Ketone homologation to produce α-methoxyketones: application to conduritol synthesis

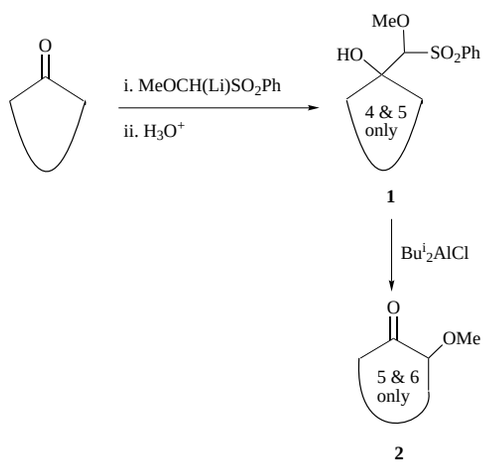
Neil Phillipson,[a] Michael S. Anson,[b] John G. Montana†,[b] and Richard J. K. Taylor*,‡,[a]

[a] *Department of Chemistry, University of York, York, UK Y01 5DD*
[b] *Glaxo Group Research, Ware, Herts, UK SG12 0DJ*

The scope of Trost's sulfone homologation procedure for the conversion of ketones into their α-methoxylated higher homologues has been dramatically expanded. The use of zirconium (or hafnium) tetrachloride in the hydroxy sulfone rearrangement step gives good yields with the adducts of aryl alkyl ketones, dialkyl ketones and cycloalkanones, and the rearrangement occurs with total regioselectivity. Mechanistic observations are presented which account for the formation of α-hydroxy aldehydes as by-products and which indicate an efficient method for their preparation. Application of the homologation methodology to the stereoselective synthesis of dihydroconduritols is described.

Introduction

Procedures for the homologation of cyclic ketones with the concomitant introduction of a substituent on the new carbon atom[1,2] are extremely useful in natural product synthesis. The sulfone-based alkoxymethylene homologation methodology introduced by Trost and Mikhail (Scheme 1)[3] has considerable

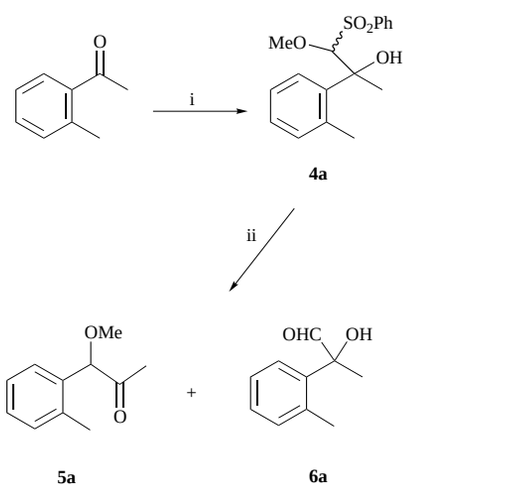


Scheme 1

synthetic potential; for example, we[4] and others,[5] have applied the method for the preparation of novel prostaglandins. The scope of the published procedure is limited, however, in that it has only been successfully applied to bicyclic cyclobutanones and cyclopentanones (although the corresponding phenylthio reagent is more versatile[3]). We decided to re-investigate this reaction with a view to expanding its scope to include larger cycloalkanones and acyclic ketones. Herein, we describe this methodological study,[6] and demonstrate the utility of the procedure for conduritol synthesis.

Results and discussion

Trost's procedure involves the formation of a β-hydroxy sulfone intermediate **1** (Scheme 1) followed by aluminium-based Lewis acid-induced ring expansion to give the α-alkoxy ketone homologue **2**. We decided to screen a variety of Lewis acids in an attempt to extend the scope of the procedure beyond cyclobutyl and cyclopentyl substrates. We therefore commenced our studies by investigating the homologation of acyclic ketones, and chose 2′-methylacetophenone for the preliminary studies (Scheme 2).



Scheme 2 *Reagents and conditions:* i, $PhSO_2CH_2OMe$ **3**, BuLi, THF, −78 °C (83%); ii, Lewis acid (see Table 1)

The lithium salt of [(methoxymethyl)sulfonyl]benzene **3** underwent smooth addition to 2′-methylacetophenone giving β-hydroxy sulfones **4a** as a separable 1:1 mixture of diastereoisomers in good yield. Treatment of **4a** with excess diisobutylaluminium chloride in dichloromethane at −78 °C produced a complex product mixture (Table 1, entry i). However, other Lewis acids proved to be more successful. Boron trifluoride–diethyl ether gave **5a** in 44% yield (entry ii), and magnesium(II) chloride, mercury(II) trifluoroacetate and zinc(II) chloride all gave the same product in even higher yields (entries iii–v). Cerium(III) chloride gave no observable product but hafnium(IV) and zirconium(IV) chlorides gave particularly clean transformations (entries vi–viii). The use of $ZrCl_4$ at room temperature (RT) gave a quantitative yield of the homologated ketone **5a** according to ^{1}H NMR spectroscopy (77% isolated yield after distillation). It is noteworthy that there was no sign of the alternative regioisomer, arising from methyl group

† Current address: Chiroscience, Cambridge Science Park, Milton Road, Cambridge, UK CB4 4WE.
‡ E-Mail: rjkt1@york.ac.uk

migration, in any of the reactions (although the by-product **6a** was observed in most cases—see later).

Zirconium tetrachloride has not received very much attention as a Lewis acid[7] but the efficiency and regioselectivity of this process are enhanced by its practical simplicity: the $ZrCl_4$ is added as a powder to a solution of the sulfone in dichloromethane at room temperature, and the heterogeneous mixture is stirred for 10 min before treatment with aqueous $NaHCO_3$. The use of fewer than six equivalents of the Lewis acid gave a slower and less clean reaction. With this procedure in hand, the scope of the methodology in terms of substrate structure was investigated as illustrated in Table 2.

Table 1 [a,b]

Entry	Lewis acid (equiv.)	Temperature	Yield of **5a** [b,c]
i	Bu^i_2AlCl (6)	−78 °C	*d*
ii	$BF_3{\cdot}OEt_2$ (6)	−78 °C to RT	44%
iii	$MgBr_2$ (6)	RT	50%
iv	$Hg(COCF_3)_2$ (6)	−78 °C to RT	70%
v	$ZnCl_2$ (10)	RT	75%
vi	$CeCl_3$ (10)	40 °C	No reaction
vii	$HfCl_4$ (6)	RT	80% [e]
viii	$ZrCl_4$ (6)	RT	99% [f,g]

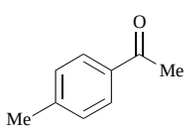
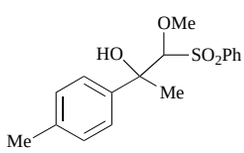
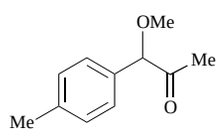
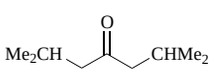
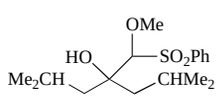
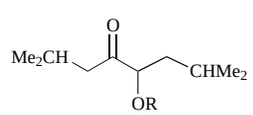
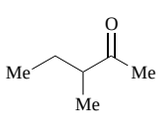
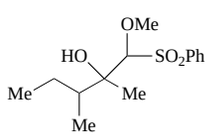
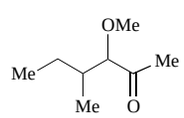
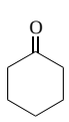
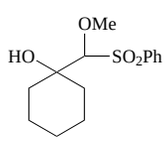
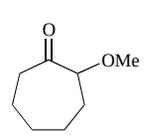
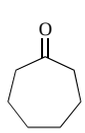
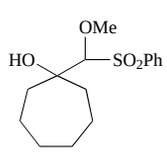
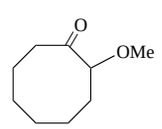
[a] All reactions were carried out in dry CH_2Cl_2 under an inert atmosphere and followed by TLC; RT reactions were complete in a few minutes whereas those carried out at −78 °C took up to 5 h. [b] Varying amounts of **6a** were observed in most reactions (see text). [c] Estimated by ^{1}H NMR spectroscopy. [d] Complex mixture of products observed. [e] 40% at −78 °C. [f] 77% isolated yield after distillation. [g] When the reaction was carried out and quenched at −78 °C, the main product was **6a** (**5a**:**6a** = 1:7).

In all examples, the addition of the α-sulfonyl anion derived from **3** proceeded efficiently giving sulfones **4b–f**. Application of the $ZrCl_4$ rearrangement conditions to adduct **4b** derived from 4′-methylacetophenone (entry i) gave another encouraging result with the efficient, regioselective formation of **5b**. Whilst we had now succeeded in extending the Trost methodology to acyclic systems, aryl groups are well known to undergo facile migration to an electron deficient centre.[8] More significant indications of the generality of this process came with the successful homologation of aliphatic ketones (entries ii and iii). The migrating group in entry ii is a saturated, primary alkyl chain which offers little stabilisation of the electron deficient centre in the reaction intermediate. The system also possesses no ring strain to act as a driving force, and yet rearrangement occurs to give **5c** in a total yield of 85% (partial demethylation was observed in this example). The efficient formation of **5d** (entry iii) provided a further example of alkyl group migration; total regioselectivity was observed with the exclusive migration of the secondary centre. The first examples of monocyclic ring expansion with the simultaneous incorporation of an α-oxygenated centre were provided by the successful formation of cycloheptanone **5e** and cyclooctanone **5f** in acceptable yields for medium size ring formation. In all of the cases illustrated in Table 2, only the expected [1,8] regioisomer was formed: the novel discovery is that, with the correct choice of Lewis acid, the Trost homologation procedure has a far greater scope than was originally realised.

Mechanistic studies

Many of the reactions described above produced α-hydroxy aldehydes (*e.g.* **6a**) as minor by-products, and they often became

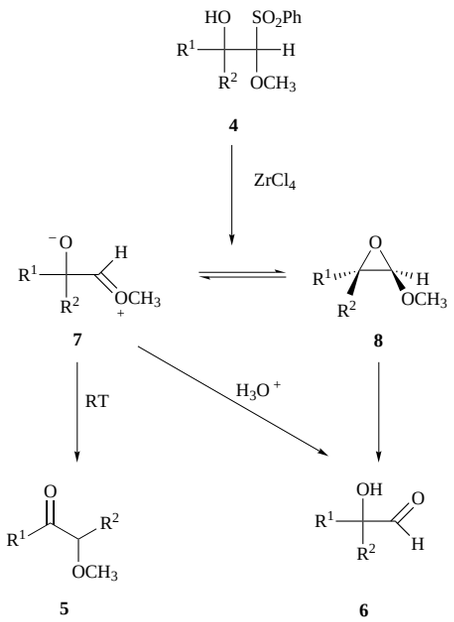
Table 2 Ketone homologation using $ZrCl_4$ for homologation [a]

Entry	Ketone	Sulfone adduct **4**	Homologated ketone **5**
i		 **4b**, 90%	 **5b**, 75%
ii		 **4c**, 82%	 **5c**, R = Me, 61% R = H, 24%
iii		 **4d**, 91%	 **5d**, 87%
iv		 **4e**, 83%	 **5e**, 51%
v		 **4f**, 92%	 **5f**, 60%

[a] Carried out using 6 equiv. of $ZrCl_4$ in dry CH_2Cl_2 at RT for 15 min under an inert atmosphere. Yields are of isolated, analytically pure, material.

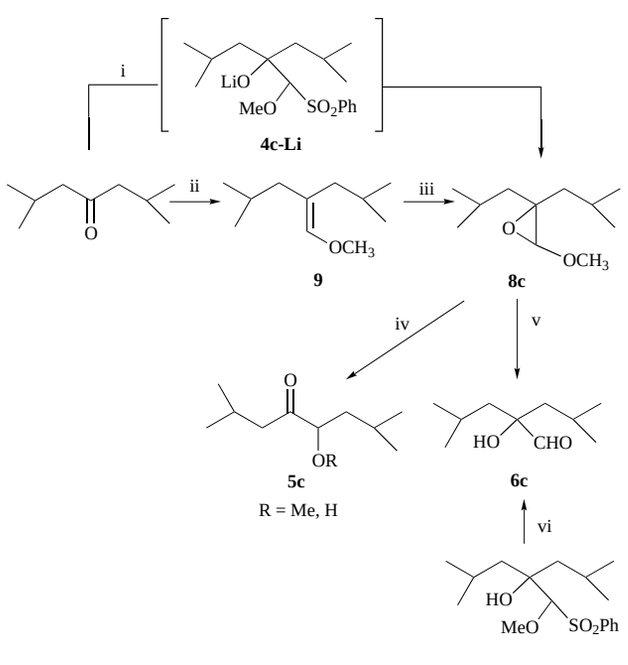
the major product if the reaction was carried out at low temperature. We rationalise these observations in terms of a semipinacol-type mechanism, as a concerted rearrangement–sulfone cleavage sequence seems unlikely.

Thus, Lewis acid-mediated carbon–sulfur bond cleavage would lead to the formation of the resonance-stabilised cation **7**, which could be in equilibrium with epoxide **8** (Scheme 3).[9] It



Scheme 3

seems likely that at low temperature the rearrangement proceeds slowly and an aqueous work-up generates significant quantities of aldehyde **6**. When the reaction is carried out at RT, the rearrangement product **5** is the major, or exclusive, product. Support for this proposal was obtained when, in a non-reproducible reaction (Scheme 4), epoxide **8c** ($R^1 = R^2 = Pr^i$) was isolated in 79% yield from a sample of the lithiated hydroxy sulfone **4c-Li** which had been allowed to warm to RT. An authentic sample of **8c** was prepared from enol ether **9**, as shown in Scheme 4, and was found to have identical properties to the original sample. When attempts were made to prepare other epoxides related to **8c** using the same procedures, the oxidation products were extremely labile undergoing hydrolysis to the corresponding aldehydes over a period of minutes. The unusual stability of epoxide **8c** is therefore noteworthy.

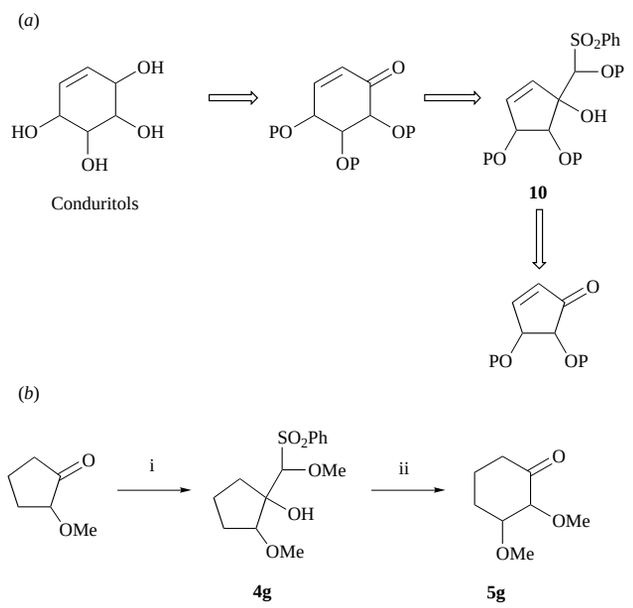


Scheme 4 *Reagents and conditions:* i, **3**, BuLi, THF, −78 °C to RT (79%); ii, $Ph_3PCH_2OCH_3{\cdot}Cl$, BuLi, diethyl ether, −12 °C (21%); iii, dimethyldioxirane, acetone, −12 °C (69%); iv, 6 equiv. $ZrCl_4$, CH_2Cl_2, RT (R = Me, 51%; R = H, 18%); v, AcOH–H_2O, acetone, RT (see text); vi, 6 equiv. $ZrCl_4$, CH_2Cl_2, −78 °C then aq. $NaHCO_3$ (81%)

When epoxide **8c** was treated with $ZrCl_4$ in dichloromethane at RT, ketones **5c** (R = Me and H) were isolated in yields similar to those obtained from rearrangement of hydroxy sulfone **4c** (Table 2). When epoxide **8c** was treated with aqueous acid, α-hydroxy aldehyde **6c** was formed rapidly according to NMR spectroscopy (although the reaction was not clean). A more straightforward route to aldehyde **6c** was to treat sulfone **4c** with $ZrCl_4$ at −78 °C and quench at the same temperature. Given the synthetic utility of α-hydroxy aldehydes,[10] this new method for their preparation warrants further study.

Application of the Trost homologation methodology to conduritol synthesis

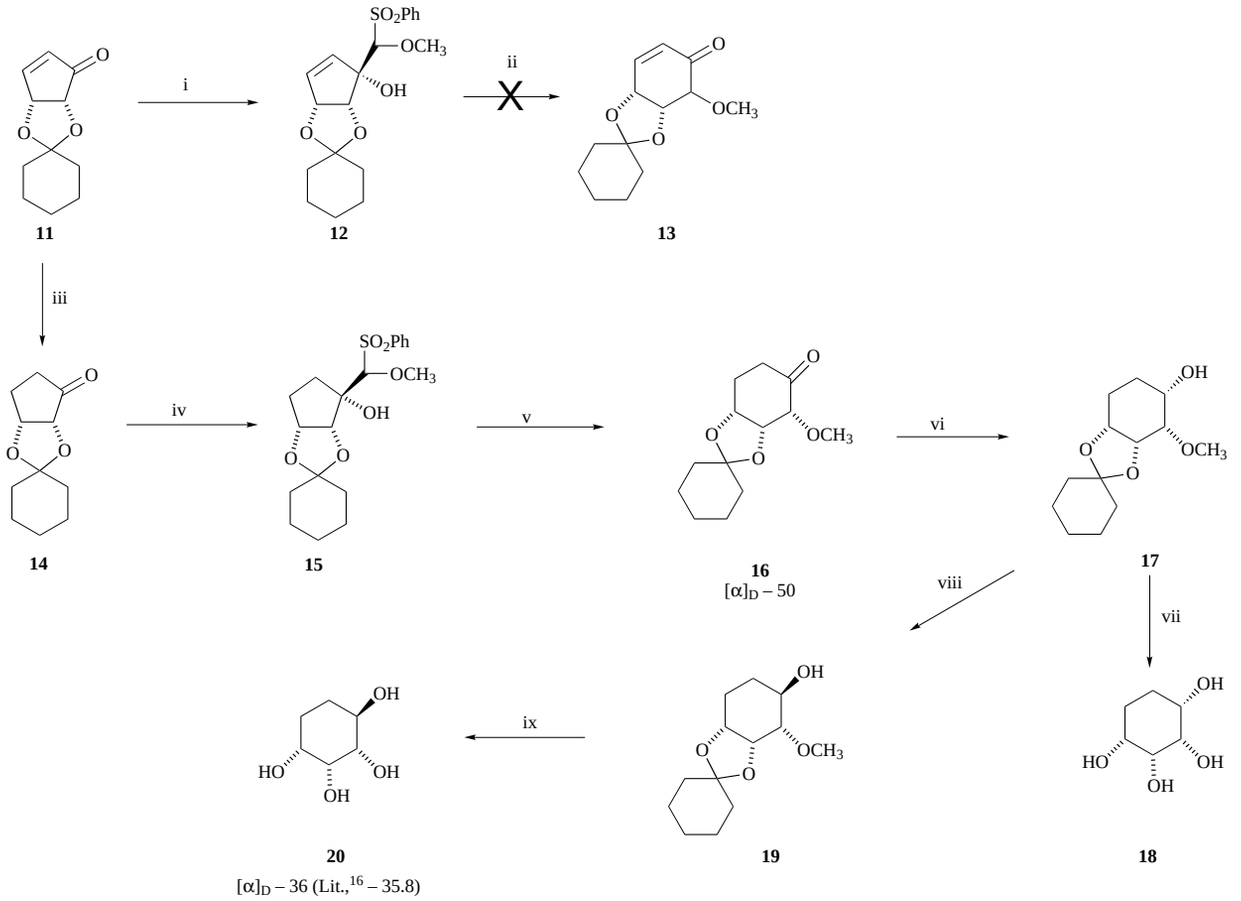
In order to demonstrate the potential of this methodology, the conduritol synthesis, illustrated in retrosynthetic form in Scheme 5, was investigated. We first established that



Scheme 5 (*a*) Retrosynthetic route for conduritol synthesis; (*b*) *Reagents and conditions:* i, $PhSO_2CH_2OMe$ **3**, BuLi, THF, −78 °C (67%); ii, $ZrCl_4$, CH_2Cl_2, RT (*ca*. 40%; see text); or $HfCl_4$, CH_2Cl_2, RT (65%; *cis* : *trans* = 2.4 : 1)

2-alkoxycyclopentanones underwent the ring expansion efficiently and with the required regiochemistry (Scheme 5). Addition of the lithium salt of [(methoxymethyl)sulfonyl]benzene **3** to 2-methoxycyclopentanone[11] proceeded efficiently to give adduct **4g**, but the standard zirconium tetrachloride procedure produced a mixture of the required product **5g** (*ca*. 40% by NMR estimate) and an aldehydic by-product. Changing to hafnium tetrachloride, however, gave the separable *cis*- and *trans*-2,3-dimethoxycyclohexanones (**5g**, 65%) with only a trace of aldehyde being present according to an NMR analysis of the crude reaction product. The process was totally regioselective with the oxygenated centre migrating preferentially (as expected[12]).

With this promising model study successfully completed we went on to prepare an adduct of type **10**. This chemistry, which



Scheme 6 *Reagents and conditions:* i, $PhSO_2CH_2OCH_3$, BuLi, THF, −78 °C (77%); ii, range of Lewis acids/reaction conditions; iii, H_2, 10% Pd/C, EtOAc (95%); iv, as i (87%); v, 6 equiv. $ZrCl_4$, CH_2Cl_2 (51–84%; see text); vi, $NaBH_4$, MeOH, −12 °C (81%); vii, 40 equiv. BCl_3, CH_2Cl_2, −78 °C to RT (97%); viii, 2 equiv. PPh_3, 2 equiv. DEAD, 2 equiv. *p*-$NO_2C_6H_4CO_2H$, C_6H_6, then 2 equiv. $LiOH·H_2O$, MeOH (22%); ix, as vii (91%)

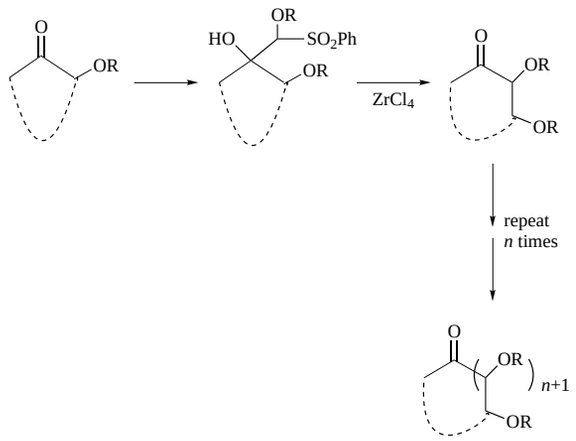
commences with the known[13,14] chiral pool derived cyclopentenone **11**, is shown in Scheme 6. Addition of the anion derived from [(methoxymethyl)sulfonyl]benzene **3** proceeded with total β-stereoselectivity to give hydroxy sulfone **12** as a separable mixture of two diastereoisomers. Treatment of **12** with six equivalents of zirconium tetrachloride in dichloromethane at RT in an attempt to prepare **13** gave an inseparable mixture of several products. The low material recovery after aqueous work-up was also disappointing, suggesting loss of the acetal protecting group. Several sets of conditions were screened in an attempt to overcome this problem, but to date it seems that α,β-unsaturated ketones are not suitable substrates for the Trost ring expansion methodology.

We therefore adapted the synthetic route by operating on the saturated system **14**, readily prepared by hydrogenation of **11**. Formation of β-hydroxy sulfones **15** proceeded in excellent yield, the product again being a separable mixture of two diastereoisomers. Treatment of either diastereoisomer, or a mixture, with excess zirconium tetrachloride in dichloromethane at RT gave clean formation of the desired ring-expanded ketone **16**. The regioselectivity was expected from the model studies; a little more surprising was the fact the process was also stereoselective giving only the all *syn*-diastereoisomer **16**. The recovery from the zirconium tetrachloride-mediated reaction was disappointing, and some effort was required to optimise the yield. It was eventually found that by using zirconium tetrachloride which had been sublimed in an inert atmosphere immediately before use, and by quenching the reaction with aqueous THF instead of $NaHCO_3$, a good yield was obtained. The use of more robust protecting groups should alleviate the need for these special conditions. NOE studies failed to provide conclusive evidence for the stereochemistry at C-2, although the proposed structure was ultimately confirmed by subsequent transformation to a known compound.

Reduction of the ketone **16** with sodium borohydride in methanol gave alcohol **17** as a single stereoisomer. Deprotection of **17** was achieved using boron trichloride in dichloromethane:[15] NMR studies showed that the acetal was rapidly removed at −78 °C whereas demethylation required warming to RT. This sequence gave *meso*-dihydroconduritol D **18**. The simplicity of the NMR spectra reflected the symmetry of the molecule and provided final confirmation of the earlier, tentative stereochemical assignments. Mitsunobu inversion of **17** gave the epimeric alcohol **19**, albeit in low, unoptimised yield. Deprotection using boron trichloride gave (−)-dihydroconduritol C **20**. Compound **20** is known and its physical and spectroscopic properties were in good agreement with those reported in the literature.[16]

Summary

The use of zirconium tetrachloride facilitates a high yielding homologation of ketones into α-methoxy ketones *via* the intermediacy of β-hydroxy sulfones. The procedure is operationally simple, totally regioselective, and is applicable to a wide range of substrates including bicyclic, monocyclic and acyclic ketones. The homologation procedure has been applied to prepare (−)-dihydroconduritol C and *meso*-dihydroconduritol D and, with the use of more robust protecting groups this new method should prove to be of general synthetic utility. The successful regioselective homologation of α-oxygenated ketones suggests that the process should be capable of iteration (Scheme 7) and therefore prove useful in the construction of polyoxygenated carbon frameworks.



Scheme 7

Experimental

General

NMR spectra were recorded on JEOL PMX 60 (60 MHz), JEOL EX 90 (90 MHz), JEOL GX-270 (270 MHz), JEOL GX-400 (400 MHz), Bruker WM 250 (250 MHz) and Bruker AMX 500 (500 MHz) instruments using $CDCl_3$ as solvent unless otherwise stated. Tetramethylsilane (TMS) or $CDCl_3$–$CHCl_3$ was used as the internal standard. Coupling constants (J) are in Hz to the nearest 0.5 Hz. Melting points were recorded on a Kopfler hot-stage or Electrothermal melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Perkin-Elmer 1720-X or ATI Mattson Genesis FT-IR spectrometers. Low resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionisation (CI) and high resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Optical rotations were recorded at ambient temperature on a Jasco DIP-370 polarimeter and values are given in units of 10^{-1} deg cm^2 g^{-1}. Concentration (c) is expressed in g 100 ml^{-1}. Standard aqueous work-up was performed as follows: the mixture was diluted with water and extracted three times with the specified solvent; the combined extracts were washed with brine, dried ($MgSO_4$ unless stated) and concentrated at reduced pressure. Chromatography is flash column chromatography and was performed using May and Baker Sorbsil C60 silica gel under pressure of nitrogen using the eluent specified. Ether is diethyl ether. Where necessary ether and THF were distilled from sodium–benzophenone ketyl immediately before use. Dichloromethane was distilled from calcium hydride. Petrol refers to the fraction of light petroleum boiling in the range 40–60 °C and was redistilled prior to use. Brine is saturated aqueous sodium chloride. Water is distilled water. Except where specified, all reagents were purchased from commercial sources and were used without further purification. 2-Methoxycyclopentanone[11a] was obtained by pyridinium chlorochromate oxidation of the corresponding alcohol (which was prepared by modification of a literature procedure[11b] used for 2-alkoxycyclohexanones).

[(Methoxymethyl)sulfonyl]benzene 3

(*a*) Potassium *tert*-butoxide (30.7 g, 274 mmol) was added portionwise to a stirred solution of thiophenol (30.14 g, 28.1 ml, 274 mmol) in dry DMF (250 ml) at 5 °C under a nitrogen atmosphere. When addition was complete the solution was allowed to warm quickly to room temperature (RT) and stirred for 1 h. A solution of chloromethoxymethane (**CAUTION**: known carcinogen) (11.27 g, 11.5 ml, 140 mmol) in dry DMF (150 ml) was added *via* a double tipped needle under pressure of nitrogen. Stirring was continued for a further 3 h before saturated aqueous ammonium chloride (100 ml) was added. The aqueous phase was extracted twice with ether and the combined organic phases washed twice with water, twice with 10% NaOH, once with brine and then dried ($MgSO_4$). The solvent was evaporated at reduced pressure to give a colourless liquid (22.0 g) which was purified by distillation at reduced pressure to give [(methoxymethyl)thio]benzene[17] (17.8 g, 83%) as a colourless liquid, bp 85–90 °C/3 mmHg; R_f 0.2 (petrol); δ_H(60 MHz) 3.40 (3 H, s, CH_3), 4.95 (2 H, s, CH_2) and 7.20–7.60 (5 H, m, ArH).

(*b*) A solution of Oxone® (72.0 g, 117 mmol) in H_2O (400 ml) was added to a stirred solution of [(methoxymethyl)thio]benzene (13.0 g, 84 mmol) in methanol (200 ml) at 5 °C. The resultant slurry was stirred at 5 °C for 1 h and at RT for 3 h before the excess Oxone® was dissolved in water. The mixture was extracted three times with ether and the combined extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated at reduced pressure to give a waxy white solid (15.7 g) which was purified by recrystallisation from ethanol–petrol to give the title compound **3** (14.0 g, 89%) as a white crystalline solid, mp 74 °C (lit.,[18] 74–75 °C); R_f 0.6 (ethyl acetate–petrol, 1:1) which was fully characterised.

Preparation of β-hydroxy sulfones

Representative procedure: 1-methoxy-2-(2-methylphenyl)-1-(phenylsulfonyl)propan-2-ol 4a. BuLi (1.52 M in hexane, 3.89 ml, 5.91 mmol) was added dropwise to a stirred solution of sulfone **3** (1.10 g, 5.91 mmol) in dry THF (70 ml) at −78 °C under a nitrogen atmosphere. The resulting yellow solution was stirred at −78 °C for 15 min before a solution of 2′-methylacetophenone (790 mg, 5.89 mmol) in dry THF (20 ml) at −78 °C was added *via* a double tipped needle under pressure of nitrogen. After stirring for a further 30 min at −78 °C the mixture was allowed to warm to RT and saturated aqueous NH_4Cl (20 ml) was added. Standard aqueous work-up (ethyl acetate) gave a pale yellow oil (1.95 g) which was purified by chromatography (petrol–ether, 3:1) to give the *title compound* **4a** (1.56 g, 83%) as two separable diastereoisomers.

Diastereoisomer 1 (775 mg, 41%) was obtained as a white solid, R_f 0.4 (petrol–ether, 1:1) (Found: C, 63.8; H, 6.2; S, 10.25. $C_{17}H_{20}O_4S$ requires C, 63.7; H, 6.3; S, 10.0%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3509, 1304 and 1143; δ_H(270 MHz) 1.85 (3 H, s, CH_3CO), 2.56 (3 H, s, $ArCH_3$), 2.90 (3 H, s, OCH_3), 4.13 (1 H, s, OH), 4.56 (1 H, s, 1-H) and 7.06–7.92 (9 H, m, ArH); δ_C(22.4 MHz) 22.8, 25.4, 62.6, 78.0, 100.6, 125.8, 127.8, 128.0, 129.1, 132.6, 134.0, 136.1, 139.1 and 140.35; m/z (EI) 135 (M − CH_3OCHSO_2Ph, 100%).

Diastereoisomer 2 (780 mg, 41%) was obtained as a colourless oil, R_f 0.3 (petrol–ether, 1:1) (Found: C, 63.4; H, 6.2; S, 10.0. $C_{17}H_{20}O_4S$ requires C, 63.7; H, 6.3; S, 10.0%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3502, 1304 and 1141; δ_H(90 MHz) 1.91 (3 H, s, CH_3CO), 2.53 (3 H, s, $ArCH_3$), 3.15 (3 H, s, OCH_3), 4.58 (1 H, s, 1-H) and 7.01–7.85 (9 H, m, ArH); δ_C(22.4 MHz) 22.4, 26.5, 62.6, 77.5, 101.9, 125.6, 127.5, 128.6, 129.0, 129.25, 132.5, 133.6, 133.9, 134.0 and 134.7; m/z (EI) 135 (M − CH_3OCHSO_2Ph, 100%).

1-Methoxy-2-(4-methylphenyl)-1-phenylsulfonylpropan-2-ol 4b. Using the representative procedure with sulfone **3** (1.44 g, 7.73 mmol) and 4′-methylacetophenone (1.02 g, 7.61 mmol) gave a crude product (2.67 g) as a pale yellow oil. Purification by chromatography (petrol–ethyl acetate, 6:1) gave the *title compound* **4b** (2.18 g, 90%) as two separable diastereoisomers.

Diastereoisomer 1 (912 mg, 38%) was obtained as a white solid, R_f 0.3 (petrol–ether, 1:1) (Found: C, 63.75; H, 6.2; S, 10.05. $C_{17}H_{20}O_4S$ requires C, 63.7; H, 6.3; S, 10.0%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3494, 1296 and 1139; δ_H(270 MHz) 1.69 (3 H, s, CH_3CO), 2.27 (3 H, s, $ArCH_3$), 3.49 (3 H, s, OCH_3), 4.19 (1 H, s, OH), 4.46 (1 H, s, 1-H), 6.91 (2 H, AB d, J 8.65, ArH), 7.20–7.32 (4 H, m, ArH) and 7.43–7.53 (3 H, m, ArH); δ_C(67.8 MHz) 20.9, 28.3, 63.0, 75.6, 104.4, 125.2, 128.2, 128.45, 129.3, 133.1, 136.7, 136.9 and 139.5; m/z (CI) 338 ($[M + NH_4]^+$, 100%).

Diastereoisomer 2 (1.27 g, 52%) was obtained as a white solid, R_f 0.3 (petrol–ether, 1:1) (Found: C, 63.8; H, 6.1; S, 10.1. $C_{17}H_{20}O_4S$ requires C, 63.7; H, 6.3; S, 10.0%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3500, 1297 and 1144; δ_H(270 MHz) 1.76 (3 H, s, CH_3CO), 2.31

(3 H, s, $ArCH_3$), 2.91 (3 H, s, OCH_3), 4.13 (1 H, s, OH), 4.20 (1 H, s, 1-H), 7.11 (2 H, AB d, *J* 8.5, ArH), 7.36 (2 H, AB d, *J* 8.5, ArH), 7.51–7.56 (2 H, m, ArH), 7.62–7.68 (1 H, m, ArH) and 7.88–7.92 (2 H, m, ArH); δ_C(67.8 MHz) 20.95, 24.2, 62.7, 76.0, 102.6, 125.8, 128.7, 129.0, 133.9, 137.3, 138.9 and 140.4; *m*/*z* (CI) 338 ($[M + NH_4]^+$, 100%).

2,6-Dimethyl-4-[(methoxy)(phenylsulfonyl)methyl]heptan-4-ol 4c. Using the representative procedure with sulfone **3** (1.95 g, 10.5 mmol) and 2,6-dimethylheptan-4-one (1.49 g, 10.5 mmol) gave a crude product (3.40 g) as a pale yellow oil. Purification by chromatography (petrol–ethyl acetate, 6:1) gave the title compound **4c** (2.82 g, 82%) as a colourless oil, R_f 0.5 (petrol–ether, 1:1); ν_{max}(neat)/cm^{-1} 3517, 1300 and 1137; δ_H(270 MHz) 0.91 (3 H, d, *J* 6.5, CH_3), 0.94 (3 H, d, *J* 6.5, CH_3), 1.00 (3 H, d, *J* 6.5, CH_3), 1.02 (3 H, d, *J* 6.5, CH_3), 1.57–1.69 (4 H, m, CH_2), 1.72–1.95 (2 H, m, CH), 3.36 (3 H, s, OCH_3), 3.57 (1 H, br s, OH), 4.35 (1 H, s, OCHS), 7.50–7.74 (3 H, m, ArH) and 7.96 (2 H, m, ArH); δ_C(67.8 MHz) 23.6, 23.7, 24.0, 24.35, 24.7, 24.8, 44.2, 44.3, 62.1, 78.7, 102.5, 128.9, 129.0, 133.8 and 139.7.

1-Methoxy-2,3-dimethyl-1-phenylsulfonylpentan-2-ol 4d. Using the representative procedure with sulfone **3** (2.79 g, 15.0 mmol) and 3-methylpentan-2-one (1.50 g, 15.0 mmol) gave a crude product (4.35 g) as a yellow oil. Purification by chromatography (cyclohexane–ethyl acetate, 5:1) gave the title compound **4d** (3.90 g, 91%) as a colourless oil and as a mixture of diastereoisomers, R_f 0.28 and 0.31 (petrol–ethyl acetate, 3:1); *m*/*z* (CI) 304 [$(M + NH_4)^+$, 65%], 287 ($[M + H]^+$, 5) and 162 (100). This mixture decomposed over a period of days at −20 °C and was therefore used immediately.

1-[(Methoxy)(phenylsulfonyl)methyl]cyclohexan-1-ol 4e. Using the representative procedure with sulfone **3** (1.00 g, 5.37 mmol) and cyclohexanone (527 mg, 5.37 mmol) gave a crude product (1.59 g) as a yellow oil. Purification by chromatography (petrol–ethyl acetate, 3:1) gave the *title compound* **4e** (1.27 g, 83%) as a colourless oil, R_f 0.2 (petrol–ethyl acetate, 2:1); ν_{max}(neat)/cm^{-1} 3527, 1302 and 1149; δ_H(270 MHz) 1.50–1.91 (10 H, m, remainder), 3.08 (1 H, br s, OH), 3.29 (3 H, s, OCH_3), 4.06 (1 H, s, OCHS), 7.56–7.71 (3 H, m, ArH) and 7.95–7.99 (2 H, m, ArH); δ_C(67.8 MHz) 20.95, 25.2, 32.8, 33.95, 62.7, 74.9, 103.0, 129.0, 129.2, 133.9 and 139.0; *m*/*z* (CI) 302 [$(M + NH_4]^+$, 50%), 285 ($[M + H]^+$, 20) and 143 ($M - SO_2Ph$, 100) (Found: 285.115 734. $C_{14}H_{21}O_4S$ requires [*M* + $H]^+$, 285.116 056; 1.1 ppm error).

1-[(Methoxy)(phenylsulfonyl)methyl]cycloheptan-1-ol 4f. Using the representative procedure with sulfone **3** (1.50 g, 8.05 mmol) and cycloheptanone (900 mg, 8.03 mmol) gave a crude product (2.50 g) as a yellow oil. Purification by chromatography (petrol–ethyl acetate, 3:1) gave the *title compound* **4f** (2.20 g, 92%) as a colourless oil, R_f 0.3 (petrol–ethyl acetate, 2:1); ν_{max}(neat)/cm^{-1} 3513, 1306 and 1151; δ_H(270 MHz) 1.48–2.03 (12 H, m, remainder), 3.08 (1 H, br s, OH), 3.30 (3 H, s, OCH_3), 4.13 (1 H, s, OCHS), 7.53–7.72 (3 H, m, ArH) and 7.95–8.00 (2 H, m, ArH); δ_C(67.8 MHz) 21.7, 21.8, 29.4, 29.7, 36.7, 38.8, 62.7, 78.4, 104.2, 129.0, 129.2, 133.9 and 139.1; *m*/*z* (CI) 316 ([$M + NH_4]^+$, 50%), 299 ($[M + H]^+$, 30), 157 ($M - SO_2Ph$, 100) (Found: 316.158 363. $C_{15}H_{26}NO_4S$ requires [$M + NH_4]^+$, 316.158 255; 0.3 ppm error).

Preparation of homologated ketones using $ZrCl_4$

Representative procedure: 1-methoxy-1-(2-methylphenyl)propan-2-one 5a. $ZrCl_4$ (1.25 g, 5.36 mmol) was added to a stirred solution of β-hydroxy sulfone **4a** (300 mg, 0.94 mmol) in dry CH_2Cl_2 (40 ml) at RT under a nitrogen atmosphere. The resulting brown mixture was stirred for 15 min before TLC analysis showed complete conversion to a single product. Saturated aqueous $NaHCO_3$ (15 ml) was added. The mixture was diluted with ethyl acetate and filtered through a plug of Celite, and the filtrate was washed with water. Standard aqueous work-up (ethyl acetate) gave the *title compound* **5a** (165 mg, 99%) as a pale yellow liquid, R_f 0.6 (petrol–ether, 1:1) (Found: C, 74.3; H, 8.0. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); ν_{max}(neat)/cm^{-1} 1717; δ_H(90 MHz) 2.10 (3 H, s, CH_3CO), 2.38 (3 H, s, $ArCH_3$), 3.35 (3 H, s, OCH_3), 4.84 (1 H, s, 1-H) and 7.16–7.45 (4 H, m, ArH); δ_C(22.4 MHz) 19.45, 25.3, 57.1, 86.9, 126.4, 127.3, 128.5, 131.0, 134.3, 136.9 and 206.25; *m*/*z* (EI) 178 (M^+, 1%), 135 ($M - COCH_3$, 100).

1-Methoxy-1-(4-methylphenyl)propan-2-one 5b. Using the representative procedure with sulfone **4b** (880 mg, 2.75 mmol) gave a crude product (550 mg) as a yellow liquid. Purification by chromatography (petrol–ether, 5:1) gave the title compound **5b** (367 mg, 75%) as a colourless liquid which was fully characterised and exhibited data corresponding to literature[19] values.

2,7-Dimethyl-5-methoxyoctan-4-one 5c. Using the representative procedure with sulfone **4c** (359 mg, 1.09 mmol) gave a crude product (230 mg) as a yellow liquid. Purification by chromatography (petrol–ether, 10:1) gave the *title compound* **5c** (R = Me) (123 mg, 61%) as a colourless liquid, R_f 0.3 (petrol–ethyl acetate, 4:1) (Found: C, 70.95; H, 11.65. $C_{11}H_{22}O_2$ requires C, 70.9; H, 11.9%); ν_{max}(neat)/cm^{-1} 1714 (C=O); δ_H(270 MHz) 0.98 (3 H, d, *J* 6.5, CH_3), 0.99 (3 H, d, *J* 6.5, CH_3), 1.00 (6 H, d, *J* 6.5, 2 × CH_3), 1.38 (1 H, ddd, *J* 4.5, 8.5 and 14.5, 6-H), 1.58 (1 H, ddd, *J* 5.5, 9.0 and 14.5, 6-H), 1.71–1.88 (1 H, m, 7-H), 2.19 (1 H, septet, *J* 6.5, 2-H), 2.35 and 2.41 (1 H, dd and 1 H, dd, *J* 17.0 and 6.5, ABX, 3-H), 3.34 (3 H, s, OCH_3) and 3.60 (1 H, dd, *J* 4.5 and 9.0, 5-H); δ_C(67.8 MHz) 21.8, 22.6, 22.6, 23.1, 23.6, 24.5, 40.8, 46.0, 58.1, 86.05 and 213.0; *m*/*z* (EI) 186 (M^+, 0.3%) and 101 ($M - C_5H_9O$, 100). 2,7-Dimethyl-5-hydroxyoctan-4-one **5c** (R = H)[20] (45 mg, 24%) was also isolated as a colourless liquid, R_f 0.2 (petrol–ethyl acetate, 4:1) and was fully characterised.

3-Methoxy-4-methylhexan-2-one 5d. Using the representative procedure with sulfone **4d** (116 mg, 0.41 mmol) gave a crude product (56.7 mg) as a yellow liquid. Purification by chromatography (petrol–ether, 10:1) gave the *title compound* **5d** (50.6 mg, 87%) as a colourless liquid and as an inseparable mixture of diastereoisomers (*ca*. 1.5:1 by NMR), R_f 0.3 (petrol–ethyl acetate, 3:1); ν_{max}(neat)/cm^{-1} 1716; δ_H(270 MHz) (data for the minor isomer is listed first) 0.76 (3 H, d, *J* 7.0, 4-CH_3 minor), 0.79 (3 H, d, *J* 6.5, 4-CH_3 major), 0.83 (6 H, t, *J* 7.5, 2 × 6-CH_3), 0.88–1.69 (6 H, m, 2 × H-4 and 2 × 5-CH_2), 2.05 (3 H, s, 1-CH_3 minor), 2.06 (3 H, s, 1-CH_3 major), 3.16 (1 H, d, *J* 7.5, 3-H minor), 3.34 (1 H, d, *J* 5.0, 3-H major), 3.25 (3 H, s, OCH_3 minor) and 3.27 (3 H, s, OCH_3 major); δ_C(67.8 MHz) (data for the minor isomer is listed first) 11.1 and 11.6, 14.8 and 14.2, 25.5 and 24.7, 26.1 and 25.8, 37.0 and 37.5, 58.6 and 58.85, 92.0 and 90.6, and 210.9 and 211.9; *m*/*z* (CI) 162 ([$M + NH_4]^+$, 98%), 145 ($[M + H]^+$, 100) [Found (CI): 162.149 824. $C_8H_{16}O_2$ requires [$M + NH_4]^+$, 162.149 404; 2.6 ppm error].

2-Methoxycycloheptan-1-one 5e. Using the representative procedure with sulfone **4e** (580 mg, 2.04 mmol) gave a crude product (319 mg) as a yellow liquid. Purification by column chromatography on silica gel using petrol–ether (7:1) as eluent gave the title compound **5e**[21] (147 mg, 51%) as a colourless liquid, R_f 0.4 (petrol–ethyl acetate, 4:1); ν_{max}(neat)/cm^{-1} 1712; δ_H(270 MHz) 1.45–1.92 (8 H, m, remainder), 2.39–2.62 (2 H, m, 7-CH_2), 3.36 (3 H, s, OCH_3) and 3.89 (1 H, dd, *J* 3.0 and 8.0, H-2); δ_C(67.8 MHz) 23.2, 25.5, 28.4, 31.1, 40.7, 57.5, 86.4 and 212.4; *m*/*z* (CI) 160 ([$M + NH_4]^+$, 40%), 143 ($[M + H]^+$, 85) (Found: 160.133 244. $C_8H_{14}O_2$ requires [$M + NH_4]^+$, 160.133 754; 3.2 ppm error).

2-Methoxycyclooctan-1-one 5f. Using the representative procedure with sulfone **4f** (561 mg, 1.88 mmol) gave a crude product (308 mg) as a yellow liquid. Purification by chromatography (petrol–ether, 9:1) gave the title compound **5f** (176 mg, 60%) as a colourless liquid, R_f 0.2 (petrol–ethyl acetate, 9:1) which was fully characterised and exhibited data corresponding to literature values.[22]

2,2-Diisobutyl-3-methoxyoxirane 8c. (*a*) BuLi (1.55 M in hexane, 5.64 ml, 8.74 mmol) was added dropwise to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (3.00

g, 8.75 mol) in dry ether (150 ml) at −10 °C under a nitrogen atmosphere. The resulting orange solution was stirred at −10 °C for 30 min before a solution of 2,6-dimethylheptan-4-one (1.13 g, 7.94 mmol) in dry ether (50 ml) at RT was added *via* a double tipped needle under pressure of nitrogen. The mixture was allowed to warm slowly to RT and stirred overnight. After a total of 15 h the yellow mixture was poured into a separatory funnel containing saturated aqueous NH_4Cl (100 ml). Standard aqueous work-up (ethyl acetate) gave a deep yellow oil which was purified by chromatography (petrol) to give the enol ether **9** (290 mg, 21%) as a colourless liquid, R_f 0.5 (petrol) which was fully characterised.

(*b*) Dimethyldioxirane (*ca*. 0.09 M in acetone, 15 ml, 1.35 mmol) was rapidly added to enol ether **9** (1.90 mg, 1.12 mmol) at 2 °C. After standing for 5 min TLC analysis showed the starting material to have been consumed. The solvent was evaporated at reduced pressure and the residue dissolved in CH_2Cl_2 and dried (Na_2SO_4). Filtration and concentration gave the *title compound* **8c** (143 mg, 69%) as a colourless liquid (which could be further purified by chromatography using petrol–ether, 5:1), R_f 0.3 (petrol); ν_{max}(neat)/cm^{-1} 2957, 1466, 1151 and 1098; δ_H(270 MHz) 0.91, 0.93, 0.95 and 0.98 (12 H, d, *J* 6.5, 4 × CH_3), 1.17 (1 H, dd, *J* 14.0 and 8.0, CH_2), 1.53–1.63 (3 H, m, CH_2), 1.68–1.91 (2 H, m, CH), 3.50 (3 H, s, OCH_3) and 4.21 (1 H, s, 1-H); δ_C(67.8 MHz) 22.7, 22.8, 22.9, 23.2, 24.9, 25.0, 37.1, 42.3, 56.2, 63.65 and 87.1; *m*/*z* (CI) 204 ([M + NH_4]$^+$, 18%), 187 ([M + H]$^+$, 85) [Found (CI): 187.169 280. $C_{11}H_{23}O_2$ requires [*M* + H]$^+$, 187.169 805; 2.8 ppm error].

2,7-Dimethyl-5-methoxyoctan-4-one 5c from epoxide 8c. Zirconium tetrachloride (230 mg, 0.99 mmol) was added to a stirred solution of epoxide **8c** (37 mg, 0.20 mmol) in dry CH_2Cl_2 (10 ml) at RT under a nitrogen atmosphere. The resulting bright pink mixture was stirred for 30 min before saturated aqueous $NaHCO_3$ (10 ml) was added. The mixture was diluted with CH_2Cl_2 and filtered through a plug of Celite, and the filtrate was washed with water. Standard aqueous work-up (ethyl acetate, Na_2SO_4) gave the crude product as a yellow liquid which was purified by chromatography (petrol–ethyl acetate, 10:1) to give the title compound **5c** (R = Me) (19 mg, 51%) as a colourless liquid. 2,7-Dimethyl-5-hydroxyoctan-4-one **5c** (R = H) (6 mg, 18%) was also isolated as a colourless liquid. Spectroscopic data for these compounds were consistent with that reported above.

2,6-Dimethyl-4-formylheptan-4-ol 6c. Zirconium tetrachloride (600 mg, 2.57 mmol) was added to a stirred solution of β-hydroxy sulfone **4c** (213 mg, 0.65 mmol) in dry CH_2Cl_2 at −78 °C under a nitrogen atmosphere. The mixture was stirred for 30 min before saturated aqueous $NaHCO_3$ (10 ml) was added. The mixture was diluted with ethyl acetate and filtered through a plug of Celite, and the filtrate was washed with water. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases washed with brine and dried ($MgSO_4$). The solvent was evaporated at reduced pressure to give a pale yellow liquid (120 mg) which was purified by column chromatography on silica gel using petrol–ethyl acetate (10:1) as eluent to give the *title compound* **6c** (91 mg, 81%) as a colourless liquid, R_f 0.3 (petrol); ν_{max}(neat)/cm^{-1} 3509 and 1727; δ_H(270 MHz) 0.76 (3 H, d, *J* 5.5, CH_3), 0.77 (3 H, d, *J* 6.5, CH_3), 0.87 (3 H, d, *J* 5.5, CH_3), 0.89 (3 H, d, *J* 6.5, CH_3), 1.48–1.71 (6 H, m, 2 × CH_2 and 2 × CH), 3.25 (1 H, s, OH) and 9.51 (1 H, s, CHO); δ_C(67.8 MHz) 23.5, 23.8, 24.35, 46.1, 81.2 and 205.0; *m*/*z* (CI) 190 ([M + NH_4]$^+$, 100%) and 173 ([M + H]$^+$, 20%) (Found: 190.180 282. $C_{10}H_{20}O_2$ requires [*M* + NH_4]$^+$, 190.180 704; 2.2 ppm error).

Synthesis of dihydroconduritols C and D and related model studies

(1*S,2*R**,1′*RS*)-2-Methoxy-1-[(methoxy)(phenylsulfonyl)-methyl]cyclopentan-1-ol 4g.** Using the representative procedure, sulfone **3** (1.05 g, 5.64 mmol) and 2-methoxycyclopentan-1-one **6d**[11] (643 mg, 5.63 mmol) gave a pale yellow oil (1.72 g) which was purified by chromatography (petrol–ether, 5:1) to give the *title compound* **4g** (1.14 g, 67%) (Found: C, 56.2; H, 6.7; S, 10.4. $C_{14}H_{20}O_5S$ requires C, 56.0; H, 6.7; S, 10.7%) as two separable diastereoisomers.

Diastereoisomer 1 (625 mg, 37%) was obtained as a white solid, mp 80–81 °C; R_f 0.4 (ethyl acetate–petrol, 1:1); ν_{max}($CHCl_3$)/cm^{-1} 3525, 1305 and 1140; δ_H(400 MHz) 1.47–2.03 (6 H, m, 3-H, 4-H and 5-H), 3.38 (3 H, s, OCH_3), 3.45 (3 H, s, OCH_3), 3.89 (1 H, dd, *J* 6.5 and 7.0, 2-H), 4.22 (1 H, s, 1′-H), 7.55–7.58 (2 H, m, ArH), 7.65 (1 H, tt, *J* 1.5 and 7.5, ArH) and 7.96–7.99 (2 H, m, ArH); δ_C(22.4 MHz) 19.8, 29.0, 35.3, 57.3, 62.3, 80.8, 81.6, 101.7, 128.3, 129.0, 133.2 and 138.9; *m*/*z* (EI) 71 (100%).

Diastereoisomer 2 (512 mg, 30%) was obtained as a colourless oil, R_f 0.3 (ethyl acetate–petrol, 1:1); ν_{max}(neat)/cm^{-1} 3501, 1305 and 1145; δ_H(400 MHz) 1.33–1.89 (6 H, m, 3-H, 4-H and 5-H), 2.91 (1 H, br s, OH), 3.29 (3 H, s, OCH_3), 3.41 (3 H, s, OCH_3), 3.51 (1 H, dd, *J* 7.5 and 9.5, 2-H), 4.21 (1 H, s, 1′-H), 7.44–7.48 (2 H, m, ArH), 7.57 (1 H, tt, *J* 1.5 and 7.5, ArH) and 7.82–7.90 (2 H, m, ArH); δ_C(100 MHz) 18.8, 26.1, 29.7, 57.4, 62.45, 80.9, 83.1, 99.5, 128.7, 129.3, 133.6 and 138.8; *m*/*z* (EI) 71 (100%).

***cis*- and *trans*-2,3-Dimethoxycyclohexan-1-one 5g.** $HfCl_4$ (2.45 g, 7.64 mmol) was added to a stirred solution of β-hydroxy sulfone **4g** (418 mg, 1.39 mmol) in dry CH_2Cl_2 (50 ml) at RT under a nitrogen atmosphere. The resulting brown mixture was stirred for 30 min before TLC analysis showed the starting material to have been consumed. Saturated aqueous $NaHCO_3$ (15 ml) was added. The mixture was diluted with ethyl acetate and filtered through a plug of Celite, and the filtrate was washed with water. Standard aqueous work-up (ether) gave a yellow liquid (223 mg) which was purified by chromatography (petrol–ether, 3:1) to give the *title compound* **5g** (144 mg, 65%) as two separable diastereoisomers.

cis-2,3-*Dimethoxycyclohexan*-1-*one* (102 mg, 46%) was obtained as a colourless liquid, R_f 0.2 (petrol–ether, 1:2) (Found: C, 60.9; H, 8.9. $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%); ν_{max}(neat)/cm^{-1} 1728; δ_H(400 MHz) 1.67–1.76 (2 H, m, 5-H), 1.89–1.99 (1 H, m, 4-H), 2.11–2.18 (1 H, m, 4-H), 2.24 (1 H, dddd, *J* 1.0, 6.0, 11.0 and 13.5, 6-H ax), 2.49 (1 H, dtd, *J* 1.5, 5.0 and 13.5, 6-H eq), 3.35 (3 H, s, OCH_3), 3.45 (3 H, s, OCH_3), 3.80 (1 H, dd, *J* 1.0 and 2.5, 2-H) and 3.86 (1 H, td, *J* 2.5 and 5.5, 3-H); *m*/*z* (EI) 158 (M$^+$, 22%), 71 (100).

trans-2,3-*Dimethoxycyclohexan*-1-*one* (42 mg, 19%) was obtained as a colourless liquid, R_f 0.3 (petrol–ether, 1:2); ν_{max}(neat)/cm^{-1} 1730; δ_H(270 MHz) 1.47–1.75 (2 H, m, 5-H), 1.90–2.02 (1 H, m, 4-H), 2.15–2.27 (1 H, m, 4-H), 2.28 (1 H, dddd, *J* 1.5, 5.5, 11.0 and 13.5, 6-H ax), 2.49 (1 H, dtd, *J* 1.5, 5.0 and 13.5, 6-H eq), 3.38–3.47 (1 H, m, 3-H), 3.46 (3 H, br s, OCH_3), 3.48 (3 H, s, OCH_3) and 3.68 (1 H, dd, *J* 1.5 and 8.0, 2-H); δ_C(67.8 MHz) 20.6, 28.3, 39.5, 57.9, 58.9, 82.8, 88.65 and 207.8; *m*/*z* (EI) 158 (M$^+$, 15%), 71 (100).

(−)-(2*R*,3*R*)-2,3-(Cyclohexylidenedioxy)cyclopentan-1-one 14. 10% Pd on activated carbon (110 mg) was weighed into a hydrogenation flask which was sequentially evacuated and flushed with nitrogen three times. A solution of ketone (−)-**11**[13] (610 mg, 3.14 mmol) in ethyl acetate (50 ml) was added to the evacuated flask. The flask was flushed with nitrogen, re-evacuated and flushed with hydrogen. The reaction was stirred at RT for 4 h after which time the flask was evacuated, flushed with nitrogen and the catalyst filtered off over Celite. The solvent was evaporated at reduced pressure to give the *title compound* (−)-**14** (585 mg, 95%) as a white solid, mp 94 °C; R_f 0.4 (petrol–ether, 1:2); $[\alpha]_D$ −242 (*c* 0.4, CH_2Cl_2) (Found: C, 67.6; H, 8.6. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%); ν_{max}($CHCl_3$)/cm^{-1} 1753; δ_H(400 MHz) 1.33–1.38 (2 H, m, CH_2), 1.50–1.64 (8 H, m, 4 × CH_2), 1.99 (1 H, dddd, *J* 5.0, 9.5, 11.5 and 14.5, 4-H), 2.18–2.30 (2 H, m, 4-H and 5-H), 2.50–2.61 (1 H, m, 5-H), 4.14 (1 H, d, *J* 5.0, 2-H) and 4.82 (1 H, t, *J* 5.0, 3-H); *m*/*z* 214 ([M + NH_4]$^+$, 100%) and 197 ([M + H]$^+$, 80).

(1*S*,2*R*,3*R*,1′*RS*)-2,3-(Cyclohexylidenedioxy)-1-[(methoxy)-(phenylsulfonyl)methyl]cyclopentan-1-ol 15. Using the representative procedure with sulfone **3** (2.00 g, 10.7 mmol) and ketone (−)-**14** (2.00 g, 10.2 mmol) gave a pale yellow oil (4.2 g) which was purified by chromatography (petrol–ethyl acetate, 4:1) to give the *title compound* **15** (3.41 g, 87%) as two separable diastereoisomers.

Diastereoisomer 1 (1.88 g, 48%) was obtained as a colourless oil, R_f 0.3 (petrol–ethyl acetate, 2:1); $\nu_{max}(CHCl_3)/cm^{-1}$ 3505, 1307 and 1144; δ_H(250 MHz) 1.35–1.76 (10 H, m, 5 × CH_2), 1.83–1.96 (3 H, m, 4-H and 5-H), 2.10–2.25 (1 H, m, 5-H), 3.29 (1 H, s, OH), 3.46 (3 H, s, OCH_3), 4.19 (1 H, s, 1′-H), 4.64–4.72 (2 H, m, 2-H and 3-H), 7.53–7.69 (3 H, m, ArH) and 7.99 (2 H, d, *J* 7.0, ArH); δ_C(67.8 MHz) 23.4, 23.9, 24.95, 28.5, 33.2, 34.0, 35.8, 63.0, 79.6, 79.6, 81.0, 100.8, 113.9, 128.7, 129.6, 133.7 and 138.8; *m*/*z* (CI) 400 ($[M + NH_4]^+$, 15%) and 383 ($[M + H]^+$, 5).

Diastereoisomer 2 (1.53 g, 39%) was obtained as a white solid, mp 84 °C; R_f 0.3 (petrol–ethyl acetate, 2:1) (Found: C, 59.7; H, 6.7; S, 8.4. $C_{19}H_{26}O_6S$ requires C, 59.7; H, 6.85; S, 8.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3505, 1306 and 1143; δ_H(250 MHz) 1.50–1.72 (10 H, m, 5 × CH_2),1.84–1.92 (2 H, m, 4-H), 1.98–2.21 (2 H, m, 5-H), 3.30 (1 H, s, OH), 3.63 (3 H, s, OCH_3), 4.22 (1 H, s, 1′-H), 4.50 (1 H, d, *J* 6.5, 2-H), 4.66 (1 H, dd, *J* 6.5 and 9.5, 3-H), 7.51–7.69 (3 H, m, ArH) and 7.97–8.02 (2 H, m, ArH); δ_C(67.8 MHz) 23.5, 24.0, 25.05, 28.3, 34.1, 35.9, 36.6, 62.75, 79.0, 80.1, 80.2, 102.0, 113.8, 128.6, 129.7, 133.65 and 138.9; *m*/*z* (CI) 400 ($[M + NH_4]^+$, 15%) and 383 ($[M + H]^+$, 10).

(−)-(2*R*,3*R*,4*R*)-3,4-(Cyclohexylidenedioxy)-2-methoxycyclohexan-1-one 16. Freshly sublimed $ZrCl_4$ (540 mg, 2.32 mmol) was added to a solution of β-hydroxy sulfone **15** (diastereoisomer 2, 157 mg, 0.41 mmol) in dry CH_2Cl_2 (15 ml) at RT under a nitrogen atmosphere. After stirring for 15 min the mixture was cooled to 3 °C and a 1:1 mixture of THF and water (4 ml) was added. The mixture was diluted with CH_2Cl_2 and filtered over a plug of Celite, and the filtrate was washed with water. Standard aqueous work-up (dichloromethane, Na_2SO_4) gave a pale yellow liquid (94 mg) which was purified by chromatography (petrol–ether, 2:1) to give the *title compound* **16** (50 mg, 51%) as a colourless liquid, R_f 0.2 (hexane–ethyl acetate, 1:1); $[\alpha]_D$ −50.0 (*c* 0.5, CH_2Cl_2); $\nu_{max}(CDCl_3)/cm^{-1}$ 1735, 1123 and 1088; δ_H(270 MHz) 1.26–1.69 (10 H, m, 5 × CH_2), 1.96 (1 H, dddd, *J* 2.5, 5, 13.5 and 15.5, 5-H ax), 2.05–2.14 (1 H, m, 5-H eq), 2.34 (1 H, ddd, *J* 2.5, 3.5 and 19, 6-H eq), 2.61 (1 H, ddd, *J* 6, 13.5 and 19, 6-H ax), 3.58 (3 H, s, OCH_3), 3.92 (1 H, d, *J* 3.5, 2-H), 4.65–4.69 (1 H, m, 4-H) and 4.77 (1 H, dd, *J* 3.5 and 7.5, 3-H); δ_C(100 MHz) 23.5, 23.8, 24.0, 25.1, 33.2, 33.5, 35.4, 59.2, 75.2, 72.4, 83.1, 109.6 and 206.4; *m*/*z* (CI) 241 ($[M + H]^+$, 80%) and 143 (100) [Found (CI): 241.1435. $C_{13}H_{20}O_4$ requires $[M + H]^+$, 241.1440; 2.1 ppm error]. Yields as high as 84% were obtained for this reaction, although 50–60% yields were more typical. Diastereoisomer 1 gave similar results.

(−)-(1*S*,2*S*,3*R*,4*R*)-3,4-(Cyclohexylidenedioxy)-2-methoxycyclohexan-1-ol 17. $NaBH_4$ (12 mg, 0.32 mmol) was added to a solution of ketone **16** (59 mg, 0.25 mmol) in methanol (10 ml) at −12 °C (salt–ice bath) under a nitrogen atmosphere. The reaction was stirred at this temperature for 30 min after which time TLC analysis showed complete conversion into a single product. Saturated aqueous NH_4Cl (2 ml) was added and the mixture was diluted with ethyl acetate (50 ml) and water (20 ml). Standard aqueous work-up (ethyl acetate, Na_2SO_4) gave a pale yellow liquid (60 mg) which was purified by chromatography (petrol–ethyl acetate, 2:1) to give the *title compound* **17** (48 mg, 81%) as a colourless liquid, R_f 0.2 (petrol–ethyl acetate, 1:1); $[\alpha]_D$ −33 (*c* 0.23 methanol); ν_{max}(neat)/cm^{-1} 3472, 1120, 1104, 1079 and 1034; δ_H(270 MHz) 1.26–2.05 (14 H, m, 7 × CH_2), 2.97 (1 H, d, *J* 8.0, OH), 3.32 (1 H, t, *J* 4.0, 2-H), 3.54 (3 H, s, OCH_3), 4.14–4.28 (2 H, m, 1-H and 4-H) and 4.43 (1 H, t, *J* 4.0, 3-H); δ_C(67.8 MHz) 22.8, 23.5, 24.0, 25.0, 26.6, 35.1, 37.8, 56.9, 65.1, 73.75, 74.6, 78.0 and 110.05; *m*/*z* (CI) 260 ($[M + NH_4]^+$, 5%), 243 ($[M + H]^+$, 100) [Found (CI): 243.159 550. $C_{13}H_{22}O_4$ requires $[M + H]^+$, 243.159 634; 0.3 ppm error).

(−)-(1*R*,2*S*,3*R*,4*R*)-3,4-(Cyclohexylidenedioxy)-2-methoxycyclohexan-1-ol 19. DEAD (0.144 ml, 159 mg, 0.92 mmol) was added to a mixture of PPh_3 (240 mg, 0.92 mmol), 4-nitrobenzoic acid (153 mg, 0.92 mmol) and alcohol **17** (111 mg, 0.46 mmol) in dry benzene (5 ml) at RT under a nitrogen atmosphere. The reaction was stirred at RT for 3 h after which time TLC analysis showed the starting material to have been consumed. The mixture was diluted with ethyl acetate (15 ml) and poured into water (30 ml). Standard aqueous work-up (ethyl acetate, Na_2SO_4) gave a pale yellow liquid which was chromatographed (petrol–ether, 2:1) to remove 1,2-bis(ethoxycarbonyl)-hydrazine. The resulting inseparable mixture (261 mg) was dissolved in MeOH (10 ml) and $LiOH·H_2O$ (38 mg, 0.91 mmol) was added. The deep yellow mixture was stirred at RT for 2 h. The methanol was removed at reduced pressure and the residue dissolved in ether and filtered through a plug of Celite. The filtrate was concentrated at reduced pressure to give a pale yellow oil which was purified by chromatography (ether–petrol, 1:1) to give the *title compound* **19** (24 mg, 22%) as a colourless liquid, R_f 0.2 (petrol–ethyl acetate, 1:2); $[\alpha]_D$ −44 (*c* 0.16, methanol); ν_{max}(neat)/cm^{-1} 3404, 1112, 1091, 1070 and 1021; δ_H(270 MHz) 1.21–2.02 (14 H, m, 7 × CH_2), 2.44 (1 H, br s, OH), 3.17 (1 H, dd, *J* 3.5 and 9.0, 2-H), 3.53 (3 H, s, OCH_3), 3.91 (1 H, dt, *J* 5.5 and 9.0, 1-H), 4.23 (1 H, dt, *J* 8.0 and 5.5, 4-H) and 4.56 (1 H, dd, *J* 3.5 and 5.5, 3-H); δ_C(67.8 MHz) 23.6, 24.0, 25.05, 26.6, 26.85, 34.9, 37.5, 57.0, 68.3, 72.0, 74.2, 83.1 and 109.8; *m*/*z* (CI) 243 ($[M + H]^+$, 100%) [Found (CI): 243.160 100. $C_{13}H_{22}O_4$ requires $[M + H]^+$, 243.159 634; 1.9 ppm error].

***meso*-(1*S*,2*S*,3*R*,4*R*)-Cyclohexane-1,2,3,4-tetrol (dihydroconduritol-D) 18.** BCl_3 (1.0 M in CH_2Cl_2, 3.0 ml, 3.0 mmol) was added to a solution of alcohol **17** (18 mg, 0.074 mmol) in dry CH_2Cl_2 (3 ml) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 10 h and then allowed to warm slowly to RT and stirred for a further 16 h (after which time TLC analysis showed a single product). The solvent was evaporated at reduced pressure to give a brown residue (13 mg) which was purified by chromatography (ethyl acetate–methanol, 5:1) to give a colourless oil which was rapidly eluted from a short column of reversed-phase silica gel (octadecyl coating) using methanol as eluent to give the *title compound* **18** (10.7 mg, 97%) as a colourless oil, R_f 0.3 (ethyl acetate–methanol, 1:1); δ_H(270 MHz; CD_3OD) 1.45–1.55 (2 H, br m, 5-H and 6-H), 1.81–1.92 (2 H, br m, 5-H and 6-H) and 3.70 (4 H, br s, 1-H, 2-H, 3-H and 4-H); δ_C(67.8 MHz; CD_3OD) 26.0, 71.6 and 74.0; *m*/*z* (CI) 166 ($[M + NH_4]^+$, 100%) and 149 ($[M + H]^+$, 10); *m*/*z* (EI) 130 ($M^+ - H_2O$, 7%) [Found (CI): 166.108 245. $C_6H_{12}O_4$ requires $[M + NH_4]^+$, 166.107 933; 1.9 ppm error].

(−)-(1*R*,2*S*,3*R*,4*R*)-Cyclohexane-1,2,3,4-tetrol (dihydroconduritol-C) 20. BCl_3 (1.0 M in CH_2Cl_2, 2.64 ml, 2.64 mmol) was added to a solution of alcohol **19** (16 mg, 0.066 mmol) in dry CH_2Cl_2 (2 ml) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 8 h and then allowed to warm slowly to RT and stirred for a further 16 h (after which time TLC analysis showed a single product). The solvent was evaporated at reduced pressure to give a brown residue (13 mg) which was purified by chromatography (ethyl acetate–methanol, 5:1) to give a colourless oil which was rapidly eluted from a short column of reversed-phase silica gel (octadecyl coating) using methanol as eluent to give the title compound **20** (8.9 mg, 91%) as a white solid, mp 154 °C (lit.,[16] 157–158 °C); R_f 0.3 (ethyl acetate–methanol, 1:1); $[\alpha]_D$ −36 (*c* 0.08, H_2O, 25 °C) [lit.,[16] −35.8 (*c* 4.7, H_2O, 20 °C) and −39 (*c* 1.0, H_2O, 25 °C)] which also gave consistent NMR data [Found (CI): 166.107 746. Calculated for $C_6H_{12}O_4$ as $[M + NH_4]^+$, 166.107 933; 1.1 ppm error].

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