829. Anal. $C_{84}H_{168}O_{28}Si_7$: requires C, 55.35, H, 9.30; found: C, 55.22, H, 10.18. We were not able to obtain a value for hydrogen within acceptable limits; $[\alpha]_D^{20}$ +87.6 (c 2.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.62 (1H, d, *J* 2.8, H-1), 4.00 (1H, m, H-4), 3.86 (1H, dd, *J* 10.9, 3.1, H-6), 3.73 (2H, m, H-2 and H-5), 3.66 (1H, dd, *J* 10.7, 2, H-6′), 1.95 (2H, m, H-3), 0.85 (9H, $C(CH_3)_3$), 0.0 (6H, $Si(CH_3)_2$), all peaks were broadened at ambient temperatures; δ_H (400 MHz, COSY, $CDCl_3$) 4.62–3.73 (H-1 to H-2), 3.73–1.95 (H-2 to H-3), 1.95–4.00 (H-3 to H-4); δ_C (100 MHz, DEPT, $CDCl_3$) 100.5 (CH, C-1), 74.5 (CH, C-5), 70.4 (CH, C-4), 68.0 (CH, C-2), 62.8 (CH_2, C-6), 32.9 (CH_2, C-3), 26.3 (CH_3, [$(CH_3)_3CSi$]), 18.7 (C, [$(CH_3)_3CSi$]), −4.8 and −4.9 (CH_3, [$(CH_3)_2Si$]); $\delta_H+\delta_C$ ($CDCl_3$) 4.62–100.5 (H-C-1), 4.00–70.4 (H-C-4), 3.86 and 3.66–62.8 (2H-C-6), 3.73–74.5 (H-C-5), 3.70–68.0 (H-C-2), 1.95–32.9 (2H-C-3), 1.95–32.9 (2H-C-3), 0.85–26.3 (9H-3C-[$(CH_3)_3CSi$]).

*6.2.4. $6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Hepta(*O-tert-*butyldimethylsilyl)-$2^A,2^B,2^C,2^D,2^E,2^F,2^G$-hepta(*O-*methyl)-$3^A,3^B,3^C,3^D,3^E,3^F,3^G$-hepta(deoxy)-hepta(*manno*)-β-cyclodextrin,* ***3b***

Sodium hydride (0.4 g, 60% mineral oil) was washed twice with petroleum ether and left to dry under nitrogen; a solution of hepta(6-*O*-*tert*-butyldimethylsilyl-3-deoxy)cyclomaltoheptaose [82a] (0.2 g, 0.11 mmol) in dry THF (3 ml) was added slowly to the neat sodium hydride. Methyl iodide (0.3 ml, 4.7 mmol) was then added dropwise (using a syringe under argon) to the first solution. The reaction mixture was stirred overnight at room temperature. Methanol was added to decompose the excess of hydride, the solvents were evaporated, and a solution of the residue in dichloromethane (10 ml) was washed with water, dried, and concentrated. Column chromatography (4:1 hexane:ethyl acetate) gave white crystals [82b] (0.19 g, 90%). M.p. 124–125°C; *m/z* (FAB$^+$, NOBA matrix), 1943 (19%, M+Na^+, $C_{91}H_{182}O_{28}Si_7Na$: requires 1943). Anal. $C_{91}H_{182}O_{28}Si_7$: requires C, 56.90, H, 9.56; found: C, 57.11, H, 10.02. $[\alpha]_D^{20}$ +83.8 (c 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.73 (1H, br s, H-1), 3.98 (2H, m, H-4 and H-6), 3.65 (1H, d, *J* 11.2, H-6′), 3.54 (1H, m, H-5), 3.29 (3H, s, Me), 3.12 (1H, br s, H-2), 1.86 (2H, m, H-3), 0.83 (9H, $C(CH_3)_3$), 0.0 (6H, $Si(CH_3)_2$), all the peaks were broad at ambient temperatures; δ_H (400 MHz, COSY, $CDCl_3$) 4.73–3.12 (H-1 to H-2), 3.12–1.86 (H-2 to H-3), 1.86–3.98 (H-3 to H-4), 3.98–3.54 and/or 3.65 (H-4, H-5, 2H-6 correlation, ambiguous); δ_C (100 MHz, DEPT, $CDCl_3$) 99.3 (CH, C-1,), 77.7 (CH, C-2), 74.2 (CH, C-4), 71.1 (CH, C-5), 63.2 (CH_2, C-6), 57.0 (Me), 31.2 (CH_2, C-3), 26.4 (CH_3, [$(CH_3)_3CSi$]), 18.7 (C, [$(CH_3)_3CSi$]), −4.7 and −4.8 [$(CH_3)_2Si$].

*6.2.5. $2^A,2^B,2^C,2^D,2^E,2^F,2^G$-Hepta(*O-*benzyl)-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-hepta(*O-tert-*butyldimethylsilyl)-$3^A,3^B,3^C,3^D,3^E,3^F,3^G$-hepta(deoxy)-hepta(*manno*)-β-cyclodextrin,* ***3c***

Sodium hydride (0.4 g, 60% mineral oil, 10 mmol) was washed twice with petroleum ether and left to dry under nitrogen; a solution of hepta(*manno*-6-*O*-*t*-butyldimethylsilyl-3-deoxy)-β-cyclodextrin **3a** (0.2 g, 0.11 mmol) in dry THF (3 ml) was added slowly to the neat sodium hydride. Benzyl bromide (0.4 ml, 1.6 mmol) was then added dropwise. The reaction mixture was stirred for 48 h at room temperature. Methanol was added to decompose the excess of hydride, the solvents were evaporated under reduced pressure (75°C, 0.5 mmHg), and a solution of residue in dichloromethane was washed with water, dried, and concentrated. Column chromatography (eluent hexane:ethyl acetate, 8:1) gave a colourless oily compound [82c] (0.16 g, 59%). M.p. 48–49°C; *m/z* (FAB$^+$, NOBA matrix), 2477 (37%, M+H+Na^+, $C_{133}H_{211}O_{28}Si_7Na$: requires 2477). Anal. $C_{133}H_{210}O_{28}Si_7$: requires C, 65.10, H, 8.63; found: C, 65.14, H, 9.00. $[\alpha]_D^{20}$ +46.9 (c 4.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.39 (5H, Ph), 4.84 (1H, d, *J* 2.4, H-1), 4.60 (1H, d, *J* 12.0, H-7), 4.50 (1H, d, *J* 12.0, H-7′), 4.06 (2H, m, H-4, H-6), 3.78 (1H, d, *J* 11.0, H-6), 3.70 (1H, m, H-5), 3.46 (1H, m, H-2), 1.96 (2H, m, H-3), 0.85 (9H, s, $C(CH_3)_3$), 0.00 (6H, s, $Si(CH_3)_2$); δ_H (400 MHz, COSY, $CDCl_3$) 4.84–3.46 (H-1 to H-2), 3.46–1.96 (H-2 to H-3), 1.96–4.06 (H-3 to H-4), 4.06–3.78 and/or 3.70 (H-4, H-5, 2H-6 correlation, ambiguous); δ_C (100 MHz, DEPT, $CDCl_3$) 139.0 (C,

C-8), 128.7, 127.8 (all CH, C-9, 10 and 11), 99.2 (CH, C-1,), 76.1 (CH, C-2), 74.3 (CH, C-5), 71.4 (CH_2, C-7), 71.2 (CH, C-4), 63.2 (CH_2, C-6), 31.4 (CH_2, C-3), 26.4 (CH_3, [$(CH_3)_3CSi$]), 18.7 (C, [$(CH_3)_3CSi$]), −4.6 and −4.8 [$(CH_3)_2Si$]; $\delta_H+\delta_C$ ($CDCl_3$), 4.84–99.2 (C-H-1), 4.60 and 4.50–71.4 (2H-C-7), 4.06 and 3.78–63.2 (2H-C-6), 4.06–74.3 (H-C-5), 3.70–71.2 (H-C-4), 3.46–76.1 (H-C-2), 1.96–31.4 (2H-C-3), 26.4–0.85 (9H-3C-[$(CH_3)_3CSi$]); TGA onset 260°C, 325°C (25%), 380°C (80%), 450°C (90%).

6.2.6. (S)-1-Phenyl-1-pentanol ***11d***[33]

A solution of valerophenone **32** (3 g, 0.019 mol) in ethanol (2 ml) was added to a yeast solution prepared from sucrose (100 g), D-glucose (100 g) and fresh yeast (200 g, NG & SF company) dissolved in water (3 l). The reaction mixture was stirred overnight at 32°C. The crude product was filtered through Celite, and extracted with petroleum ether (40–60). The ether extracts were washed with water (1×200 ml) and dried over sodium sulfate. Flash silica gel column chromatography using petroleum ether and ether (95:5 to 90:10) as eluant gave (*S*)-1-phenyl-1-pentanol **11d** as a yellowish liquid (0.24 g, 8% yield). *m/z* EI+: 164, (6%, M^+, $C_{11}H_{16}O$: requires 164.1201, found 164.1201, 0 ppm, error) 108 (9), 107 (100, $PhCHOH^+$ or hydroxytropylium), 106 (29), 105 (7), 80 (5), 79 (57), 78 (29), 77 (35), 76 (13), 51 (6), 50 (6), 39 (9); δ_H (360, $CDCl_3$) 0.87 (3H, t *J* 7.1 Hz, H-5), 1.35 (4H, m, H-3 and 4), 1.72 (2H, m, H-2), 4.65 (1H, t *J* 6.7, H-1), 7.29 (5H, m, Ar); δ_C (100 MHz, DEPT) 143.9 (C, C-6), 127.3, 126.3, 124.9 (3CH, C-7 to C-9), 73.5 (CH, C-1), 37.7 (CH_2, C-2), 26.9 (CH_2, C-3), 21.8 (CH_2, C-4), 13.0 (CH_3, C-5); $[\alpha]_D^{26}$ −13.65 (c 13.3, benzene), 79% ee based on the original literature rotation $[\alpha]_D^{25}$ −17.17, (c 13.3, benzene)[57] which has now been revised[44] to $[\alpha]_D^{25}$ −20.61. On the basis that the original material had 83.3% ee, the revised value is 66% ee. Chiral GC–MS measurement, 45% ee; ν_{max} (neat)/cm^{-1} 3362 (br, OH), 2950 (s), 2859 (m), 1708 (w), 1493 (m), 1040 (m); GC t_R 28.02 min for the (*S*)-enantiomer (72%) and 28.90 min for the (*R*)-enantiomer (28%), CDX-B (30 m×0.32 mm, 0.25 μm J & W), 110°C isothermal (40 min).

*6.2.7. (1*S*,13*S*)-α-Methoxy-α-trifluoromethyl(phenylacetyl)-1-phenyl-1-pentanol* ***33***

A mixture of the 1-phenyl-1-pentanol **11d** (0.16 g, 1.0 mmol, prepared by yeast reduction), 4-dimethylaminopyridine DMAP (a few crystals), and triethylamine (0.5 ml, 5.0 mmol) in dichloromethane (10 ml) was stirred for 60 min at 0°C. (*R*)-α-Methoxy-α-trifluoromethyl(phenylacetyl) chloride[58] (0.53 g, 2.1 mmol) was added slowly and the mixture was stirred for 24 h. The mixture was diluted with dichloromethane (30 ml), washed with dilute hydrochloric acid (5 ml), a saturated solution of sodium hydrogen carbonate (2×5 ml) and water (2×10 ml). It was then dried over sodium sulfate. The crude residue was purified by flash silica column chromatography using petroleum ether and ether (95:5 to 90:10) as eluant and recolumned using benzene as eluent to give a yellowish liquid (0.22 g, 58% yield). Crystallisation was attempted using hexane, benzene, ether, petroleum ether and mixtures thereof, but no crystals could be obtained. *m/z* CI+: (28%, $M+NH_4^+$, found 398.1943. $C_{21}H_{27}NF_3O_3$: requires 398.1943), 381 [M+1] (3), 252 (36), 198 (29), 164 (100), 147 (84), 108 (22), 91 (70), 46 (12); ν_{max} (neat)/cm^{-1} 2950 (m), 2859 (m), 1747 (s, C=O), 1453 (w), 1260 (s), 1169 (s), 1018 (m); δ_H (360, $CDCl_3$) 0.82 (3H, t *J* 7.0 Hz, H-5), 1.25 (4H, m, H-3 and 4), 1.78 and 1.95 (2H, m, H-2), 3.43 (3H, s, OMe), 5.92 (1H, dd *J* 8.1, 5.8, H-1), 7.32 (10H, m, Ar). This ^1H NMR data is for the major diastereoisomer. Signals for the minor component were observed at δ_H 5.86 (1H, dd *J* 7.8, 6.3), 3.52 (1H, s, OMe), but all other signals overlapped with those of the major diastereoisomer. The ratio was circa 82:16 (64% de) from NMR integration.

Table 5
Unretained peak retention times (t_0) in minutes at different temperatures

Column	30°C	40°C	50°C	60°C	70°C	80°C	90°C	100°C
h(Bn)-CM	0.42	0.41	0.38	0.37	0.36	0.35	0.34	0.34
Permethyl-CD	0.35	0.34	0.33	0.33	0.31	0.30	0.28	0.27

6.3. Manufacture and evaluation of capillary columns

Columns prepared in this work were 12 m in length, 0.25 mm internal diameter and 0.20 μm stationary film thickness (β=313). The commercial column was permethyl β-cyclodextrin (J & W, 12 m length, 0.32 mm internal diameter, 0.25 μm film thickness) which has the same phase ratio (β=320).

Fused silica tubing was washed with nitric acid (20%) for 3 h (20 ml) to remove reactive cations, water (1 h, 7 ml), acetone (1 h, 10 ml) and dichloromethane (1 h, 10 ml) and dehydrated at 200°C for 1 h. The column was deactivated with diphenyltetramethyldisilazane using the static coating method (sealed with Super glue), installed in the gas chromatograph and heated for 1 h at 300°C under helium. Finally the column was washed with dichloromethane before coating with the cyclodextrin stationary phases.

The derivatised cyclodextrin (15% w/w) was mixed with the liquid matrix (OV-1701, 85% w/w) diluted with dichloromethane and statically coated to form a 0.20 μm film thickness using a water bath at 40°C and a vacuum pump. Columns were 'conditioned' in the GC–MS for at least 6 h at 60–80°C before tests for enantioselection.

Racemic analytes were commercial products or were prepared in these laboratories. Homogeneity was determined by ^{1}H and/or ^{13}C NMR. The spectra of α-ionone **6** were checked repeatedly, because it can isomerise to the thermodynamically more stable and achiral isomer, β-ionone. The 7-*endo*-alkyl-bicyclo[3.2.0]hept-2-ene-6-ones **12b**,**c**,**d** contained 10–30% of the 7-*exo*-isomer which was ignored in the column evaluations.[59]

All amines (except DL-valine methyl ester, **32**) were trifluoroacetylated prior to analysis. The amino compound (1 mg) was reacted with trifluoroacetic anhydride (50 μl) in dichloromethane (200 μl) for 60 min at 100°C. Excess reagent was removed by evaporation and the residue dissolved in dichloromethane.

6.4. Retention times and thermodynamic study

Retention times of homologous series were determined simultaneously. GC detection normally requires a solvent delay (3–5 min) in which the filament current is reduced and no peaks can be detected. This maximises the dynamic range of the data system and prevents carbonisation/destruction of the filament. In a few cases, analytes had retention times that were less than the normal solvent delay, even at ambient oven temperatures and the solvent delay was reduced to 1 min or less. Analytes (20 mg) were dissolved in dichloromethane (1 ml) and 1 μl was injected into the GC–MS.

The unretained peak retention times were determined by injection of methane and are shown in Table 5.

All retention times used in the calculation of thermodynamic data are at least duplicates and are averaged, although in most cases the retention times differences were less than or equal to the scan time of the mass spectrometer (0.9 s+0.1 s interscan time). The uncertainties in the retention times were used to calculate the error ranges for α, ΔΔH and ΔΔS in Tables 2 and 3 using the methods described below.

The mean and harmonic means of the temperatures used in the thermodynamic study were: 60–90°C, T_m 348.16 K, T_{hm} 347.80 K; 60–80°C, T_m 343.16 K, T_{hm} 342.97 K; 40–80°C, T_m 333.16 K, T_{hm} 332.56

K; 40–70°C, T_m 328.16 K, T_{hm} 327.78 K. For the four runs, T_m 337.54, T_{hm} 336.94. The difference between the harmonic mean and the mean in each case is <1 K which is comparable to the accuracy of the temperature control of the oven; circa ±0.5 K.

The enthalpy difference ($\Delta\Delta H$), entropy difference ($\Delta\Delta S$), free energy difference ($\Delta\Delta G$) and free energy difference at the harmonic mean temperature ($\Delta\Delta G_{Thm}$) for each pair of enantiomers were calculated in three ways.

(i) Application of the van't Hoff and Gibbs–Helmholtz equations for the free energy of interaction ($\Delta\Delta G=-RT\ln\alpha$ and $\ln\alpha=-\Delta\Delta H/RT+\Delta\Delta S/R$). A plot of $\ln\alpha$ vs $1/T$ enables $\Delta\Delta H$ to be calculated from the gradient and $\Delta\Delta S$ from the intercept by multiplying by the gas constant (R).[60] All gradients and intercepts were determined by linear regression ($R\geq 0.99$, Cricket Graph).

(ii) Graphically by using the modification of Klug et al. of the Gibbs–Helmoltz equation.[50] A plot of $\ln\alpha$ vs $(1/T-1/T_{hm})$ enables $\Delta\Delta H$ to be calculated from the gradient and $\Delta\Delta S$ from ((gradient/T_{hm})-intercept)×R. This method removes bias in the results, due to the temperature at which the measurements were made.

(iii) $\Delta\Delta H$ and $\Delta\Delta G_{Thm}$ were calculated (non-graphically) by adapting the second method of Klug et al.[50] For measurements of $\ln\alpha$ at 1,n temperatures T (subscripts indicate range of summations):

$$\Delta\Delta G_{Thm} = -RT_{hm}(\sum \ln\alpha_{1,n})/n \text{ at } T_{hm}$$

and

$$\Delta\Delta H = -R(\sum(\ln\alpha_{1,n} \times (1/T_{1,n} - 1/T_{hm}))/\sum((1/T_{1,n} - 1/T_{hm})^2)).$$

These values were then used to calculate $\Delta\Delta S$ and are reported in Tables 2 and 3.

The ratio of $\Delta\Delta H$ to $\Delta\Delta S$ was used to calculate the temperature at which no separation occurs for each analyte on each column. This is derived as follows: $\Delta\Delta G=\Delta\Delta H-T\Delta\Delta S$. If $\Delta\Delta G=0$ then $\Delta\Delta H=T\Delta\Delta S$ and hence $\Delta\Delta H/\Delta\Delta S=T$.

For each set of analytes on each column, the compensation temperature (T_c; also designated T_{iso} or β by some authors) was calculated from the slope of a graph of $\Delta\Delta H$ vs $\Delta\Delta G_{Thm}$ (Fig. 3) as follows:

If a linear enthalpy–entropy compensation exists, $\Delta\Delta H/\Delta\Delta S=T_c$ where T_c is a constant for all the analytes.

Substituting $\Delta\Delta S=\Delta\Delta H/T_c$ in the Gibbs–Helmholtz equation ($\Delta\Delta G_{Thm}=\Delta\Delta H-T_{hm}\Delta\Delta S$) gives

$$\Delta\Delta G_{Thm} = \Delta\Delta H - T_{hm}\Delta\Delta H/T_c$$

which rearrranges to

$$\Delta\Delta G_{Thm} = \Delta\Delta H((T_c - T_{hm})/T_c)$$

and hence

$$\Delta\Delta H = \Delta\Delta G_{Thm}(T_c/(T_c - T_{hm})).$$

Consequently a graph of $\Delta\Delta H$ vs $\Delta\Delta G_{Thm}$ for a series of analytes showing linear enthalpy–entropy compensation has a $\Delta\Delta H$ intercept of zero and a gradient $m=(T_c/(T_c-T_{hm}))$

Rearrangement gives $T_c=T_{hm}/(1-(1/m))$.

It should be noted that compensation temperatures for individual analytes are designated as $\Delta\Delta H/\Delta\Delta S$, whereas common compensation temperatures for series of analytes are designated T_c. This avoids the use of subscripts and avoids the implication that a compensation temperature for a given analyte necessarily forms part of a series.

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