Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2471–2480

TETRAHEDRON:
ASYMMETRY

Stereoelectronic effects in the reactions of conformationally restricted, substituted cyclohexane-1,2-diones with 1,2-diols

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Received 18 May 1998; accepted 9 June 1998

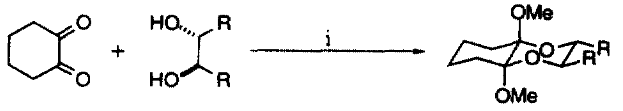
Abstract

The asymmetric synthesis of a C_2-symmetric cyclic 1,2-diketone is reported along with investigations into its properties as a potential asymmetric protecting group for 1,2-diols as the corresponding 1,2-diacetal. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have recently introduced the concept of 1,2-diacetals as a highly effective protecting group for *trans*-vicinal diols (Fig. 1).[1,2] In line with the progress achieved with chiral dispiroketal protection of diols,[3] it was felt that an asymmetric version of the cyclohexane-1,2-diacetal (CDA) procedure would represent an attractive advance.

In order to develop a suitable chiral diacetal, it was reasoned that introduction of substituents onto the initial cyclohexane-1,2-dione reagent would provide the opportunity for further chirality control upon reaction with a 1,2-diol. It was anticipated that any substituents on the *reagent* ring should have a preference for equatorial orientation in the corresponding 1,2-diacetal products. Incorporation of these substituents in an asymmetric fashion, in combination with the preference for their equatorial arrangement of the 1,2-diol, should control the *absolute* stereochemistry of each acetal centre formed. The other selectivity control elements operating during acetal formation, precedented in the achiral



Reagents and conditions: i. cat. CSA, $CH(OMe)_3$, MeOH, reflux.

Fig. 1.

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PII: S0957-4166(98)00227-4

(S,S)-1 (R,R)-1

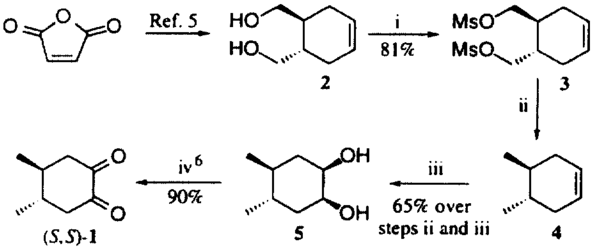
Fig. 2.

reagent series, of full anomeric stabilisation and the formation of an all-chair array, should lead to the formation of a single diastereomeric diacetal product on reaction with the 1,2-diol.

2. Results and discussion

The potential availability of both enantiomers of the 1,2-diketone **1** fulfils the reagent criteria for this study (Fig. 2). Substitution at the 4- and 5-positions of the cyclohexane in a *trans*-relationship maintains the C_2-symmetry of the reagent and avoids functionalisation at the potentially epimerisable 3- and 6-sites. The methyl control substituents also allow characteristic doublets to appear well away from the key structural diagnostic area of the ^{1}H NMR spectrum between 3 and 5 ppm.

The reagent is synthesised using an asymmetric Diels–Alder reaction as the important step, leading to diol **2**.[4,5] The synthesis of this reagent yields optically pure material (as judged by chiral GC) and may be applied to furnish diketones (*S*,*S*)-**1** and (*R*,*R*)-**1** as both enantiomers of the menthol chiral auxiliary are readily available (Scheme 1).

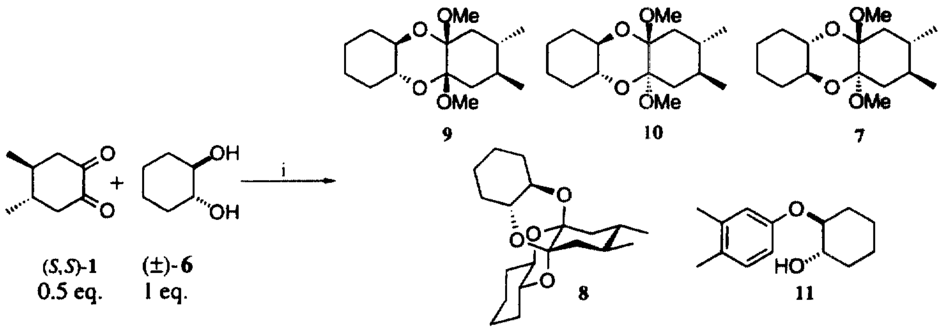


Scheme 1. *Reagents and conditions*: i. MsCl, pyridine; ii. $LiAlH_4$, Et_2O, THF; iii. cat. OsO_4, NMO, *t*-BuOH, THF, H_2O; iv. TFAA, DMSO, DCM, Et_3N[6]

The potential resolution of (±)-cyclohexane-1,2-diol **6** was selected as the initial application for the new reagent. It was anticipated that the chirality of the reagent 1,2-diketone would match that of a single enantiomer of the racemic diol mixture, employing the control elements discussed earlier. The reagent **1** was therefore expected to effect a resolution of the diol material by selective formation of a single diacetal diastereoisomer.

However, reaction of diketone (*S*,*S*)-**1** with (±)-cyclohexane-1,2-diol **6** under the standard CDA forming conditions[7] yielded *four* major diacetal-like products **7**–**10** and a minor aromatic compound **11** (Scheme 2).

The relative amounts of these compounds on isolation depended greatly as to when the reaction was terminated. The desired chirality matched CDA-like product **7**, incorporating the (*S*,*S*)-enantiomer of the diol, was isolated along with three mismatched diol adducts. These were a double addition product **8** of exclusively the (*R*,*R*)-diol into the asymmetric diketone, a monoaddition of the (*R*,*R*)-diol to yield the non-symmetric dimethoxydiacetal **9** and a monoaddition of the (*R*,*R*)-diol to give a symmetrical dimethoxydiacetal **10**. A fifth, aromatised compound **11** was also observed in small quantities from the reaction. This product was thought to have been formed by double elimination of methanol from the diacetal followed by a series of hydride shifts to gain aromaticity.



Scheme 2. *Reagents and conditions*: i. cat. CSA, $CH(OMe)_3$, MeOH, reflux

Structural assignment of the products could be made on a crude level, regarding whether the diacetal product had C_2-symmetry or not, by ^{13}C NMR analysis. Although it was possible to isolate all of the adducts from reaction of the racemic diol with the homochiral diketone by chromatography, the adducts were also synthesised in crossover experiments by reaction of the homochiral diol with the homochiral diketone. In separate experiments, both the matched and mismatched enantiomers of the homochiral diol were reacted with the homochiral diketone to confirm the enantiomer of the diol incorporated in the observed products. Extensive efforts to try and equilibrate the racemic diol reaction mixture to a single diacetal product indicated that mixtures of these competing dione adducts would always be obtained over the timescales employed. As these experiments did not lead substantially to any of the desired CDA reactivity, it remained to explain the observed product outcome in Scheme 2, particularly relating to the diacetal adducts **8**, **9** and **10** featuring the mismatched enantiomer of the diol.

The low molecular weight of the monoaddition compounds involved allowed the progress of the reaction to be readily followed by GC. The reaction of homochiral diketone **1** with racemic cyclohexane-1,2-diol **6**, yielding the mixture of diacetal compounds, was analysed at regular intervals by GC using 18-crown-6 as an internal standard. It was possible to observe the changes in the relative diacetal product distribution with time by this method. The results of the study were encouraging as they indicated that the fully stabilised matched CDA adduct **7** appeared to be the thermodynamically favoured course for the reaction. The amount of the matched CDA product **7** continued to rise with time. In contrast to this trend, the amounts of mismatched monoadducts **9** and **10** fell, over the timescale of the reaction, suggesting that these were kinetic adducts and thermodynamically less favoured (Fig. 3).

Confident in the status of the fully stabilised CDA product **7** as the thermodynamically most stable diacetal product from the GC data meant that sealed tube reactions with the dimethyl reagent, to force the thermodynamic course of the process, was a sensible option. It was hoped that high temperature conditions would overcome the formation of the kinetic mismatched diol adducts and effect the desired resolution by exclusive formation of the thermodynamically favoured matched CDA **7**. The failure of this approach however was hinted at earlier as the aromatic byproduct **11** had been observed. The most thermodynamically favourable and totally non-reversible pathway was aromatisation and this was indeed the course followed by the reaction under these harsh conditions. Reaction in a sealed tube therefore at 150°C for 22 hours lead to exclusive formation of the aromatised product **11**.

Structural variants on the diketone reagent **1** were also synthesised. Both the dimethyl and dibenzyl ethers of diol **2** (Scheme 1) were synthesised and progressed through to give the corresponding diketone reagents **12** and **13** (Fig. 4). The GC experiments were repeated using these diketones and similar trends in product distribution were observed. Reaction of these diketones was *slower* than with the dimethyl diketone **1**. These diketones also showed a greater tendency to aromatise when incorporated in diacetal structures. A small amount of a second symmetrical diacetal **14**, formed by reaction of the matched (*S*,*S*)-

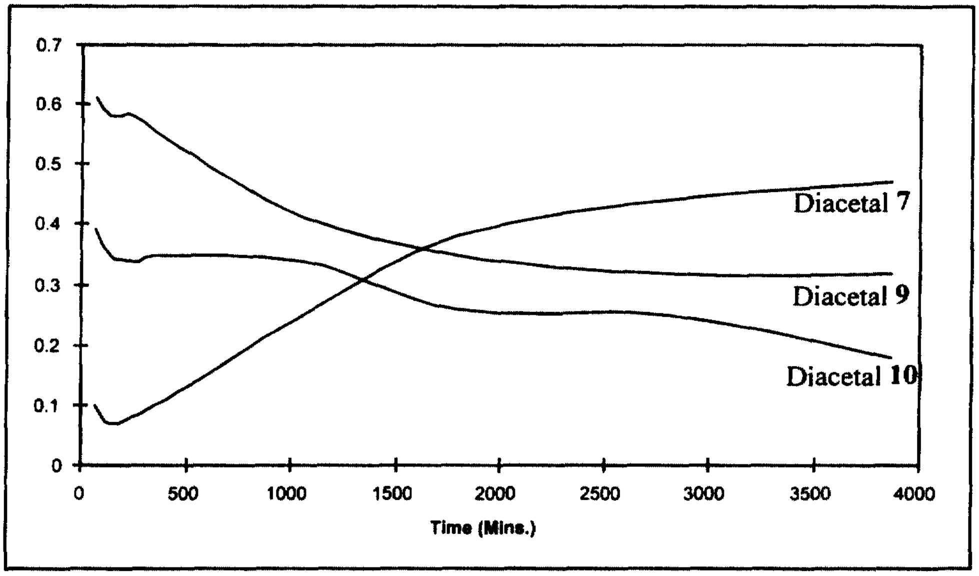
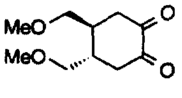


Fig. 3.



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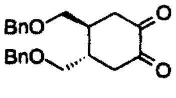

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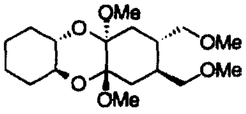

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Fig. 4.

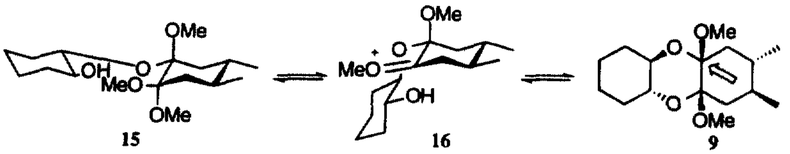

Fig. 5.

diol with the dimethylated diketone **12** was observed in this series of reactions (Fig. 4). This was not seen in the first series using diketone **1**.

The clearest way of addressing the explanation for the formation of the products observed is to consider the fates of the two enantiomers of the diol racemate separately, on reaction with the *homochiral* diketone reagent. These theories are governed by a number of assumptions concerning the reactivity of the system, the most important being the ubiquitous presence of equatorially orientated control groups on the *reagent* ring. Considering the case of the mismatched diol first, the assumption has been made that initial equatorial attack is made on a planar methoxonium ion by the first alcohol of the 1,2-diol to give **15**. The second alcohol group of the 1,2-diol then takes part in a tethered ring closure onto the vicinal methoxonium ion **16**. The six membered tether enforces an axial orientation of attack for the hydroxyl group. Initial attack of the alcohol, whether it be axial or equatorial, leads to the same product **9** on tethered ring closure. This chair dioxane-fused product **9** is observed and isolated from the reaction mixture (Fig. 5). The dioxane ring formed by this process adopts a chair conformation very easily. However, despite its all-chair conformation it is lacking an anomeric effect at one of the formed acetal centres.

Had the central dioxane ring been able to flip its conformation at this stage, the non-fully anomerically

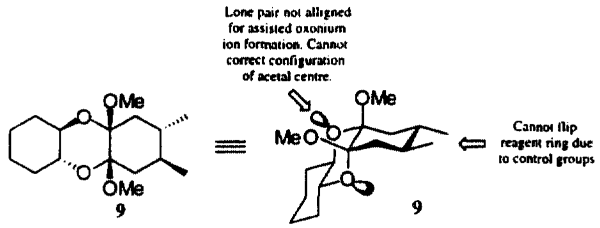

Fig. 6.

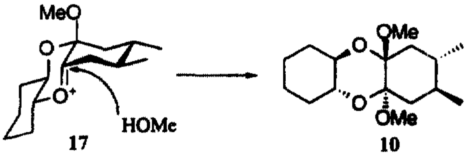

Fig. 7.

stabilised acetal centre indicated in **9** (Fig. 5) would have been able to invert and lead to a fully anomerically stabilised CDA. However, the required simultaneous ring flip of the reagent ring on inversion of the dioxane would have forced the conformationally restricting methyl groups into a diaxial orientation. This breaks the fundamental assumption for the explanation of this reactivity — diequatorial control groups must be retained. Therefore, the indicated oxygen lone pair of **9** (Fig. 6) cannot assume an antiperiplanar orientation with the methoxy leaving group, thus preventing assisted oxonium ion formation.

It is proposed that both symmetrical fused product **10** and double addition product **8** are formed from the initial chair fused adduct **9**. Of the three potential oxonium ions that can be formed from **9**, only **17**, where the central dioxane is not cleaved, offers a route to the symmetrical product **10**. Trapping of oxonium ion **17** with methanol from the opposite face to the methoxy group at the vicinal acetal centre leads to the symmetrical mismatched diol addition product **10** (Fig. 7).

The double addition product **8** must come about by initial cleavage of the equatorial dioxane bond in **9** to give oxonium ion **18**. Attack on oxonium ion **18** from the least hindered face by a second equivalent of mismatched diol gives the *trans*-diaxial intermediate **19**. Sequential oxonium ion formation and tethered ring-closure gives the mismatched diol double addition product **8**, which is C_2-symmetric (Fig. 8). These proposals, within the stated parameters, account for the formation of the three observed mismatched diol adducts. The theory depends on the formation of the non-symmetrical chair fused product **9** as the initial intermediate for the formation of the other two mismatched compounds observed.

Considering the fate of the matched diol, two products containing the matched diol enantiomer have been observed. Assuming the fixed conformation of the reagent cyclohexane ring, the stereochemistry of the matched diol now enforces a tethered ring closure that can only take place to yield a boat dioxane **20** (Fig. 9). This is in contrast to the mismatched diol case (Fig. 5) which could close to a more favourable chair conformation in the formation of non-symmetrical **9**. Any attempt to join the matched diol onto the diketone reagent to give a chair dioxane fusion would demand a ring flip of the reagent cyclohexane ring leading to disfavoured diaxial control groups. This boat fused dioxane **20** was not however observed as an intermediate in the reaction.

The most probable mechanism for the formation of the matched CDA product **7** invokes the unsymmetrical boat fusion product of type **20** as a disfavoured but highly reactive intermediate (Fig. 10). The lone pairs in **20** are aligned for oxonium ion formation at each acetal centre, unlike in **9** in the mismatched diol case (Fig. 6). If the matched diol boat fusion product **20** could be formed initially, its pathway to the matched CDA adduct **7** should be rapid and facile as the lone pair orientations always appear to be

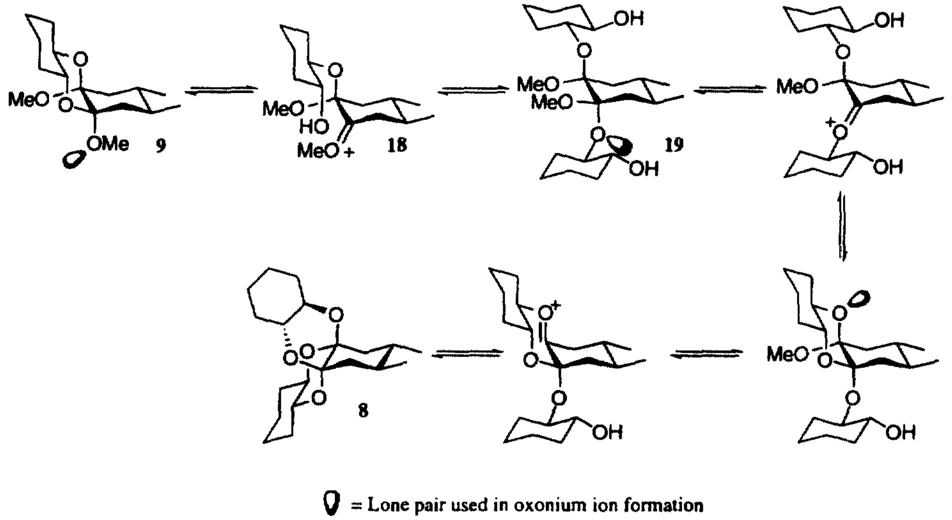

Fig. 8.

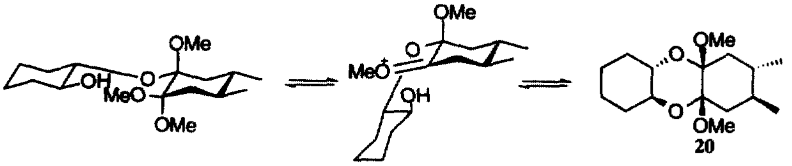

Fig. 9.

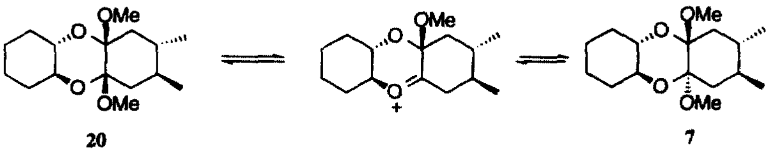

Fig. 10.

favourable. Evidently the formation of this boat fused precursor is not facile and this is illustrated in the low amounts of matched diol adducts formed relative to mismatched adducts **8**, **9** and **10**.

In summary, the initial reaction of the mismatched diol kinetically consumes the asymmetric diketone reagent. Reaction of the matched diol is slow and initially disfavoured due to the energetic penalty of forming boat fused **20**. Therefore, the thermodynamic CDA product **7** only forms *via* a slow equilibration process. By this time, a competing, irreversible degradation process is also taking place through an aromatisation reaction.

Studies in the deprotection of the separated diacetal adducts **7**, **8** and **9**, using TFA:water (9:1) at 40°C, yielded the expected enantiomer of diol in each case. The diols, derivatised as their diacetates for analysis were recovered in greater than 95% e.e. as judged by chiral GC.

In conclusion, the synthesis of an asymmetric 1,2-diketone variant for the CDA procedure has illustrated some interesting constraints on the use of such cyclic 1,2-diketones in procedures that had previously enjoyed success in the asymmetric application of dispiroketal chemistry. (±)-Cyclohexane-1,2-diol has served as an excellent model in the elucidation of the mechanistic aspects of the CDA reaction. These observations have added to our understanding of the CDA process and have clarified the implications for this type of asymmetric cyclic diketone reagent in synthesis.

3. Experimental

^1H NMR spectra were recorded on a Bruker DRX-600, a Bruker DRX-500, a Bruker AM-400, a Bruker AC-250 or a Bruker AC-200 spectrometer as solutions in deuteriochloroform ($CDCl_3$) using the residual $CHCl_3$ as a reference (7.26 ppm) unless otherwise stated. ^{13}C spectra were recorded on a Bruker AC-200, a Bruker AC-250 or Bruker AM-400 spectrometer and chemical shifts are quoted relative to the middle peak of $CDCl_3$ (77 ppm). Coupling constants are quoted in hertz. Mass spectra were obtained on a Kratos MS890MS spectrometer at the Department of Chemistry, University of Cambridge. Microanalyses were performed in the University of Cambridge microanalyses laboratory. Optical rotations were measured using an Optical Activity AA-1000 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Ether refers to diethyl ether and petrol refers to light petroleum ether (b.p. 40–60°C). All solvents were purified before use: petroleum ether was redistilled, dichloromethane was distilled from calcium hydride, ether and terahydrofuran were distilled from sodium–benzophenone ketyl and methanol was distilled from magnesium. Unless otherwise stated, reactions were carried out under an argon atmosphere in oven dried glassware (150°C overnight). Reagents were either dried by standard procedures or used as purchased. Flash chromatography was carried out using Merck Kieselgel 60 (0.040–0.063 mm) under pressure. Thin layer chromatography was visualised with UV light (254 nm) and acidified ammonium molybdate(IV) as appropriate.

3.1. (1S,2S)-1,2-Di-(methanesulfonyloxymethyl)-cyclohex-4-ene 3

A solution of (1*S*,2*S*)-cyclohex-4-ene-1,2-dimethanol **2** (12.58 g, 88.5 mmol) in pyridine (100 ml) was stirred at 0°C. Methanesulfonyl chloride (27.44 ml, 354 mmol) was added to the mixture dropwise over a period of 40 minutes. The mixture was stirred at room temperature for a further 17 hours. Ice water (*ca.* 100 ml) was added and the mixture was extracted with DCM (3×75 ml). The combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: ether:petrol=4:1) to give the dimesylate **3** as a white solid (21.4 g, 81%). Found: C 40.55, H 6.05. $C_{10}H_{18}O_6S_2$ requires C 40.26, H 6.08%; m.p. 55°C; $[\alpha]_D^{22}$ +59.4 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 1758, 1655, 1462, 1336, 1174, 1070, 981, 849, 785, 747; δ_H (400 MHz; $CDCl_3$), [1.98–1.99 (2H, m), 2.14–2.17 (4H, m), H-1, H-2, H-3, H-6], 3.03 (6H, s, $2\times OSO_2CH_3$), 4.21 (2H, dd, *J*=5.0, 10.0, $2\times CH_aH_bOSO_2Me$), 4.27 (2H, dd, *J*=5.0, 10.0, $2\times CH_aH_bOSO_2Me$), 5.63 (2H, s, vinyl-H); δ_C (100 MHz; $CDCl_3$) 25.9 (C-3, C-6), 33.7 (C-1, C-2), 37.4 ($2\times SO_2CH_3$), 70.8 ($2\times CH_2OSO_2Me$), 124.8 (C-4, C-5); *m/z* (EI) 202 (7%, $M-HOSO_2CH_3^+$), 106 (83), 91 (100), 78 (61); found: $[M-HOSO_2CH_3]^+$ 202.0644. $C_9H_{14}O_3S$ requires $M-HOSO_2CH_3$ 202.0644.

3.2. (1S,2S)-Dimethyl cyclohex-4-ene 4

To a solution of lithium aluminium hydride (493 mg, 13.0 mmol) in ether (16.5 ml) heated to reflux was added (1*S*,2*S*)-cyclohex-4-ene-1,2-dimethanol dimethanesulfonate **3** (822 mg, 2.76 mmol) in the minimum amount of THF (2.5 ml). The reaction was left at reflux for 15 hours. On cooling, careful addition of saturated aqueous ammonium chloride solution (5 ml) was followed by stirring for 1 hour. The organic phase was then dried (Na_2SO_4). Evaporation of the solvent was carried out with care due to the volatilty of the product **4** using a rotary evaporator with the water bath set to 50°C and no vacuum applied. This allowed the solvent to be distilled off leaving the product oil still slightly contaminated with THF. δ_H (500 MHz; $CDCl_3$) 0.94 (6H, d, *J*=7.5, $2\times CH_3$), 5.62 (2H, d, *J*=2.5, vinyl-H).

3.3. (1R,2S,4S,5S)-4,5-Dimethyl cyclohexane-1,2-diol 5

Osmium tetroxide (2.5% wt. solution in *t*-butanol, 2.4 ml, 0.24 mmol) was added to a biphasic solution of (1*S*,2*S*)-dimethylcyclohex-4-ene **4** (*ca.* 2.4 g), *N*-methylmorpholine-*N*-oxide (2.5 ml, 24.0 mmol) in THF (15 ml), *t*-BuOH (9 ml) and water (2 ml). The mixture was stirred for 17 hours. Sodium sulfite (3 g) was added to the mixture followed by water (10 ml). The mixture was extracted once with ethyl acetate (15 ml). The organic phase was then extracted with *n*-BuOH (3×15 ml). The combined organic portions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: ether:methanol=99:1) to yield the diol **5** (2.0 g, 65% over 2 steps from (1*S*,2*S*)-cyclohex-4-ene-1,2-dimethanol dimethanesulfonate) as a white solid. Found: C 66.76, H 11.39. $C_8H_{16}O_2$ requires C 66.63, H 11.19%; m.p. 88–89°C; $[\alpha]_D^{22}$ +34.3 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3329, 3022, 2892, 1436, 1069, 1023, 957, 661; δ_H (400 MHz; $CDCl_3$), 0.85 (3H, d, *J*=6.5, 4-CH_3), 0.92 (3H, d, *J*=6.5, 5-CH_3), 0.97–1.10 (1H, m, H-5), 1.16 (1H, ddd, *J*=2.5, 12.5, 14.0, H-3$_{ax}$), 1.28–1.39 (1H, m, H-4), 1.39 (1H, dd *J*=12.0, 24.0, H-6$_{ax}$), 1.61 (1H, dddd, 1.0, 3.5, 4.5, 12.0, H-6$_{eq}$), 1.87 (1H, dt, *J*=3.5, 14.0, H-3$_{eq}$), [2.11 (1H, br s) and 2.29 (1H, br s), 2×OH], 3.61 (1H, m, H-1), 3.91 (1H, d, *J*=2.5, H-2); δ_C (100 MHz; $CDCl_3$), [19.1 and 19.8 (2×CH_3)], [31.3 and 37.0 (C-4, C-5)], [37.4 and 39.7 (C-3, C-6)], [69.9 and 71.7 (C-1, C-2)]; *m/z* (EI) 143 (4%, $M-H^+$), 124 (20), 106 (46), 93 (100), 79 (66), 67 (29), 57 (22), 53 (20); found; $[M-H]^+$ 143.1066. $C_8H_{15}O_2$ requires M−H 143.1072.

3.4. (4S,5S)-2-Hydroxy-4,5-dimethyl-cyclohex-2-enone [(4S,5S)-4,5-dimethyl-cyclohexane-1,2-dione] 1

Trifluoroacetic anhydride (0.89 ml, 6.30 mmol) was added dropwise over a period of 20 minutes to a solution of DMSO (0.49 ml, 6.95 mmol) in DCM (30 ml) at −60°C. The solution was allowed to stir for a further 20 minutes. A solution of (1*R*,2*S*,4*S*,5*S*)-4,5-dimethyl-1,2-cyclohexanediol **5** in DCM (4 ml) was added *via* cannula and the solution left stirring at −60°C for 1.5 hours. Triethylamine (2 ml, 14.3 mmol) was added dropwise and the yellow solution left at −60°C for 1 hour. The solution was then allowed to reach room temperature. The reaction was poured into 10% aqueous HCl (30 ml) which was extracted with DCM (2×10 ml). The combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: ether:petrol=1:9) to yield an off-white solid **1** (273 mg, 90%) of highly characteristic smell. Found: C 68.27, H 8.61. $C_8H_{12}O_2$ requires C 68.55, H 8.63%; m.p. 35°C; $[\alpha]_D^{21}$ +100 (*c* 1.0, DCM); ν_{max} (film)/cm^{-1} 3420, 2964, 2877, 1676, 1452, 1407, 1279, 1223, 1170; δ_H (200 MHz; $CDCl_3$), [1.05 (3H, d, *J*=6.5) and 1.13 (3H, d, *J*=7.0), 2×CH_3], [1.71–1.94 (1H, m) and 2.15–2.36 (1H, m), H-4, H-5], 2.52 (1H, dd, *J*=12.5, 16.5, H-6$_{ax}$), 2.57 (1H, dd, *J*=4.0, 16.5, H-6$_{eq}$), 5.75 (1H, br s, OH), 5.90 (1H, d, *J*=3.0, H-3); δ_C (400 MHz; $CDCl_3$), [19.1 and 19.5 (2×CH_3)], [37.0 and 37.7 (C-4, C-5)], 43.8 (C-6), 124.1 (C-3), 146.1 (C-2), 195.7 (C-1); *m/z* (EI) 140 (23%, M^+), 125 (21), 111 (5), 98 (29), 91 (12), 81 (24), 70 (68), 55 (16), 50 (42), 41 (23); found; $[M]^+$ 140.0831. $C_8H_{12}O_2$ requires M 140.0837.

3.5. Attempted resolution of trans-*cyclohexane-1,2-diol*

(4*S*,5*S*)-4,5-Dimethyl-cyclohexane-1,2-dione **1** (110 mg, 0.79 mmol), (±)-CSA (23 mg, 0.01 mmol), (±)-*trans*-cyclohexane-1,2-diol **6** (220 mg, 1.89 mmol) and trimethylorthoformate (0.35 ml, 3.2 mmol) were heated at reflux for 36 hours in dry methanol (13 ml). The reaction was neutralised with triethylamine (0.1 ml) and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution: ether:petrol=1:9 to ether:petrol=2:3) to allow the separation of the following four diacetal compounds as white solids.

3.5.1. (1R,2R,1′R,2′S,4′S,5′S)-(1′,2′-Dimethoxy-4′,5′-dimethyl-cyclohexan-1′,2′-diyl) cyclohexane-1,2-diol 9

Found: C 67.55, H 9.95. $C_{16}H_{28}O_4$ requires C 67.57, H 9.92%; m.p. 91–93°C; $[\alpha]_D^{22}$ +58.0 (*c* 1.0, DCM); ν_{max} (film)/cm^{-1} 2921, 1454, 1375, 1225, 1193, 1114, 1072, 1053, 1026, 975; δ_H (400 MHz; CDCl$_3$), [0.86 (3H, d, *J*=6.0) and 0.92 (3H, d, *J*=6.0), 2×CH$_3$], [1.16–1.34 (5H, m), 1.40–1.48 (1H, m), 1.68–1.75 (2H, m) and 1.77–1.85 (2H, m), H-3, H-4, H-5, H-6, H-4′, H-5′], 1.41 (1H, dd, *J*=12.5, 13.0, H-3′$_{ax}$/H-6′$_{ax}$), 1.69 (1H, dd, *J*=3.5, 14.0, H-3′$_{eq}$/H-6′$_{eq}$), 1.90 (1H, dd, *J*=3.5, 13.0, H-3′$_{eq}$/H-6′$_{eq}$), 1.98 (1H, dd, *J*=12.0, 14.0, H-3′$_{ax}$/H-6′$_{ax}$), [3.25 (3H, s) and 3.33 (3H, s), 2×OCH$_3$], 3.42–3.54 (2H, m, H-1, H-2); δ_C (100 MHz; CDCl$_3$), [19.0 and 19.2 (2×CH$_3$)], [24.2, 24.5, 29.6, 30.3, 34.3, 34.5, 35.0 and 39.6 (C-3, C-4, C-5, C-6, C-3′, C-4′, C-5′, C-6′)], [47.5 and 48.7 (2×OCH$_3$)], [72.0 and 75.5 (C-1, C-2)], [98.1 and 98.8 (C-1′, C-2′)]; *m/z* (EI) 284 (4%, M$^+$), 269 (13), 171 (83), 155 (9), 139 (100), 111 (10), 95 (13), 82 (20), 67 (35); found; [M]$^+$ 284.1986. $C_{16}H_{28}O_4$ requires M 284.1987.

3.5.2. (1R,2R,1′R,2′R,4′S,5′S)-(1′,2′-Dimethoxy-4′,5′-dimethyl-cyclohexan-1′,2′-diyl) cyclohexane-1,2-diol 10

Found: C 67.45, H 9.89. $C_{16}H_{28}O_4$ requires C 67.56, H 9.93%; m.p. 108–109°C; $[\alpha]_D^{19}$ −18.4 (*c* 1.0, DCM); ν_{max} (film)/cm^{-1} 2865, 2823, 2805, 1410, 1245, 1180, 1148, 1129, 1107, 1089, 1035, 1010, 975, 936, 840, 802; δ_H (600 MHz; CDCl$_3$) 0.89 (6H, d, *J*=6.0, 2×CH$_3$), 1.14–1.29 (6H, m, H-4, H-5, H-4′, H-5′), 1.44 (2H, dd, *J*=12.0, 13.5, H-3′$_{ax}$, H-6′$_{ax}$), 1.65–1.68 (2H, m, H-3$_{ax}$, H-6$_{ax}$), 1.86 (2H, dd, *J*=3.0, 13.5, H-3′$_{eq}$, H-6′$_{eq}$), 1.95–1.99 (2H, m, H-3$_{eq}$, H-6$_{eq}$), 3.26 (6H, s, 2×OCH$_3$), 3.94–4.01 (2H, m, H-1, H-2); δ_C (100 MHz; CDCl$_3$) 19.1 (2×CH$_3$), [24.0, 31.9 and 37.1 (C-3, C-4, C-5, C-6, C-3′, C-6′)], 34.6 (C-4′, C-5′), 47.0 (2×OCH$_3$), 75.2 (C-1, C-2), 99.7 (C-1′, C-2′); *m/z* (EI) 269 (20), 222 (8), 171 (97), 139 (100), 95 (23); found; [M−Me]$^+$ 269.1758. $C_{15}H_{25}O_4$ requires M 269.1753.

3.5.3. (1S,2S,1′R,2′R,4′S,5′S)-(1′,2′-Dimethoxy-4′,5′-dimethyl-cyclohexan-1′,2′-diyl) cyclohexane-1,2-diol 7

Found: C 67.36, H 9.99. $C_{16}H_{28}O_4$ requires C 67.56, H 9.93%; m.p. 112–114°C; $[\alpha]_D^{22}$ −96.4 (*c* 1.0, DCM); ν_{max} (film)/cm^{-1} 2930, 1453, 1200, 1108, 1072, 1045, 1012; δ_H (400 MHz; CDCl$_3$) 0.89 (6H, d, *J*=6.0, 2×CH$_3$), 1.16–1.31 (4H, m, H-4$_{ax}$, H-5$_{ax}$, H-4′, H-5′), 1.31–1.43 (2H, m, H-3$_{ax/eq}$, H-6$_{ax/eq}$), 1.51 (2H, dd, *J*=12.0, 13.5, H-3′$_{ax}$, H-6′$_{ax}$), 1.69–1.75 (4H, m, H-4$_{eq}$, H-5$_{eq}$, H-3′$_{eq}$, H-6′$_{eq}$), 1.75–1.82 (2H, m, H-3$_{ax/eq}$, H-6$_{ax/eq}$), 3.18 (6H, s, 2×OCH$_3$), 3.57–3.61 (2H, m, H-1, H-2); δ_C (100 MHz; CDCl$_3$) 19.3 (2×CH$_3$), [24.6, 30.0 and 35.6 (C-3, C-4, C-5, C-6, C-3′, C-6′)], 34.6 (C-4′, C-5′), 46.8 (2×OCH$_3$), 72.5 (C-1, C-2), 98.1 (C-1′, C-2′); *m/z* (EI) 284 (3%, M$^+$), 269 (57), 253 (28), 220 (23), 171 (84), 139 (100), 95 (24), 67 (36); found; [M]$^+$ 284.1993. $C_{16}H_{28}O_4$ requires M 284.1987.

3.5.4. (4aR,5aR,6aR,10aR,11aR,12aR,14S,15S)-14,15-Dimethyl-5a,11a-butano-5,6,11,12-tetraoxa-perhydrotetracene 8

Found: C 71.33, H 9.74. $C_{20}H_{32}O_4$ requires C 71.30, H 9.59%; m.p. 208°C; $[\alpha]_D^{22}$ +85.1 (*c* 1.0, DCM); ν_{max} (Nujol)/cm^{-1} 1450, 1376, 1228, 1194, 1108, 1069, 1029, 991, 858; δ_H (200 MHz; CDCl$_3$), 0.90 (6H, d, *J*=6.0, 2×CH$_3$) [1.28–1.49 (12H, m) and 1.71–2.09 (10H, m), H-1, H-2, H-3, H-4, H-7, H-8, H-9, H-10, H-13, H-14, H-15, H-16], [3.54 (2H, ap dt, *J*=4.0, 10.0) and 3.89 (2H, ap dt, *J*=4.0, 10.0), H-4a, H-6a, H-10a, H-12a]; δ_C (100 MHz; CDCl$_3$) 18.7 (2×CH$_3$), [24.2, 24.4, 29.6, 30.1 and 40.6 (C-1, C-2, C-3, C-4, C-7, C-8, C-9, C-10, C-13, C-16)], 34.8 (C-14, C-15), [71.5 and 76.0 (C-4a, C-6a, C-10a, C-12a)], 96.1 (C-5a, C-11a); *m/z* (EI) 336 (9%, M^+), 222 (100), 139 (13), 95 (7), 81 (13); found; $[M]^+$ 336.2303. $C_{20}H_{32}O_4$ requires M−Me 336.2300.

Acknowledgements

We thank the Swiss National Science Foundation (RL), the LINK Asymmetric Synthesis Programme (DRO), SmithKline Beecham (SLW) and the Novartis Research Fellowship (to SVL) for funding this work.

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