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A Synthetic Study towards (5*R**,6*S**)-6-(2-Indenyl)spiro[4,5]decan-2-one

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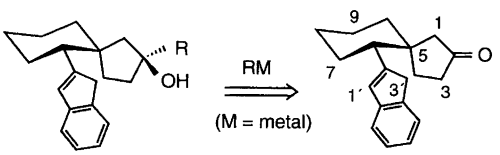
The title compound is an immediate precursor to the model compounds designed for probing the elusive hydroxy–carbanion interaction. The relative configuration of the spirocycle is controlled by a contrasteric alkylation of methyl 2-alkoxymethylcyclohexanecarboxylate. The construction of the indene moiety is arranged later in the synthesis for the convenience of incorporating the ^{13}C atoms, which are needed in the eventual spectroscopic studies. Simple 1,2-elimination (commonly used for preparing 1- or 3-substituted indenes) is found unsuitable here for the formation of the double bond in the indene ring, as the by-products caused by the migration of the substituent at C-2′ are very difficult to remove.

The interaction between a hydroxy group and a carbanion is one of the few instances where hydrogen-bonded carbanions can be probed. Previous results[1] from this group have showed that indene derivatives are particularly useful for this purpose because of their relatively low pK_a values. In order to explore further details of the hydrogen bonding between carbanion and hydroxy group, a new type of indene derivative (**1**) has been designed. In these compounds, the hydroxy groups are held between the indene ring and the five-membered ring, with a very favourable geometry for hydrogen-bonding to either C-1′ or C-3′ (after deprotonation with a strong base). Compared with the indene derivatives used in the previous studies, the current spirocyclic framework is more rigid and the OH group is sterically more hindered for intermolecular proton exchange reactions. It may therefore provide a much better opportunity to examine the effect of different R groups on the hydrogen bonding. In combination with ^{13}C labelling technique (inserting a ^{13}C atom at either C-1′ or C-3′ or both positions of the indene ring) it may even be possible to find out whether there exists $^{1}H-^{13}C$ coupling due to OH–carbanion hydrogen-bonding.



1 **2**

Scheme 1.

Since all the model compounds (**1**) were expected to be accessible by reaction of proper organometallics with the ketone **2** (Scheme 1, the nucleophilic attack can occur only on one face of the carbonyl plane because the other is blocked by the indene ring), the main task of this project could be reduced to the construction of the immediate precursor ketone **2**. The position of the carbonyl group (i.e., at C-2 or C-3 position, corresponding to the 5*R**,6*S** or 5*R**,6*R** isomer) does not make much difference in spectroscopic studies. However, since a mixture of both isomers would lead to complicated NMR spectra, it is necessary to obtain **2** in diastereomerically pure form (either 5*R**6*S** or 5*R**6*R**).

Even judged from the number of stereogenic centres and functionalities, ketone **2** is still a simple compound. Both of its moieties, the spirocycle and the indene, are rather common structures. However, this particular combination of the two subunits via a σ-bond between the C-6 and C-2′ does introduce remarkable difficulty that is not easily seen from the two-dimensional drawing. The strong acidity of the protons at C-3′ imposes another hidden problem in that the indene ring cannot be introduced in the early stages of the synthesis.

Direct coupling between C-6 and C-2′ from a ready-made spirocycle and indene is unlikely to give satisfactory results here because of the steric hindrance caused by the five-membered ring and the risk of losing control over the relative configurations at C-5 and C-6. To avoid this disfavoured situation, the σ-bond between C-6 and C-2′ is better formed before the construction of the five-membered ring. Owing to the eventual requirement for the ^{13}C

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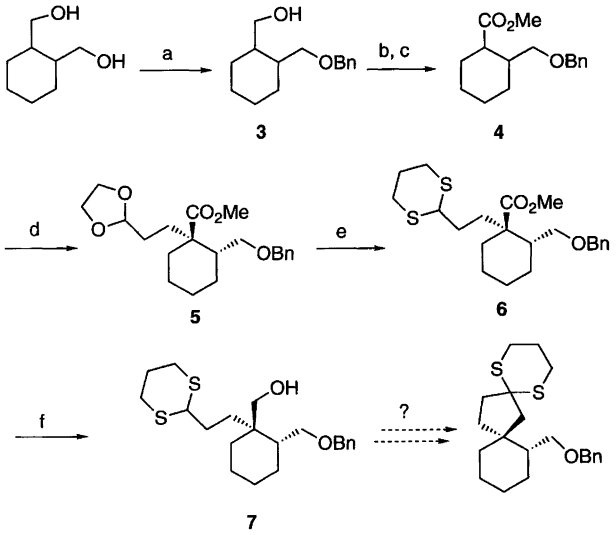
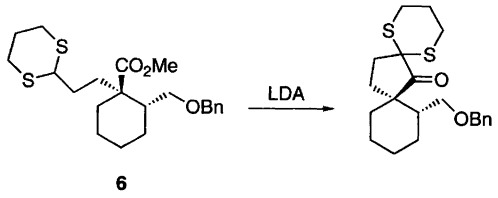
labelling at the C-1′ and/or C-3′, these two carbons should come from those reagents that are also available in ^{13}C-labelled forms. Although we probably need to label the molecule at one position only, a route with maximum flexibility for labelling at both positions is still highly desirable.



Scheme 2. a, NaH–DMSO–BnCl; b, $(COCl)_2$–DMSO–NEt_3; c, Br_2–$NaHCO_3$–MeOH; d, LDA–THF, −75 °C then HMPA–RBr; e, $BF_3 \cdot OEt_2$–$HS(CH_2)_3SH$; f, $LiAlH_4$.

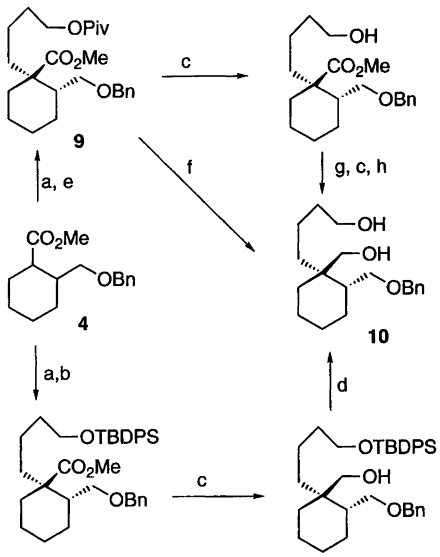
We first (Scheme 2) tried to prepare a fully functionalized spirocycle moiety starting with conversion of the *cis* diol into monobenzyl ether **3** (83%). Swern oxidation followed Br_2 oxidation[2] gave ester **4** (using the 4-methoxybenzyl group to replace the benzyl protective group led to incorporation of one bromine atom in the aromatic ring. A more convenient way to prepare ester **4** was established later, see the Experimental).

Treatment of the resulting *cis* methyl ester (83% from **3**, often containing small amounts of the *trans* isomer) with LDA and the bromide in the presence of one equivalent of HMPA (rt–43 h) led to **5** (80%). Thioketalization (1,3-propanedithiol–$BF_3 \cdot OEt_2$, 95%) and reduction ($LiAlH_4$–diethyl ether–rt, 89%) led to alcohol **7**. Conversion of the mesylate of **7** into the spirocycle (BuLi–THF, −20 °C overnight), however, was unsuccessful. Several attempts to prepare the corresponding chloride from **7** or its counterpart derived from $LiAlH_4$ reduction of **5** also ended in failure. We attributed these negative results to the steric hindrance around the reaction centres and reasoned that replacement of the mesylate with a more reactive and less bulky carbonyl group, might lead to the expected cyclization. Although the aldehyde made from oxidation of **7**, when treated with LDA was converted back into the alcohol **7** (LDA as a reducing reagent has been reported[3]), the ester **6** afforded the expected spiro ketone (ca. 50%, Scheme 3). This route was later discontinued, because removal of the undesired carbonyl group in the molecule would essentially cancel the expeditiousness of this route, and, by then, we became aware of the additional steric hindrance created by the thioketal functionality in the elaboration at C-2′ position.



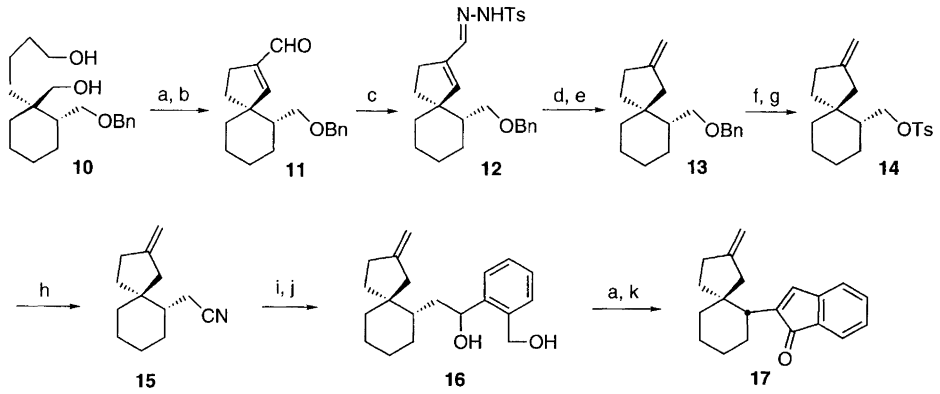
Scheme 3.

An alternative cyclization strategy was based on aldol condensation. To obtain the same diastereomer as in Scheme 2, an additional carbon (to serve first as an activating group during the cyclization and later as a protecting group) was needed in the side chain (Schemes 4 and 5). The alkylation (taking place contrasterically[4] with high diastereoselectivity; the relative configuration was established later from the NOESY spectrum of compound **13**) and reduction could be achieved in several ways (Scheme 4) but the **4–9–10** path gave the best results (77% for the alkylation and 89% for the reduction).



Scheme 4. 1, LDA, −75 °C; b, RBr; c, $LiAlH_4$–ether; d, NH_4F–MeOH; e, R′I; f, $LiAlH_4$–THF–reverse addn; g, $Me_2C(OMe)_2$–TsOH; h, H^+–H_2O. TBDPS = Me_4CSiMe_2. Piv = Me_4CCO.

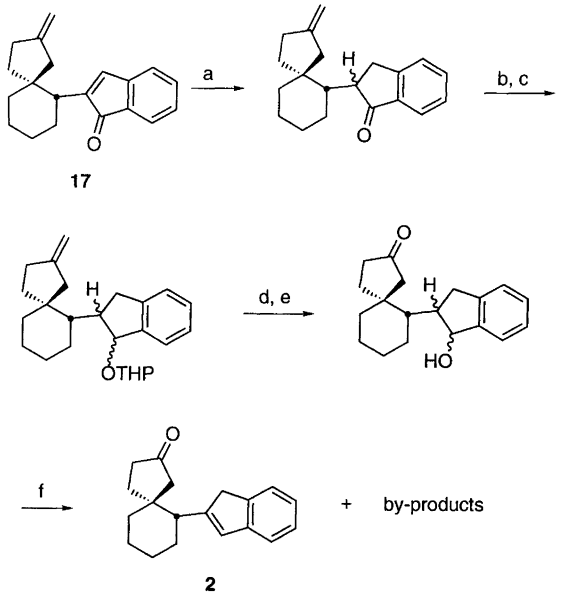
The diol **10** was converted into enal **11** (86% from **10**) by first Swern oxidation and then NaOH–MeOH (Scheme 5). Conversion of **11** into the alkene **13** followed Kabalka's procedure[5] (97% to the hydrazone, then 85% to **13**). The assignment of the relative configuration of the quaternary carbon (C-5) was based on the NOESY spectrum of **13** (which showed a significant cross-peak correlation H-6 with H-1 but not with H-3).



Scheme 5. a, $(COCl)_2$–DMSO–NEt_3; b, NaOH–MeOH; c, H_2NNHTs–EtOH; d, catechol–borane; e, $NaOAc \cdot 3H_2O$; f, Na–NH_3; g, TsCl–NEt_3–DMAP; h, KCN–DMSO, 100°C; i, DIBAL–hexane, −60°C; j, *o*-$LiPhCH_2OLi$; k, DBU–MsCl–LiBr.

The benzyl protecting group in **13** was removed by Na in liquid ammonia. The resulting alcohol was directly used in the tosylation without any purification. Although the tosylate **14** (92% from **13**) was sterically hindered due to the adjacent five-membered ring, the conversion into the nitrile **15** proceeded smoothly at elevated temperatures, providing a convenient way of introducing ^{13}C atom (since KCN is also commercially available in ^{13}C-labelled form at relatively low prices). The following partial reduction with DIBAL led to the intermediate aldehyde, which was directly treated with the dilithium reagent,[6] prepared *in situ* from *o*-bromobenzyl alcohol and *n*-butyllithium, to afford the diol **16** as a mixture of both isomers (90% from **15**). This mixture was then oxidized to the keto-aldehyde by Swern oxidation. The cyclization of the crude keto-aldehyde with NaOH in MeOH led to a mixture of the desired enone and corresponding 3-methoxyindan-1-one (presumably formed from the Michael addition of MeOH to the enone **17**). Later, it was found that this cyclization could be better (72% from **16**) achieved by using DBU–MsCl in the presence of LiBr.

With the enone **17** in hand, the remaining task was to reduce the indenone to indene and cleave the C–C double bond in the spirocycle. Initial efforts were made selectively to reduce the C–C double bond in the indene ring, aiming at the eventual construction of indene ring by elimination as shown in Scheme 6. A number of methods for this type of reduction have appeared in the literature. However, most of them did not suit the present system. The classic Na–NH_3 method[7] for instance, gave irreproducible yields (ranging from 0 to some 60%). Under strictly anhydrous conditions the reduction was very slow, while too much moisture led to over-reduction of the resulting indanone. $NiCl_2$–Al in THF–H_2O[8] and Ph_2SiH_2–$Pd(PPh_3)_4$–$ZnCl_2$[9] failed here, too. CuMe–DIBAL in THF–HMPA[10] led to a mixture of unreduced enone, 1,2-reduction (major), and 1,4-reduction products (minor), although it did work very well on simpler, sterically less hindered compounds (e.g., 2-butylinden-1-one, 2-cyclohex-3-enylinden-1-one). Finally, we found that the



Scheme 6. a, NaTeH–EtOH; b, $NaBH_4$–MeOH; c, DHP–H^+; d, OsO_4–$NaIO_4$; e, H^+–H_2O; f, DBU–MsCl–LiBr.

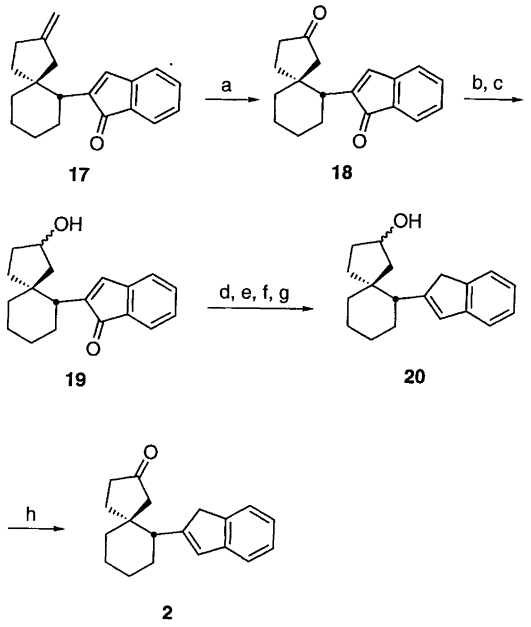
desired selectivity and high yield could be achieved by use of NaTeH,[11] which afforded two diastereomers (differing only at the configuration of the carbon α to the carbonyl group), with the less polar one (larger R_f on TLC) being the same as obtained from Na–NH_3 reduction. It is noteworthy that the Te dark stains/mirrors on the glassware surface (caused by air oxidation), which is almost impossible to remove by conventional cleaning means, can be easily removed with dilute H_2O_2.

Treatment of this mixture with K_2CO_3 in MeOH led to a single diastereomer (which had smaller R_f on TLC). Reduction of the carbonyl group ($NaBH_4$–MeOH) resulted in the alcohol as a mixture of *cis* and *trans* isomers. By protecting the OH as the THP ether, performing oxidative cleavage (OsO_4–$NaIO_4$), removing THP protecting group, and finally eliminating the OH (DBU–MsCl–LiBr), we obtained the desired ketone **2**. However, the product was very difficult to purify. The impurities were

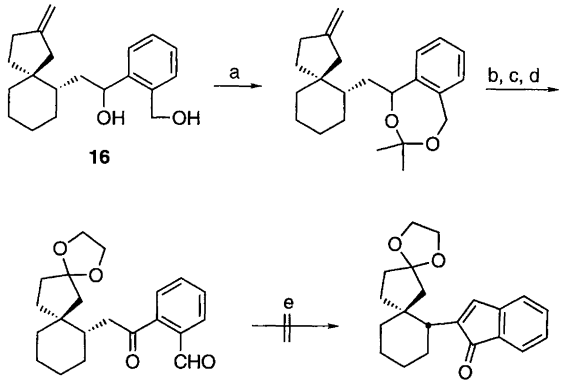
most likely the rearranged isomers, with the spirocycle attached at C-1′ (or C-3′) instead of C-2′ position. (They had exactly the same polarity on TLC and gave a broadened peak in the reconstructed ion chromatogram from GC–MS analysis. The mass spectra taken at different positions of this broadened peak showed the same molecular ion peak.) Similar complications were also encountered with simpler compounds when we tried to construct the indene ring by an elimination reaction. Probably a small portion of the elimination occurred via an E1 mechanism and the 1,2-migration of the spirocyclohexyl occurred when it was *trans* to the leaving group. If this were the case, a stereoselective reduction of the ketone (giving only *cis* alcohol) could be a solution. Unfortunately, it did not seem to be possible to realize exclusive *trans* reduction (leading to the *cis* alcohol) in the present system. After examining quite a few reducing agents and reaction conditions, we decided to seek other access to the indene ring.

An obvious way to circumvent the 1,2-migration of the spirocyclohexyl is to keep the sp^2 hybridization at the C-2′ position. Thus (Scheme 7), the enone **17** was treated with OsO_4–$NaIO_4$ to give dione **18**. Reduction[12] ($NaBH_4$–MeOH–$CeCl_3$) followed by subsequent selective oxidation[13] of allylic/benzylic OH (activated MnO_2) regenerated the indenone structure. Condensation with *p*$TsNHNH_2$ followed by catechol–borane reduction, hydrolysis, and finally PCC oxidation,[14] yielded the expected ketone **2**. In sharp contrast with the previous sample from the elimination approach, the ketone obtained this way was highly pure as judged from the ^1H and ^{13}C NMR spectra. Owing to the low yields this route is not very practical for preparative purposes, but it does show that in a successful route to ketone **2** the C-2′ carbon should keep its sp^2 configuration throughout all later manipulations of the indene ring.

The oxidative cleavage of the C–C double bond in the spirocycle is the bottleneck step in the above route. OsO_4 normally prefers to attack electron-rich C = C double bonds; those conjugated to a carbonyl group are therefore expected to be less reactive. We noted a few examples[15] in the literature, where R′RC = CH_2 was selectively cleaved in the presence of α,β-unsaturated ketone or ester partial structures. However, in the present system we could obtain only ca. 44% (based on the consumed starting enone) of the expected dione (while there were still substantial amounts of starting enone left). We attribute this low yield to the fact that one face of the double bond (in the spirocycle) is blocked by the indenone ring. To avoid this disfavoured selectivity we also tried to cleave the double bond in the spirocycle before the indenone was formed. Thus, the diol **16** (Scheme 8) was protected as the acetonide before being exposed to OsO_4–$NaIO_4$. The crude ketone was converted into the ethylene ketal with concurrent removal of the isopropylidene protecting group. The following Swern oxidation produced the keto-aldehyde. The cyclization, however, did not occur as expected, presumably due to the additional steric hindrance caused by one of the oxygens in the ketal functionality.



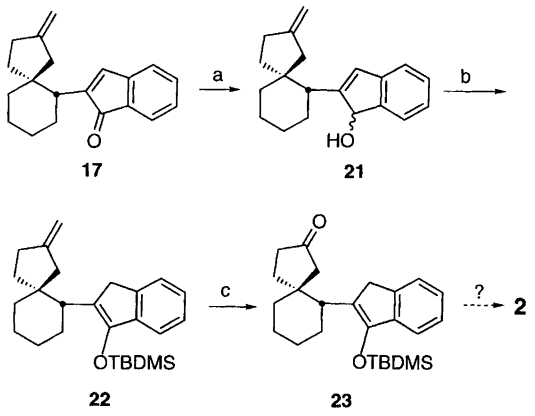
Scheme 7. a, OsO_4–$NaIO_4$; b, $NaBH_4$–$CeCl_3$–MeOH; c, MnO_2; d, H_2NNHTs–EtOH; e, catechol–borane; f, $NaOAc \cdot 3H_2O$; g, TsOH–MeOH–H_2O; h, PCC–NaOAc.



Scheme 8. a, $Me_2C(OMe)_2$–TsOH; b, OsO_4–$NaIO_4$; c, $HO(CH_2)_2OH$–TsOH; d, $(COCl)_2$–DMSO–NEt_3; e, DBU–MsCl–LiBr.

In another effort to reverse the selectivity of the oxidative cleavage, we reduced the enone **17** to the allylic alcohol (Scheme 9). The alcohol was then masked as its TBDMS ether **22** (95% from **17**). The double bond was easily rearranged[16] (which provided a potential alternative to NaTeH in selective reduction of the enone **17**) at the same time. This rearranged double bond (in the indene ring) was more hindered than the one in the spirocycle: on one face by the five-membered ring and on the other by the TBDMS group. Although ozonation failed to show any selectivity, OsO_4–$NaIO_4$ reacted mainly at

the desired site, giving the expected ketone **23** in 70% yield. The final transformation is still to be explored.



17 21 22 23

Scheme 9. a, $NaBH_4$–$CeCl_3$–MeOH; b, TBDMSCl–DBU; c, OsO_4–$NaIO_4$.

Experimental

All NMR spectra were recorded on a spectrometer operating at 500 MHz for ^1H with $CDCl_3$ as the solvent and the Me_4Si singlet (set to 0 ppm in ^1H spectra) or the middle line of the $CDCl_3$ triplet (set to 77.0 ppm in ^{13}C spectra) as internal standards. The figures in the parentheses following the carbon chemical shifts are the chemical shifts of the protons to which the carbons are directly bonded as seen in HMQC (^1H–^{13}C correlation) spectra. IR spectra were recorded on an FT instrument. MS spectra were taken at 70 eV. High resolution MS spectra were determined with PFK as reference. Elemental analyses were performed by Micro Kemi AB, Uppsala, Sweden. All glassware, syringes, needles and cannulas used in air-moisture-sensitive reactions were dried in a 120°C oven for 10 h before being cooled to rt in a dessicator. HMPA (hexamethylphosphoric triamide. **WARNING: CARCINOGEN!**) was stirred with CaH_2 at rt for a week then distilled under reduced pressure and kept over 4 Å molecular sieves under nitrogen. DMSO was dried over 4 Å molecular sieves. THF was refluxed and distilled from Na–benzophenone under nitrogen prior to use. CH_2Cl_2 and NEt_3 were freshly distilled from CaH_2 under nitrogen. The hexane used in the preparation of **16** was dried over Na wire. Column chromatography was performed on 230–400 mesh silica gel obtained from either Merck or Riedel-de Haën. Other chemicals and solvents were obtained from either Aldrich or Fluka and used as received.

*cis-2-Benzyloxymethylcyclohexylmethanol (**3**).* To a solution of the starting diol (2.990 g, 20.33 mmol) in DMSO (20 ml) was added NaH (55–60% suspension in mineral oil, 890 mg, added in small portions). The mixture was stirred at rt for 1.5 h before benzyl chloride (2.400 ml, 21 mmol) was introduced slowly (with occasional cooling). Stirring was then continued at rt for 48 h. The reaction mixture was diluted with diethyl ether, washed with water (four times) and brine (all aqueous phases were back-extracted twice), and dried over Na_2SO_4. Filtration and evaporation followed by column chromatography on silica gel (2:1 diethyl ether–hexane) afforded the monobenzyl ether **3** as a colourless oil (3.972 g, 16.95 mmol, 83%): IR: (film) 3402 cm^{-1}. MS [*m/z* (% rel. int.)]: 234 (M^+, 1.2), 204 (0.6), 137 (16), 125 (22), 107 (68), 95 (38), 91 (100). ^1H NMR: δ 1.24–1.52 (m, 6 H), 1.58 (m, 1 H), 1.64 (m, 1 H), 1.88 (m, 1 H), 2.16 (m, 1 H), 2.97 (m, 1 H, OH), 3.40 (dd, *J* 9.0, 4.0 Hz, 1 H), 3.46–3.59 (m, 2 H), 3.68 (t, *J* 9.0 Hz, 1 H), 4.51 (s, 2 H), 7.35 (m, 5 H). ^{13}C NMR: δ 23.40 (1.30, 1.42), 24.61 (1.33, 1.58), 25.78 (1.35, 1.40), 28.70 (1.46, 1.64), 36.22 (2.16, CH), 40.66 (1.88, CH), 64.63 (3.50, 3.56), 71.82 (3.40, 3.68), 73.39 (4.51, CH_2), 127.74 (7.35), 127.77 (7.35), 128.46 (7.35), 137.71 (quat). Exact mass calc. for $C_{15}H_{22}O_2$: 234.162. Found: 234.165. *Anal.* for $C_{15}H_{22}O_2$: C, H.

*Methyl cis-2-benzyloxymethylcyclohexanecarboxylate (**4**) via Jones oxidation.* Jones reagent[17] (prepared from 1.21 g of CrO_3, 1.8 ml of H_2O, 1.05 ml of conc. H_2SO_4, and 3.5 ml of H_2O) and a solution of **3** in acetone (1.395 g, 5.95 mmol, in 3 ml of acetone) were added to acetone (5 ml) stirred at 0°C. (Two reactants were added more or less at the same time to avoid forming the ester from two molecules of **3**.) Stirring was continued at 0°C for 35 min. Excess of the oxidant was destroyed with $NaHSO_3$ (ca. 100 mg, and a few millilitres of water). The resultant dark green mixture was diluted with diethyl ether, washed with water and brine, and dried over Na_2SO_4. Removal of solvent left the intermediate carboxylic acid as an oil (1.468 g). To a solution of this acid (1.133 g, 4.56 mmol) in dry benzene (16 ml) were added DBU[18] (0.75 ml) and MeI (500 µl). The mixture was then stirred at rt for 18 h. The white precipitates were filtered off (washed thoroughly with diethyl ether) and the filtrate/washings were concentrated and chromatographed on silica gel (3:1 hexane–diethyl ether) to give the ester **4** as an almost colourless oil (1.010 g, 3.85 mmol, 84% from **3**): IR (film): 1730 cm^{-1}. MS [*m/z* (% rel. int.)]: 262 (M^+, 1.1), 230 (1.4), 202 (1.3), 171 (11), 156 (22), 139 (72), 124 (24), 91 (100). ^1H NMR: δ 1.35–1.45 (m, 2 H), 1.46–1.57 (m, 2 H), 1.58–1.66 (m, 2 H), 1.72–1.85 (m, 2 H), 2.19 (m, 1 H, CH), 2.72 (m, 1 H), 3.45 (m, 2 H), 3.59 (s, 3 H), 4.46 (s, 2 H), 7.30 (m, 5 H). ^{13}C NMR: δ 23.32 (1.36, 1.53), 23.67 (1.39, 1.62), 26.16 (1.62, 1.81), 26.38 (1.52, 1.76), 38.08 (2.19, CH), 42.37 (2.72, CH α to CO_2Me), 51.15 (3.59, OCH_3), 71.39 (3.45), 73.12 (4.46, CH_2, benzylic), 127.47 (7.30), 127.64 (7.30), 128.28 (7.30), 138.53 (quat), 175.11 (quat). Exact mass calc. for $C_{16}H_{21}O_3$ ($M+1$): 263.165. Found: 263.167. *Anal.* for $C_{16}H_{22}O_3$: C, H.

*Methyl cis-2-benzyloxymethylcyclohexanecarboxylate via Swern oxidation (**4**).* With stirring and cooling (−75°C bath), dry DMSO (3.2 ml, 45 mmol, diluted with 2 ml of

dry CH_2Cl_2) was added dropwise to a solution of oxalyl chloride (1.70 ml, 19.5 mmol) in dry CH_2Cl_2 (30 ml). After stirring for 30 min, the alcohol **3** (3.972 g, 16.95 mmol, dissolved in 20 ml of dry CH_2Cl_2) was added via cannula over 15 min. Stirring was continued at −75°C for another 30 min before dry NEt_3 (8.0 ml) was introduced. The bath was allowed to warm slowly to −25°C over 1.5 h. The reaction mixture was diluted with diethyl ether, washed with water (three times), brine (aqueous phases were back-extracted once), and dried over Na_2SO_4. Removal of the drying agent and solvents left a yellowish oil (crude aldehyde), which was immediately dissolved in MeOH (36 ml). To the mixture were added in turn, water (5 ml) and $NaHCO_3$ (11.0 g, 130 mmol), and, with cooling (0°C bath) and rapid stirring, Br_2 (ca. 3.0 ml, 58 mmol, added over ca. 5 min). Stirring was continued at rt for 2.5 h before quenching the excess Br_2 with $Na_2S_2O_3 \cdot 5H_2O$ and water (cooled in a 0°C bath). The mixture was diluted with diethyl ether, washed with water (three times) and brine (aqueous phases were back-extracted three times) and dried over Na_2SO_4. Filtration and evaporation followed by column chromatography on silica gel (3:1 hexane–diethyl ether) afforded the ester **4** as an oil (3.691 g, 14.07 mmol, 83%).

*4-Iodobutyl pivalate (**8**).* With stirring and cooling (0°C bath), pivaloyl chloride (2.0 ml, ca. 16 mmol) was added dropwise (over ca. 13 min) to a mixture of 1,4-butanediol (4.370 g, 48.5 mmol), DMAP (173 mg, 1.42 mmol), and NEt_3 (10.0 ml) in CH_2Cl_2 (30 ml). The mixture was stirred at 0°C for 20 min and then at rt for 24 h. The mixture was diluted with diethyl ether, washed with water (twice, the aqueous phase was back-extracted once) and brine, and dried over Na_2SO_4. Filtration and evaporation left a yellow oil (2.357 g). The crude oil was dissolved in CH_2Cl_2 (30 ml) and to this solution were added, in turn, NEt_3 (10 ml), DMAP (173 mg, 1.42 mmol), and, with cooling (0°C bath) and stirring, *p*TsCl (3.206 g, 16.82 mmol). Stirring was continued at 0°C for another 30 min and then at rt for 20 h. The mixture was diluted with diethyl ether, washed with water (4 × 10 ml, aqueous phases were back-extracted), brine, and dried over Na_2SO_4. Removal of drying agent and solvents left an orange oil (4.98 g), which could be purified on silica gel (3:2 hexane–diethyl ether) to give the pure tosylate as a colourless oil: ^{1}H NMR: δ 1.18 (s, 9 H), 1.70 (m, 2 H), 2.46 (s, 3 H), 4.02 (t, *J* 6.2 Hz, 2 H), 4.07 (t, *J* 5.3 Hz, 2 H), 7.35 (d, *J* 7.9 Hz, 2 H), 7.80 (d, *J* 7.9 Hz, 2 H). ^{13}C NMR: δ 21.61, 24.75, 25.60, 27.10, 38.67, 63.31, 69.90, 127.84, 129.83, 132.96, 144.78, 178.40.

The main portion of the above crude tosylate (4.488 g) was dissolved in acetone (60 ml) and stirred with NaI (14.60 g, 97 mmol) at rt for 2 h. The mixture was diluted with diethyl ether, washed with water (twice, aqueous phases were back-extracted) and brine and dried over Na_2SO_4. Filtration and evaporation followed by column chromatography (4:1 hexane–diethyl ether) gave the unstable iodide **8** as a colourless oil (3.120 g, 10.98 mmol; this could be kept in the dark at −20°C for several weeks without significant change): IR (film): 1728 cm^{-1}. MS [*m/z* (% rel. int.)]: 183 (*M* − 101, 5.5), 157 (70), 103 (13), 85 (15), 57 (100): ^{1}H NMR: δ 1.19 (s, 9 H), 1.75 (m, 2 H), 1.90 (m, 2 H), 3.21 (t, *J* 7.0 Hz, 2 H), 4.08 (t, *J* 6.6 Hz, 2 H). ^{13}C NMR: δ 6.02 (3.21, C-4), 27.19 (1.19, CH_3), 29.54 (1.75, C-2), 30.03 (1.90, C-3), 38.74 (quat), 63.09 (4.08, C-1), 178.48 (quat). The assignment was backed up by ^{1}H-decoupling and INEPT spectra.

Methyl (1S,2R*)-1-(4-pivaloyloxybutyl)-2-benzyloxycyclohexanecarboxylate (**9**).* With cooling (−75°C bath) and stirring, LDA (7.75 ml, 1.5 M in hexanes) was added dropwise to a solution of the ester **4** (2.872 g, 10.94 mmol) in dry THF (50 ml) under nitrogen. Stirring was continued at −75°C for 1 h, before dry HMPA (2.0 ml) was introduced via a syringe. The iodide–Piv ether (3.120 g, 10.98 mmol, dissolved in 9 ml of dry THF) was then added via a cannula. The reaction mixture was stirred at −75°C for 1 h, at −40°C for 2 h, and kept in a −20°C freezer for 17 h. After another hour of stirring at 0°C the reaction mixture was diluted with diethyl ether, washed with water and brine, dried over Na_2SO_4. Filtration and evaporation left a red-brown oil, which was purified by column chromatography on silica gel (4:1 hexane–diethyl ether) to furnish the diester **9** as a yellowish oil (3.515 g, 8.40 mmol, 77%): IR (film): 1728 cm^{-1}. MS [*m/z* (% rel. int.)]: 387 (*M* − 31, 0.4), 311 (36), 295 (12), 211 (16), 193 (35), 92 (100). ^{1}H NMR: δ 1.10 (m, 1 H), 1.18 (s, 9 H), 1.20–1.43 (m, 4 H), 1.44–1.64 (m, 4 H), 1.69 (m, 2 H), 1.78–1.93 (m, 3 H), 3.46 (m, 1 H), 3.57 (s, 3 H), 3.60 (m, 1 H), 4.03 (t, *J* 6.5 Hz, 2 H), 4.44 and 4.48 (AB type, *J* 12 Hz, 2 H), 7.24–7.36 (m, 5 H). ^{13}C NMR: δ 20.38 (1.10, 1.35), 22.24 (1.47, CH_2), 23.34 (1.29, 1.52), 25.74 (1.42, 1.82), 27.19 (1.18, CH_3), 29.06 (1.57, CH_2), 29.94 (1.35, 1.88), 36.19 (1.69, CH_2), 38.72 (quat), 43.78 (1.81, CH), 48.35 (quat), 51.24 (3.57, OCH_3), 63.99 (4.03, CH_2OPiv), 71.07 (3.46, 3.60), 73.03 (4.44, 4.48, benzylic CH_2), 127.46 (7.32), 127.63 (7.32), 128.29 (7.32), 138.57 (quat), 176.71 (quat), 178.51 (quat). *Anal.* for $C_{25}H_{38}O_5$: C, H.

(1S,2R*)-1-(4-Hydroxybutyl)-2-(benzyloxymethyl)cyclohexylmethanol (**10**).* A suspension of $LiAlH_4$ (2.85 g, 52.6 mmol) in dry THF (150 ml) was stirred and heated under reflux for 1 h. The heating was then stopped. While the LAH mixture was still warm a solution of the diester **9** (4.923 g, 11.76 mmol) in dry THF (30 ml) was introduced via a cannula over 30 min. The mixture was then stirred at rt for 17 h. The excess hydride was carefully destroyed with water and aq. HCl. The mixture was extracted with diethyl ether, washed with water and brine (aqueous phases were back-extracted twice) and dried over Na_2SO_4. Removal of the drying agent and solvents left a yellow oil, which was chromatographed on silica gel (3:1 EtOAc–hexane) to give the diol (3.214 g, 89% yield): IR (film): 3347 cm^{-1}; MS [*m/z* (% rel. int.)]: 288

(*M* − 18, 0.4), 276 (1.3), 197 (17), 168 (40), 149 (15), 135 (10), 121 (21), 108 (22), 95 (30), 91 (100). ^{1}H NMR: δ 1.19 (m, 1 H), 1.25–1.47 (m, 7 H), 1.47–1.62 (m, 5 H), 1.62–1.72 (m, 2 H), 3.23 and 3.71 (AB type, *J* 12 Hz, 2 H), 3.49 (m, 1 H), 3.61–3.67 (m, 3 H), 4.48 and 4.53 (AB type, *J* 12 Hz, 2 H), 7.33 (m, 5 H). ^{13}C NMR: δ 18.55 (1.33, CH_2), 21.56 (1.35, 1.42), 25.37 (1.31, 1.53), 26.25 (1.57, 1.68), 32.42 (1.30, 1.66), 33.21 (1.55, CH_2), 34.44 (1.31, 1.66), 39.56 (quat), 43.10 (1.54, CH), 62.43 (3.62, CH_2), 64.67 (3.24, 3.71), 71.90 (3.49, 3.64), 73.58 (4.48, 4.53, benzylic), 127.83 (7.33), 127.91 (7.33), 128.51 (7.33), 137.38 (quat). Exact mass calc. for $C_{19}H_{30}O_3$: 306.220. Found: 306.223.

(5S,6S*)-6-Benzyloxymethylspiro[4,5]dec-1-ene-2-carboxaldehyde* (**11**). With cooling (−70°C bath) and stirring dry DMSO (1.0 ml, dissolved in 1.0 ml of dry CH_2Cl_2) was added slowly via a syringe to a solution of oxalyl chloride (0.520 ml, 5.96 mmol) in dry CH_2Cl_2 (12 ml). The mixture was stirred at −70°C for 30 min. The diol **10** (818 mg, 2.67 mmol, dissolved in 7 ml of dry CH_2Cl_2) was introduced via a syringe (2 × 3 ml of dry CH_2Cl_2 to wash the syringe/needle) over ca. 5 min. The white turbid mixture was stirred at −70°C for another hour, before dry NEt_3 (2.5 ml) was introduced via syringe. Stirring was continued for 1 h 50 min during which the bath was allowed to warm to −10°C. The mixture was diluted with diethyl ether, washed with water (three times, aqueous phases were back-extracted twice) and brine and dried over Na_2SO_4. Filtration and evaporation gave the unstable intermediate dialdehyde: ^{1}H NMR: δ 1.30–1.50 (m, 3 H), 1.50–1.66 (m, 7 H), 1.74–1.89 (m, 3 H), 2.41 (m, 2 H), 3.51 (dd, *J* 9.3, 5.4 Hz, 1 H, part A of ABX system), 3.58 (dd, *J* 9.3, 5.4 Hz, 1 H, part B of ABX system), 4.42 and 4.45 (AB type, *J* 12 Hz, 2 H), 7.31 (m, 5 H), 9.68 (s, 1 H), 9.73 (t, *J* 1.5 Hz, 1 H). ^{13}C NMR: δ 15.94 (1.46, 1.64), 21.96 (1.60, CH_2), 24.33 (1.38, 1.64), 26.33 (1.59, 1.83), 28.50 (1.46, 1.86), 32.86 (1.64, CH_2), 42.59 (1.88, CH), 44.09 (2.41, CH_2), 50.96 (quat), 70.84 (3.51, 3.58), 73.13 (4.42, 4.45), 127.55 (7.31), 127.62 (7.31), 128.31 (7.31), 138.09 (quat), 201.86 (9.73), 206.54 (9.68). The crude dialdehyde was dissolved in MeOH (12 ml) and stirred with NaOH (2.0 ml, prepared from 98 mg in 4.0 ml of MeOH and 0.2 ml of water) at rt for 18 h. The mixture was diluted with diethyl ether, washed with water and brine (aqueous phases were back-extracted twice), and dried over Na_2SO_4. The two-phase residue, after removal of the drying agent and solvents, was chromatographed on silica gel (1:1 hexane–diethyl ether) to give the aldehyde as a yellowish oil with a peculiar smell (651 mg, 2.29 mmol, 86% from diol): IR (film): 1677 cm^{-1}. MS [*m/z* (% rel. int.)]: 284 (M^+, 1.9), 256 (1.5), 213 (1.0), 193 (13), 178 (7.7), 147 (6.1), 121 (5.9), 91 (100). ^{1}H NMR: δ 1.32–1.51 (m, 4 H), 1.61 (m, 1 H), 1.65–1.74 (m, 2 H), 1.74–1.80 (m, 2 H), 1.92 (m, 1 H), 2.12 (m, 1 H), 2.48 (m, 2 H), 3.17 (dd, *J* 9.4, 7.5 Hz, 1 H), 3.49 (dd, *J* 9.4, 4.5 Hz, 1 H), 4.40 and 4.45 (AB type, *J* 12 Hz, 2 H), 6.95 (br t, *J* 1.6 Hz, 1 H), 7.31 (m, 5 H), 9.73 (s, 1 H). ^{13}C NMR: δ 23.63 (1.39, 1.61), 25.22 (1.35, 1.75), 27.12 (2.48, CH_2), 27.78 (1.36, 1.92), 36.18 (1.68, 2.12), 39.22 (1.44, 1.67), 45.85 (1.76, CH), 53.14 (quat), 72.32 (3.17, 3.49), 73.19 (4.40, 4.45), 127.52 (7.31), 127.55 (7.31), 128.36 (7.31), 138.35 (quat), 146.09 (quat), 156.98 (6.95), 190.54 (9.93). Exact mass calc. for $C_{19}H_{24}O_2$: 284.178. Found: 284.178.

The p-*tosylhydrazone of* **11** (**12**). A mixture of the aldehyde **11** (847 mg, 7.81 mmol) and *p*-tosylhydrazine (1.70 g, 8.85 mmol) in 95% EtOH (11 ml) was heated to reflux with stirring for 25 min. The mixture was then concentrated on a rotary evaporator to ca. half of the initial volume and while still hot (to avoid crystalization) was loaded onto a pre-packed silica gel column and eluted with 5:1 diethyl ether–hexane to afford the hydrazone **12** as a white solid (3.433 g, 7.58 mmol, 97%): ^{1}H NMR: δ 1.16–1.43 (m, 5 H), 1.51–1.64 (m, 4 H), 1.69 (m, 2 H), 1.89 (m, 1 H), 2.04 (m, 1 H), 2.42 (s, 3 H), 2.47 (m, 2 H), 3.06 (t, *J* 8.8 Hz, 1 H), 3.44 (dd, *J* 9.0, 4.2 Hz, 1 H), 4.35 and 4.43 (AB type, *J* 12 Hz, 2 H), 7.22–7.34 (m, 7 H), 7.53 (s, 1 H), 7.73 (br s, 1 H), 7.82 (d, *J* 8.3 Hz, 2 H). ^{13}C NMR: δ 21.59, 23.64, 25.21, 27.74, 29.29, 36.27, 39.75, 45.94, 52.55, 72.53, 73.03, 127.40, 127.92, 128.26, 129.50, 135.13, 138.48, 139.61, 143.14, 144.09, 146.26. *Anal.* for $C_{26}H_{32}N_2O_3S$: C, H, N.

(5R,6S*)-2-Methylene-6-benzyloxymethylspiro[4,5]decane* (**13**). Catechol–borane (1.9 ml, 17.82 mmol) was added to a stirred solution of the hydrazone **12** (3.433 g, 7.58 mmol) dissolved in dry $CHCl_3$ (40 ml) at 0°C (bath). The mixture was stirred at 0°C for 2 h, before $NaOAc \cdot 3H_2O$ (4.60 g, 33 mmol) was added quickly. The mixture was stirred at 0°C for 15 min, rt for another 15 min, and finally heated under reflux for 2 h. After being cooled to rt, the mixture was filtered through a short pad of silica gel (eluting with diethyl ether). The filtrate was concentrated on a rotary evaporator and the residue was chromatographed on silica gel (10:1 hexane–diethyl ether) to give **13** as a colourless oil (1.754 g, 6.49 mmol, 85%): IR (film): 1658, 1448, 1096, 875, 734 cm^{-1}. MS [*m/z* (% rel. int.)]: 270 (M^+, 0.8), 241 (1.3), 179 (47), 161 (14), 133 (10), 119 (14), 105 (21), 91 (100). ^{1}H NMR: δ 1.22 (m, 1 H), 1.30–1.46 (m, 4 H), 1.47–1.70 (m, 4 H), 1.72–1.82 (m, 2 H), 2.08 and 2.18 (AB type, *J* 16 Hz, 2 H), 2.32 (m, 2 H), 3.36 (t, *J* 8.8 Hz, 2 H), 3.58 (dd, *J* 8.8, 4.1 Hz, 1 H), 4.46 and 4.53 (AB type, *J* 12 Hz, 2 H), 4.79 (m, 1 H), 4.82 (m, 1 H), 7.32 (m, 5 H). ^{13}C NMR: δ 22.85 (1.36, 1.53), 23.99 (1.34, 1.58), 26.97 (1.38, 1.80), 30.47 (2.32, CH_2), 35.70 (1.22, 1.43), 36.99 (1.62, 1.77), 41.02 (2.08, 2.18), 44.53 (quat), 44.72 (1.67, CH, confirmed by ^{1}H-coupled spectrum), 71.53 (3.36, 3.58), 73.06 (4.46, 4.53, benzylic), 105.50 (4.79, 4.82), 127.42 (7.32), 127.51 (7.32), 128.33 (7.32), 138.75 (quat), 152.71 (quat). Exact mass calc. for $C_{19}H_{26}O$: 270.198. Found: 270.199.

(5R,6S*)-2-Methylenespiro[4,5]decan-6-ylacetonitrile (**15**).* To ca. 40 ml of liquid NH_3 were added Na cuts (ca. 105 mg, added in portions) and **13** (569 mg, 2.10 mmol, dissolved in 2.0 ml of diethyl ether, added over ca. 3 min). The mixture was then stirred for 15 min before NH_4Cl was introduced (cooled in a −70°C bath) to quench the reaction. The liquid NH_3 was allowed to evaporate off and the residue was partitioned between diethyl ether and water. The ethereal phase was washed with water and brine, and dried over Na_2SO_4 (the first aqueous phase was back-extracted once). After removal of the drying agent and solvents, the residue (crude alcohol) was dissolved in dry CH_2Cl_2 (6.0 ml). With cooling (0°C bath) and stirring, DMAP (50 mg) and *p*TsCl (484 mg, 2.54 mmol) were added in turn and the resulting mixture was then stirred at rt for 10 h before being diluted with diethyl ether, washed with water and brine, and dried over Na_2SO_4. The crude oil obtained after removal of drying agent and the solvents was chromatographed on silica gel (10:3 hexane–diethyl ether) to afford the pure tosylate **14** as a colourless oil (644 mg, 1.93 mmol, 92%): IR (film): 1360, 1171 cm^{-1}. MS [*m/z* (% rel. int.)]: 334 (M^+, 31), 279 (9.0), 162 (77), 149 (43), 147 (26), 146 (26), 133 (60), 120 (29), 119 (33), 107 (75), 105 (50), 91 (100). ^1H NMR: δ 1.15–1.70 (m, 11 H), 1.99 and 2.05 (AB type, *J* 16 Hz, 2 H), 2.25 (m, 2 H), 2.45 (s, 3 H), 3.90 (t, *J* 9.3 Hz, 1 H), 4.10 (dd, *J* 9.7, 4.1 Hz, 1 H), 4.77 (m, 2 H), 7.34 (d, *J* 8.2 Hz, 2 H), 7.78 (d, *J* 8.2 Hz, 2 H). ^{13}C NMR: δ 21.64, 22.42, 23.10, 25.80, 30.06, 35.08, 36.64, 41.31, 43.82, 44.19, 106.16, 127.84, 129.77, 133.06, 144.62, 151.43. Exact mass calc. for $C_{19}H_{26}O_3S$: 334.160. Found: 334.159.

The tosylate **14** (644 mg, 1.92 mmol) and dry KCN (224 mg, 3.99 mmol) were added to dry DMSO (2.5 ml). The mixture was heated with stirring on a 100°C hotplate for 5 h. After being cooled to rt, the mixture was diluted with diethyl ether, washed with water and brine, and dried over Na_2SO_4. The crude oil obtained after removal of the drying agent and solvents was chromatographed on silica gel (10:3 hexane–diethyl ether) to give the nitrile **15** as a colourless oil (325 mg, 1.72 mmol, 89%): IR (film): 2242 cm^{-1}. MS [*m/z* (% rel. int.)]: 189 (M^+, 17), 174 (22), 159 (8.0), 149 (18), 146 (19), 136 (17), 133 (21), 107 (100), 91 (57), 79 (52). ^1H NMR: δ 1.25 (m, 1 H), 1.34–1.68 (m, 8 H), 2.06 and 2.11 (AB type, *J* 16 Hz, 2 H), 2.23 (dd, *J* 17, 11 Hz, 1 H), 2.34 (m, 2 H), 2.45 (dd, *J* 17, 4.1 Hz, 1 H), 4.81 (m, 1 H), 4.85 (m, 1 H). ^{13}C NMR: δ 18.73 (2.24, 2.45), 22.41 (1.40, 1.54), 23.48 (1.40, 1.60), 28.37 (1.40, 1.86), 30.42 (2.34, CH_2), 34.93 (1.24, 1.45), 36.67 (1.64, CH_2), 40.49 (2.06, 2.11), 41.95 (1.76, CH), 45.16 (quat), 106.46 (4.81, 4.85), 119.94 (quat, CN), 151.10 (quat). Exact mass calc. for $C_{13}H_{19}N$: 189.152. Found: 189.151.

(5R,6S*)-2-Methylene-6-(2-indenyl)spiro[4,5]decan-2-one (**17**).* The lithium reagent was prepared as follows: *n*-BuLi (1.6 M, in hexanes, 3.60 ml) was added, with cooling (−70°C) and stirring, to a solution of *o*-bromobenzyl alcohol (530 mg, 2.77 mmol) in dry THF (15 ml) under nitrogen. The stirring was continued while the bath was allowed to warm to −40°C over 45 min, kept at −40°C for 1.5 h and finally at −20°C for another 1.5 h.

The aldehyde was obtained by reducing nitrile **15** with DIBAL: a solution of the nitrile (325 mg, 1.72 mmol) in dry hexane (4 ml) under nitrogen was cooled to −60°C (bath). With stirring DIBAL (1.0 M, in hexanes, 3.0 ml) was added via a syringe. The stirring was continued while the bath was warmed to −10°C over ca. 40 min and kept at −10°C for 1 h 40 min. Water was carefully added to destroy the excess of hydride. The mixture was then diluted with diethyl ether and shaken vigorously with 10% HCl (the aqueous phase was back-extracted three times), washed with brine, and dried over Na_2SO_4. The solids were filtered off and the filtrate was concentrated to minimum volume, diluted with hexane, and finally dried over $MgSO_4$. Removal of the drying agent and solvent left the crude aldehyde as a fragrant oil (306 mg, 1.59 mmol, 93%). This oil was dissolved in dry hexane (2 ml) and added via a cannula to the freshly prepared lithium reagent (see above) stirred at −60°C. The stirring was continued while the bath was allowed to warm to 0°C over ca. 1 h, and then at rt for 20 h. The reaction mixture was diluted with diethyl ether, washed three times with water (aqueous phases were back-extracted three times) and brine, dried over Na_2SO_4. The crude oil after removal of the drying agent and solvent was chromatographed on silica gel (3:1 diethyl ether–hexane) to give diol **16** (464 mg, 1.54 mmol, 90% from the nitrile) as a mixture of two diastereomers: IR (film): 3336 cm^{-1}. MS [*m/z* (% rel. int.)]: 282 (*M* − 18, 3.8), 264 (4.1), 161 (8.5), 148 (8.6), 137 (22), 133 (9.3), 118 (100), 106 (26), 94 (19), 91 (56). Exact mass calc. for $C_{20}H_{28}O_2$: 300.209. Found: 300.209. This mixture was used in the next step.

A solution of oxalyl chloride (0.30 ml, 3.44 mmol) in dry CH_2Cl_2 (6 ml) under nitrogen was cooled to −70°C. With stirring dry DMSO (0.60 ml, 8.45 mmol, dissolved in ca. 0.2 ml of dry CH_2Cl_2) was added via syringe. The mixture was stirred at −70°C for 30 min before a solution of the diol **16** (464 mg, 1.54 mmol) was introduced via a cannula. The stirring was then continued at −70°C for another hour. Dry NEt_3 (1.5 ml) was added via a syringe. After stirring for 2.5 h, during which time the bath was warmed to −5°C the mixture was diluted with diethyl ether, washed with water and brine (aqueous phases were back-extracted once), and dried over Na_2SO_4. Filtration and evaporation left a yellow oil (crude aldehyde/ketone), which was immediately dissolved in dry CH_2Cl_2 (6.0 ml) and treated at rt with DBU (0.9 ml) and MsCl (190 µl, dissolved in 2.0 ml of CH_2Cl_2, added over 5 h 45 min) in the presence of dry LiBr (110 mg). After the completion of addition, stirring was continued for another hour before the mixture was diluted with diethyl ether, washed with water (twice, back-extracted once) and brine, and dried over Na_2SO_4. After filtration and evaporation, the crude oil was chromatographed on silica gel (4:1 hexane–diethyl ether) to give

the enone **17** as a yellow oil (309 mg, 1.11 mmol, 72% from **16**): IR (film): 1708, 1657, 1601 cm^{-1}. MS [*m/z* (% rel. int.)]: 278 (M^+, 19), 250 (12), 158 (69), 146 (100), 133 (57), 128 (53), 120 (57), 115 (46), 91 (38). ^1H NMR: δ 1.25–1.67 (m, 9 H), 1.74 (m, 1 H), 2.08 (m, 1 H), 2.22 (m, 2 H), 2.25 (m, 1 H), 2.61 (dd, *J* 11, 4.1 Hz, 1 H), 4.73 (m, 1 H), 4.81 (m, 1 H), 6.94 (d, *J* 7.2 Hz, 1 H), 7.13 (s, 1 H), 7.14 (t, *J* 7.9 Hz, 1 H), 7.29 (t, *J* 7.5 Hz, 1 H), 7.39 (d, *J* 7.2 Hz, 1 H). ^{13}C NMR: δ 22.80 (1.40, 1.60), 25.90 (1.36, 1.74), 29.36 (1.55, CH_2), 30.38 (2.08, 2.25), 36.74 (1.28, 1.64), 37.99 (2.22, CH_2), 38.30 (1.43, 1.51), 39.94 (2.61, CH), 46.34 (quat), 105.67 (4.73, 4.81), 121.34 (6.94), 122.76 (7.39), 128.01 (7.14), 130.35 (quat), 133.82 (7.29), 142.81 (quat), 143.94 (7.13), 144.87 (quat), 152.38 (quat), 198.72 (quat). Exact mass calc. for $C_{20}H_{22}O$: 278.167. Found: 278.168.

(5R,6S*)-6-(2-Indenyl)spiro[4,5]decan-2-one* (**2**). The enone **17** (646 mg, 2.32 mmol) was dissolved in aq. THF (20 ml of THF containing 6.6 ml of water) and treated with OsO_4 (33 mg) and $NaIO_4$ (2.0 g). The reaction was monitored with TLC. After 1 h 25 min of reaction, almost all starting enone had been consumed. The solids were filtered off (washed with diethyl ether). The filtrate was washed with water and aq. $NaHSO_3$ (twice, alternatively shaking–standing for ca. 1 h, ca. 170 mg in 15 ml for each washing), and brine (all aqueous phases were back-extracted), and dried over Na_2SO_4. The crude oil after filtration and evaporation was chromatographed on silica gel (2:1 diethyl ether–hexane) to afford unchanged **17** (156 mg, 0.56 mmol, 24%) and the dione (**18**) as a yellow oil (215 mg, 44% based on consumed **17**): IR (film): 1738, 1712, 1604 cm^{-1}. MS [*m/z* (% rel. int.)]: 280 (M^+, 17), 219 (17), 165 (37), 157 (34), 153 (34), 13 (28), 122 (31), 115 (68), 109 (100), 97 (29), 95 (29), 93 (26), 91 (23). ^1H NMR: δ 1.35 (m, 2 H), 1.50 (m, 2 H), 1.58 (m, 1 H), 1.64–1.75 (m, 3 H), 1.78 (m, 1 H), 1.80–1.98 (m, 2 H), 2.12 and 2.29 (AB type, *J* 18 Hz, 2 H), 2.16 (m, 1 H), 2.64 (dd, *J* 3.3, 12 Hz, 1 H), 6.98 (d, *J* 7.2 Hz, 1 H), 7.10 (s, 1 H), 7.15 (dt, *J* 0.99, 7.9 Hz, 1 H), 7.30 (dt, *J* 1.31, 7.9 Hz, 1 H), 7.39 (dd, *J* 0.99, 7.2 Hz, 1 H). ^{13}C NMR: δ 22.89 (1.35, 1.68), 25.87 (1.35, 1.78), 29.18 (1.50, 1.58), 35.05 (1.71, 1.85), 36.41 (1.91, 2.16), 38.40 (1.50, 1.67), 40.05 (2.64, CH), 44.09 (quat), 44.58 (2.12, 2.29), 121.85 (6.98), 123.03 (7.39), 128.43 (7.15), 129.99 (quat), 134.20 (7.30), 141.99 (quat), 144.39 (7.10), 144.40 (quat), 198.42 (quat), 219.57 (quat). Exact mass calc. for $C_{19}H_{20}O_2$: 280.146. Found: 280.145.

The dione **18** (215 mg, 0.76 mmol) was dissolved in MeOH (3 ml). With cooling (0°C bath) and stirring, $CeCl_3 \cdot 7H_2O$ (323 mg) and $NaBH_4$ (59 mg) were added. The stirring was continued at 0°C for 10 min, then at rt for 1 h, before the reaction mixture was diluted with diethyl ether, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation left a sticky gum (213 mg), which was directly dissolved in CH_2Cl_2 (8 ml) and treated with activated MnO_2 (added in three portions, 372 mg, 107 mg, 157 mg). After stirring at rt for 16 h, when TLC showed complete oxidation, the solids were filtered off (washed thoroughly with CH_2Cl_2) and the filtrate was concentrated and chromatographed on silica gel (3:1 diethyl ether–hexane) to give **19** (145 mg, 67% from dione **18**) as a yellow oil (^1H NMR showed that it contained both epimers). This oil (141 mg, 0.49 mmol) was dissolved in EtOH (99.5%, 2.5 ml) and refluxed with *p*TsNHNH$_2$ (113 mg, 0.59 mmol) for 30 min. The solvent was removed on a rotary evaporator, followed by an oil pump. The residue (232 mg) was dissolved in dry $CHCl_3$ (3.5 ml) under nitrogen. With cooling (0°C bath) and stirring, catechol–borane (neat, 0.5 ml) was introduced via a syringe. The mixture was stirred at 0°C for 2 h before $NaOAc \cdot 3H_2O$ (1.5 g) was added. The mixture was then stirred at 0°C for 15 min, at rt for 15 min, and finally at reflux for 2 h. The solids were filtered off through a short pad of silica gel (eluting with diethyl ether). The filtrate was concentrated and chromatographed on silica gel (2:1 diethyl ether–hexane) to give a solid (124 mg), the main portion of which (113 mg, 0.29 mmol) was dissolved in MeOH (2.5 ml, containing ca. 0.2 ml of water) and stirred with *p*TsOH (ca. 18 mg) at rt for 13 h. The mixture was diluted with diethyl ether, washed with aq. $NaHCO_3$, water and brine, and dried over Na_2SO_4. The crude solid obtained after filtration and evaporation was chromatographed on silica gel (2:1 hexane–EtOAc) to give the hydrolysis product (**20**, 24 mg, 0.09 mmol). From the early fractions containing only one of the two epimers (late fractions contained both) the following were recorded: MS [*m/z* (% rel. int.)]: 268 (M^+, 32), 250 (30), 155 (61), 167 (32), 153 (61), 142 (68), 141 (100), 129 (75), 128 (94), 115 (94). ^1H NMR: δ 1.17 (br s, 1 H, OH), 1.22–1.39 (m, 4 H), 1.44 (m, 1 H), 1.50–1.65 (m, 4 H), 1.65–1.76 (m, 2 H), 1.81 (m, 1 H), 1.86–1.95 (m, 2 H), 2.48 (dd, *J* 3.3, 12 Hz, 1 H), 3.43 and 3.51 (AB type, *J* 22 Hz, 2 H), 4.22 (m, 1 H), 6.61 (s, 1 H), 7.10 (t, *J* 7.4 Hz, 1 H), 7.21 (t, *J* 7.4 Hz, 1 H), 7.29 (d, *J* 7.4 Hz, 1 H), 7.38 (d, *J* 7.4 Hz, 1 H). ^{13}C NMR: δ 23.11 (1.44, 1.59), 25.79 (1.30, 1.71), 30.65 (1.54, 1.68), 34.35 (1.25, 1.80), 36.70 (1.32, 1.90), 39.98 (1.26, 1.60), 40.70 (1.62, 1.90), 42.67 (3.43, 3.51), 45.56 (quat), 48.77 (2.48, CH), 73.65 (4.22, CH), 120.13 (7.29), 123.31 (7.38), 123.75 (7.10), 126.21 (7.21), 128.66 (6.61), 143.00 (quat), 145.04 (quat), 153.07 (quat). Exact mass calc. for $C_{19}H_{24}O$: 268.183. Found: 268.181.

A mixture of **20** (20 mg, 0.075 mmol), anhydrous NaOAc (48 mg), and PCC (72 mg) in dry CH_2Cl_2 (2 ml) was stirred at rt for 1 h 30 min. The reaction mixture was then filtered through a short pad of silica gel (eluting with dry diethyl ether). The filtrate was concentrated and chromatographed on silica gel (3:2 hexane–diethyl ether) to give the ketone **2** as a colourless oil (16 mg, 81% from **20**): MS [*m/z* (% rel. int.)]: 266 (M^+, 51), 237 (22), 167 (21), 165 (17), 155 (50), 153 (44), 152 (19), 142 (41), 141 (98), 130 (36), 129 (86), 128 (54), 115 (100). ^1H NMR: δ 1.32–1.49 (m, 3 H), 1.57 (m, 1 H), 1.65–1.77 (m, 4 H), 1.80 (m, 1 H), 1.91 (m, 1 H), 2.05 (m, 1 H), 2.15 (m, 1 H), 2.18 and 2.43 (AB type, *J* 18 Hz, 2 H), 2.54 (dd, *J* 3.0,

12 Hz, 1 H), 3.32 and 3.40 (AB type, *J* 23 Hz, 2 H), 6.57 (s, 1 H), 7.12 (t, *J* 7.4 Hz, 1 H), 7.23 (t, *J* 7.4 Hz, 1 H), 7.29 (d, *J* 7.4 Hz, 1 H), 7.38 (d, *J* 7.4 Hz, 1 H). ^{13}C NMR: δ 22.96 (1.40, 1.71), 26.15 (1.39, 1.80), 30.46 (1.57, 1.75), 35.12 (1.72, 2.05), 36.41 (1.91, 2.15), 38.91 (1.44, 1.72), 42.60 (3.32, 3.40), 44.32 (quat), 45.02 (2.8, 2.43), 47.99 (2.54, CH), 120.36 (7.29), 123.39 (7.38), 124.10 (7.12), 126.44 (7.23), 129.08 (6.57), 142.55 (quat), 144.84 (quat), 151.24 (quat), 219.63 (quat). Exact mass calc. for $C_{19}H_{22}O$: 266.167. Found: 266.167.

(5R,6R*)-2-Methylene-6-(1-*tert*-butyldimethylsilyloxylinden-2-yl)spiro[4,5]decane (**22**).* With stirring and cooling (0°C), $NaBH_4$ (76 mg) was added to a mixture of the enone **17** (186 mg, 0.67 mmol) and $CeCl_3 \cdot 7H_2O$ (573 mg) in MeOH (5 ml). Stirring was continued for 30 min. The reaction mixture was then diluted with diethyl ether, washed with water and brine, and dried over Na_2SO_4. Removal of drying agent and solvent left **21** as a colourless oil (182 mg, 0.65 mmol, 97%): MS [*m/z* (% rel. int.)]: 280 (M^+, 10), 263 (11), 171 (14), 145 (52), 132 (85), 115 (45), 107 (58), 103 (25), 94 (53), 91 (89), 79 (100). ^1H NMR: δ 1.30 (m, 1 H), 1.37 (m, 1 H), 1.45–1.64 (m, 6 H, including one OH), 1.65–1.76 (m, 3 H), 2.18–2.36 (m, 3 H), 2.44 (d, *J* 16 Hz, 1 H), 2.60 (m, 1 H), 4.76 (br s, 1 H), 4.80 (br s, 1 H), 4.91 (d, *J* 9.7 Hz, 1 H), 7.11 (t, *J* 7.5 Hz, 1 H), 7.13 (d, *J* 7.5 Hz, 1 H), 7.21 (t, *J* 7.5 Hz, 1 H), 7.43 (d, *J* 7.5 Hz, 1 H). ^{13}C NMR: δ 22.77 (1.52, CH_2), 24.34 (1.37, 1.60), 30.15 (1.56, 1.73), 30.67 (2.25, CH_2), 36.10 (1.30, 1.70), 37.76 (1.54, 1.71), 41.45 (2.27, 2.44), 44.20 (2.60, CH), 45.88 (quat), 78.56 (4.91), 105.59 (4.76, 4.80), 120.43 (7.13), 123.23 (7.43), 125.05 (7.11), 127.57 (6.46), 128.53 (7.21), 142.79 (quat), 144.46 (quat), 152.68 (quat), 154.56 (quat). Exact mass calc. for $C_{20}H_{24}O$: 280.183. Found: 280.181. The indenol (182 mg, 0.65 mmol) was dissolved in dry CH_2Cl_2 (3 ml) and treated with DBU (0.4 ml) and TBDMS-Cl (239 mg) at room temperature for 13 h. The reaction mixture was diluted with diethyl ether, washed with water and brine, and dried over Na_2SO_4. The crude oil obtained after removal of the drying agent and solvent was chromatographed on silica gel (10:1 hexane–diethyl ether) to give **22** as a colourless oil (245 mg, 0.62 mmol, 92% from **17**): MS [*m/z* (% rel. int.)]: 394 (M^+, 3.5), 337 (22), 285 (11), 259 (15), 201 (8), 115 (11), 73 (100). ^1H NMR: δ 0.17 (s, 3 H), 0.22 (s, 3 H), 1.09 (s, 9 H), 1.26–1.48 (m, 4 H), 1.54–1.72 (m, 4 H), 1.77–1.90 (m, 2 H), 2.04 (m, 1 H), 2.22 (m, 1 H), 2.24 and 2.42 (AB type, *J* 16 Hz, 2 H), 2.85 (m, 1 H), 3.23 and 3.29 (AB type, *J* 22 Hz, 2 H), 4.68 (m, 1 H), 4.76 (m, 1 H), 7.15 (dt, *J* 1.3, 6.9 Hz, 1 H), 7.26 (t, *J* 7.6 Hz, 1 H), 7.27 (d, *J* 7.8 Hz, 1 H), 7.33 (t, *J* 7.8 Hz, 1 H). ^{13}C NMR: δ −4.11 (0.17, CH_3), −3.01 (0.22, CH_3), 18.37 (quat), 23.22 (1.44, 1.63), 26.04 (1.09, CH_3), 26.70 (1.35, 1.80), 30.06 (1.58, CH_2), 31.04 (2.04, 2.20), 35.45 (3.23, 3.29), 38.51 (1.40, 1.84), 38.92 (2.24, 2.42), 39.17 (1.30, 1.64), 42.71 (2.85, CH), 47.58 (quat), 105.08 (4.68, 4.76), 117.81 (7.27), 123.40 (7.33), 124.02 (7.15), 125.79 (7.26), 127.28 (quat), 141.63 (quat), 141.88 (quat), 148.23 (quat), 153.21 (quat). Exact mass calc. for $C_{26}H_{38}OSi$: 394.269. Found 394.272.

(5R,6R*)-6-(1-*tert*-Butyldimethylsilyloxylinden-2-yl)spiro[4,5]decan-2-one (**23**).* The compound **22** (81 mg, 0.205 mmol) was dissolved in THF (1.5 ml) and water (0.5 ml) and treated with a catalytic amount of OsO_4 and $NaIO_4$ (250 mg, added in small portions over 2 h). One hour later when TLC showed complete consumption of the starting material, the reaction mixture was filtered and the filtrate was diluted with diethyl ether, washed with water, diluted aq. $NaHSO_3$ (with repeated shaking) and brine, and dried over Na_2SO_4. Removal of the drying agent and solvent left a dark-yellow oil, which was chromatographed in silica gel (10:3 hexane–diethyl ether) to afford the ketone **23** as an oil (57 mg, 0.144 mmol, 70%): MS [*m/z* (% rel. int.)]: 396 (M^+, 8), 339 (18), 285 (24), 259 (13), 223 (8), 201 (8), 165 (6), 141 (9), 129 (8), 73 (100). ^1H NMR: δ 0.18 (s, 3 H), 0.23 (s, 3 H), 1.10 (s, 9 H), 1.30–1.75 (m, 8 H), 1.86 (m, 1 H), 1.97 (m, 1 H), 2.09–2.25 (m, 2 H), 2.15 and 2.40 (AB type, *J* 18 Hz, 2 H), 2.92 (dd, *J* 3.6, 12 Hz, 1 H), 3.10 and 3.25 (AB type, *J* 22 Hz, 2 H), 7.15 (dt, *J* 2.3, 7.6 Hz, 1 H), 7.26 (t, *J* 7.5 Hz, 1 H), 7.28 (d, *J* 7.5 Hz, 1 H), 7.33 (d, *J* 7.2 Hz, 1 H). ^{13}C NMR: δ −4.08 (0.18, CH_3), −2.99 (0.23, CH_3), 18.36 (quat), 23.21 (1.39, 1.70), 26.02 (1.10, CH_3), 26.53 (1.37, 1.86), 29.63 (1.58, CH_2), 35.05 (1.66, 2.20), 35.17 (3.10, 3.25), 36.76 (1.97, 2.14), 40.05 (1.45, 1.68), 42.90 (2.92, CH), 45.49 (quat), 45.54 (2.15, 2.40), 118.06 (7.28), 123.67 (7.33), 124.56 (7.15), 125.59 (quat), 125.99 (7.26), 141.25 (quat), 141.33 (quat), 149.15 (quat), 220.40 (quat). Exact mass calc. for $C_{25}H_{36}O_2Si$: 396.248. Found: 396.251.

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