Synthesis and Conformational Analysis of *meso*-Ter(1,3-dioxan-4-yls)[‡]

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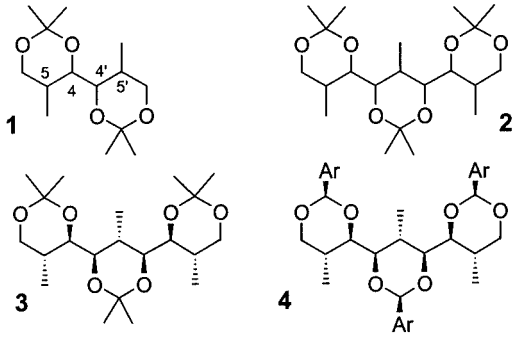
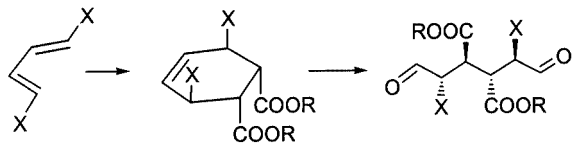
A convergent synthesis of the *meso*-ter(1,3-dioxanyls) **8**–**11** has been achieved, starting from two enantiomeric building blocks in each case. The stereogenic centres in the central linkage region were set up by stereocontrolled aldol additions. Structure assignment of the final products was based on comparisons between experimental and calculated $^3J_{H,H}$ coupling constants, which reflect distinct conformer populations.

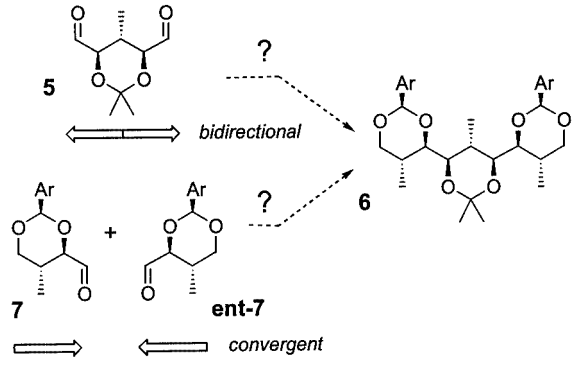
Certain di(1,3-dioxan-4-yls) **1** have a preferred conformation at the inter-ring bond when properly substituted in the 5,5′-positions.[1,2] This also holds for the inter-ring bonds in the ter(1,3-dioxan-4-yls) **3** and **4**.[3] Our previous synthesis of **3** and **4** was rather ineffective and did not capitalise on the symmetry (*meso*) of these compounds. As we wanted to study the conformational preferences of additional (*meso*) symmetric ter-dioxanyls **2**, a different synthetic approach to this class of *meso* compounds appeared necessary.



The synthesis of open-chain *meso* compounds with up to four contiguous stereocentres can be addressed by, for example, the Diels–Alder or related cycloaddition reactions, as long as they are inherently symmetric. The cyclic adducts then have to be subjected to a ring-opening process, as shown in the following generalised example.



The synthesis of *meso* compounds with more than four stereocentres (e.g., of **6**) in turn requires totally different approaches. There are two options for an efficient synthesis of such compounds: one is to start from a central achiral (*meso*) building block (e.g., **5**[4]) and to create the additional stereogenic centres by bidirectional synthesis.[5,6]



The difficulty in this approach is that only substrate-based asymmetric induction can be applied, since identically substituted stereogenic centres of opposite configuration have to be created in a single step. We have recently utilised that approach successfully for the synthesis of other *meso* compounds with more than four stereogenic centres.[7,8]

The second approach is based on two enantiomeric building blocks (e.g., **7** and *ent*-**7**), which constitute the "outer wings" of the target structure. This approach appears unattractive at first, because both enantiomers of the building blocks have to be prepared. This disadvantage may be balanced by the convergency of the approach. The joining of these building blocks is easy if the linkage region is devoid of stereogenic centres. In the case of *meso* derivatives of **2**, such as **6**, however, there are further stereocentres in the linkage region, the control of which constitutes an additional challenge. This control is difficult to master, as asymmetric induction may originate from either building block,

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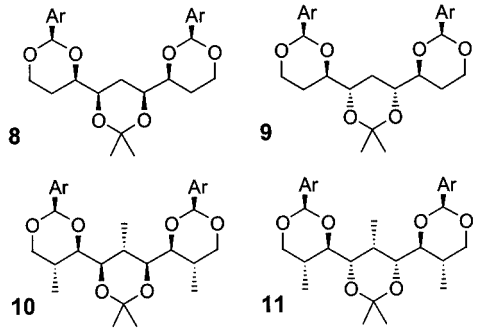
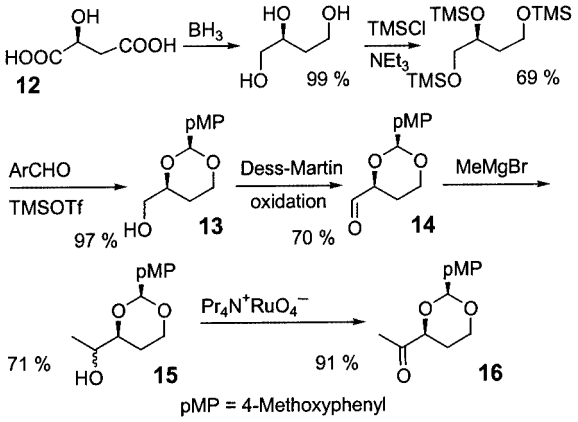
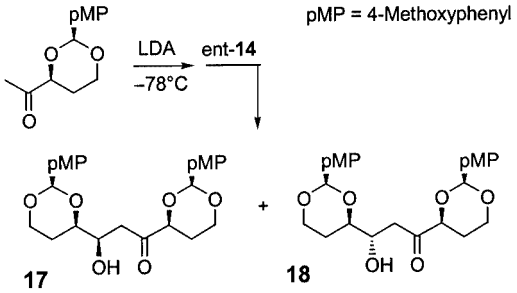
resulting in matched or mismatched situations. Again, chiral reagents or chiral auxiliaries are less likely to be applicable to such a problem. We nevertheless hoped that the techniques of 1,2- and 1,4-asymmetric induction, highly developed in the field of aldol additions[9] might provide a solution to this problem. We discuss in this paper how a convergent approach can indeed be used in conjunction with the aldol addition for a quick synthesis of the *meso* compounds **8**–**11**.



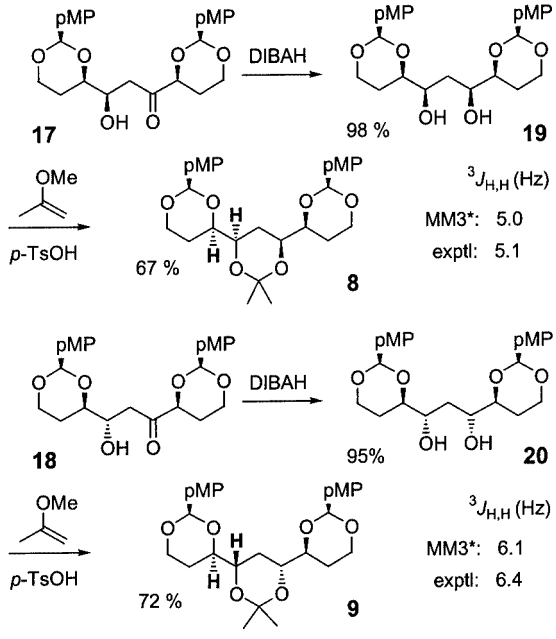
As a prelude to the synthesis of more complex *meso* compounds of type **2**, we tested the convergent approach in a synthesis of the ter(1,3-dioxanyl)s **8** and **9**. To this end, both L-malic acid (**12**) and D-malic acid were converted into **13** and *ent*-**13** by literature procedures.[10] Reduction of **12** with borane–methyl sulfide complex[11] was followed by persilylation of the resulting triol (69%). Subsequent Noyori acetalisation[12] regioselectively furnished the dioxane **13** (97%).



Dess–Martin oxidation[13] provided the aldehyde **14** (70%), which was converted via the alcohol **15** (71%) into the ketone **16** (91%). To initiate the aldol addition, the ketone **16** was deprotonated with lithium diisopropylamide and the resulting enolate was added to the aldehyde *ent*-**14**. This afforded a mixture of the two aldol products **17** and **18** (92%) in a 1:1 ratio. A boron-mediated aldol addition (chlorodicyclohexylborane, triethylamine)[9,14] likewise furnished the two aldols in a 1:1 ratio. The aldol products could be separated by chromatography and were subjected individually to *syn*-selective DIBAL reduction.[15] In each case, according to the ^{13}C NMR spectra, a symmetrical product was obtained. The diols were then converted into the ter-dioxanes **8** and **9** by acetalization.



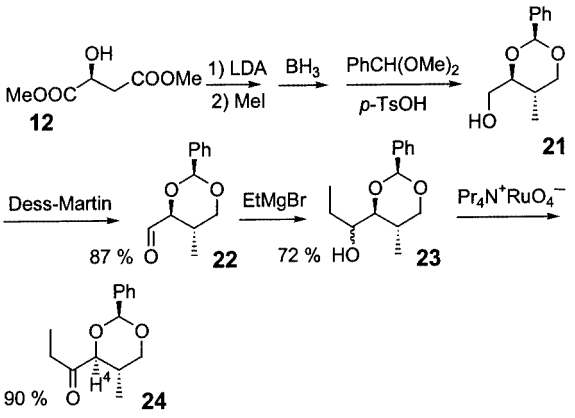
Assignment of the relative configuration was not obvious either at the stage of **17/18**, or at the stages of **19/20** or **8/9**. A tentative assignment was achieved by considering the conformational properties of the ter-dioxanes **8** and **9**. The conformer population can be analysed by force-field (MM3*) calculations with the program MACROMODEL.[16] Compound **8** is calculated to populate several conformations at the inter-ring bond, resulting in a predicted $^3J_{H,H}$ coupling constant of 5.0 Hz for the protons at the inter-ring bonds of compound **8**.



A similar analysis for compound **9** predicts a value of 6.1 Hz. This difference is clearly too small to allow a reliable assignment. Nevertheless, the almost perfect match to the experimentally determined values of 5.1 and 6.4 Hz encouraged us to make a tentative assignment as given in the formula scheme.

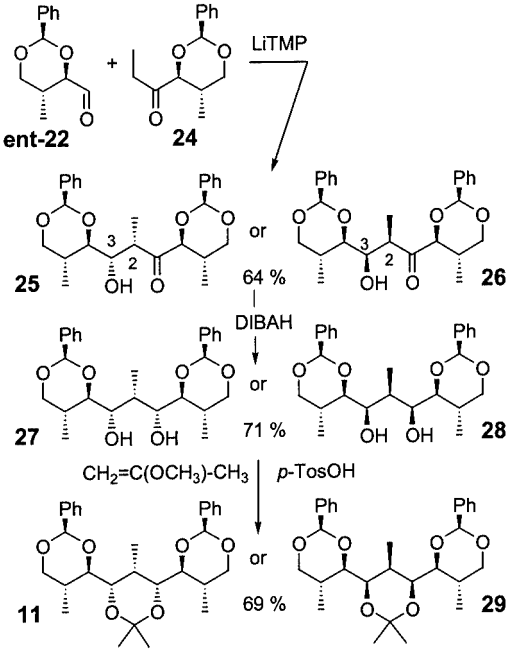
With the synthesis of **8** and **9** we were able to demonstrate that a convergent route to *meso* compounds by use of the aldol addition is feasible and concise. However, control of the stereogenic centres in the linkage region clearly needs further attention, for example by turning to $(ipc)_2$boron-enolates.[9]

In the synthesis of the ter-dioxanes **10** and **11**, the additional methyl groups might aid in attaining higher stereoselectivity in the aldol addition step. The building blocks required for a convergent synthesis of the *meso* compounds **10** and **11** are the alcohols **21** and *ent*-**21**. These were again elaborated from L- and D-malic acid by following literature precedent, with a Frater alkylation,[17−20] followed by borane reduction and regioselective acetalization.[21,22]



Dess−Martin oxidation[13] of **21** provided the aldehyde **22**, which on treatment with ethylmagnesium bromide furnished a 2:1 mixture of the alcohols **23**. Ley oxidation[23,24] provided the ketone **24** in 90% yield. The methyl and propionyl substituents are in equatorial positions, as indicated by the 10.5 Hz coupling displayed by 4-H.

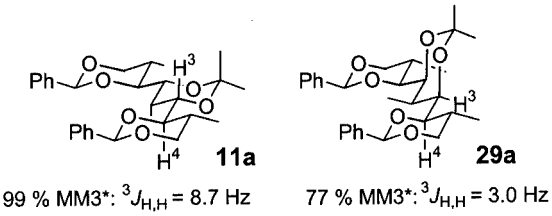
The aldol addition between the lithium enolate of **24** and the aldehyde *ent*-**22** furnished a single aldol product in 64% yield. The 2-H/3-H coupling constant of 2.9 Hz and the chemical shift of the methyl carbon at C-2 of $\delta = 6.0$ ppm indicate the formation of a *syn*-aldol.[25] The lithium enolate



of **24** was generated with Li-tetramethylpiperidide, a reagent that usually generates an *E* enolate. The formation of a *syn*-aldol on addition to *ent*-**22** is therefore noteworthy. At this stage, however, it is not clear whether the *syn*-aldol **25** or **26** was obtained.

The aldol product was carried forward by reduction with DIBAL to form a *syn*-diol (**27** or **28**, NMR spectra show the product to be symmetrical), which was converted into the acetonide (**11** or **29**).

The central dioxane ring in **11** or **29** was clearly derived from a *syn*-1,3-diol (^{13}C NMR signals at 19.4, 29.4, and 98.5 ppm[28,29]) with an axial methyl group (^{13}C NMR signal at 6.2 ppm).[26,27] As before, no obvious distinction between **11** or **29** was available. We therefore again resorted to conformational analysis for both **11** and **29**, regarding the conformer population at the inter-ring bonds. MM3* calculations showed that **11** has a ca. 99% preference to populate conformation **11a**, reflected in a predicted coupling constant of 8.7 Hz between 3-H and 4-H. Diastereomer **29** is calculated to have a sizeable preference (77%) for conformation **29a**, giving a predicted coupling constant of 3.0 Hz between 3-H and 4-H.

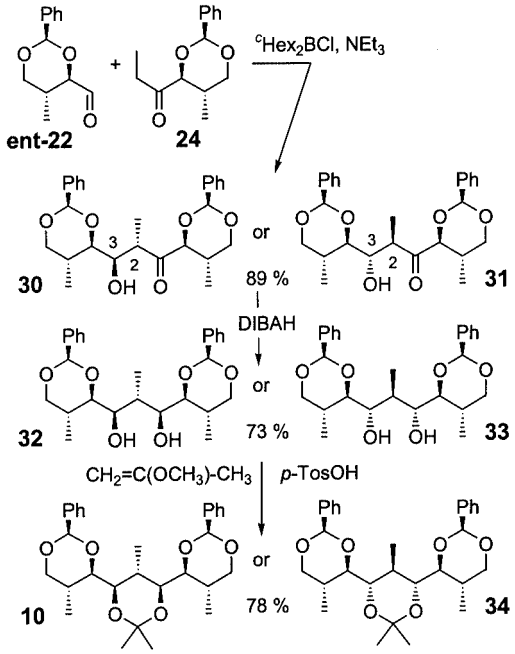


The compound obtained had a 3-H/4-H coupling constant of 8.3 Hz and should therefore be the diastereomer **11**. This suggests that, in the aldol addition between the lithium enolate of **24** and the aldehyde *ent*-**22**, a Felkin−Anh preference on the side of the aldehyde[30] (chelation control should not be favoured, due to the low basicity of acetals) was working in concert with a 1,3-*anti* induction across the enolate moiety. The latter result is surprising (cf. the usual transition state models[9,31]), given the fact that the lithium enolate of **24** was probably a *Z* enolate.

The aldol addition between **24** and *ent*-**22** produced a *syn*-aldol, indicating an unexpected formation of a *Z* lithium enolate from **24**. In order to generate an *anti* aldol, we converted the ketone **24** into its *E* enolborinate by treatment with chlorodicyclohexylborane and triethylamine.[9,14] Subsequent addition to *ent*-**22** furnished a single aldol product (89%), which was clearly different from **24**. The 2-H/3-H coupling of 10.3 Hz and the methyl signal at $\delta = 12$ ppm suggested[25] it to be an *anti* aldol (either **30** or **31**).

Since, once again, no obvious means of distinction between **30** and **31** was available, we converted the aldol into the ter-dioxane (**10** or **34**). The central dioxane ring in the product is derived from a *syn*-1,3-diol (δ_C at 19.0, 29.9, and 98.0 ppm)[28,29] with an equatorial methyl group (δ_C at 13.6 ppm).[26,27]

In order to make a distinction between **10** and **34**, we resorted as before to conformational analysis of the pre-

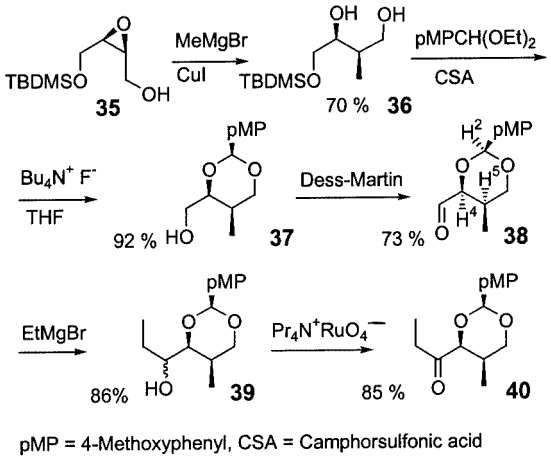


ferred conformation at the inter-ring bond. MM3* predicts **10** to exist in an essentially monoconformational situation, with conformer **10a** being populated to 90%. This should give a predicted H/H-coupling constant of 1.9 Hz across the inter-ring bond. Compound **34** should, in turn, have no marked conformational preference at the inter-ring bonds. In line with this, force-field calculations predict the H/H-coupling constant across the inter-ring bond of **34** to be 4.5 Hz.

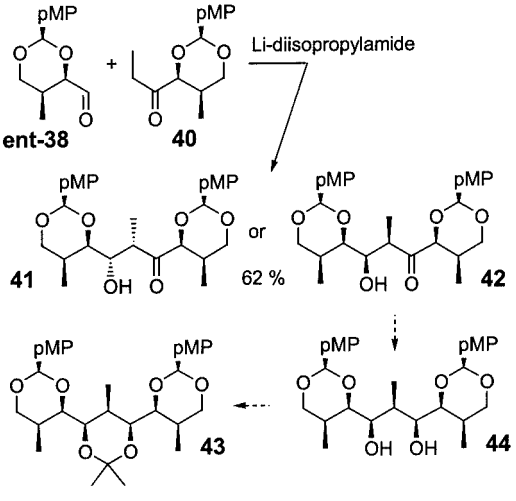
The product obtained had a H/H-coupling constant of 1.3 Hz (cf. the values of 2.4 and 2.5 Hz for the previously described[3] compounds **3** and **4**). We therefore conclude that the product is compound **10** and not **34**. Thus, the aldol addition between the aldehyde *ent*-**22** and the boron *E* enolate of **24** was dominated by the usual[9,31] 1,3-*anti* induction across the enolate moiety, but entailing an unexpected *anti* Felkin addition to the aldehyde *ent*-**22**.

In a continued attempt to access *meso* compounds of the type **2**, we targeted compound **43**, which was calculated to have a high (98%) conformational preference at the inter-ring bonds as well. We therefore investigated the aldol addition between the ketone **40** and the aldehyde *ent*-**38**.

The synthesis started from the known[32] epoxide **35**, obtained by a Sharpless epoxidation. The material obtained by us had an optical purity of only ca. 75%, but this is not detrimental in a synthesis of a *meso* compound. To obtain the 1,3-diol **36**, of several methods tested,[33] a copper(I)-catalysed Grignard addition[34] gave the highest (7:1) selectivity towards the formation of a 1,3- over a 1,2-diol. The diol **36** was then converted into the *p*-methoxybenzylidene acetal **37** (92%). Dess–Martin oxidation[13] furnished the aldehyde **38** (73%), in which 4-H showed a 2.7 Hz coupling to 5-H. Together with an NOE contact between 2-H and 4-H, this indicates an equatorial placement of the aryl and aldehyde groups and an axial arrangement of the methyl group. The enantiomeric aldehyde *ent*-**38** was obtained by a corresponding sequence of reactions.



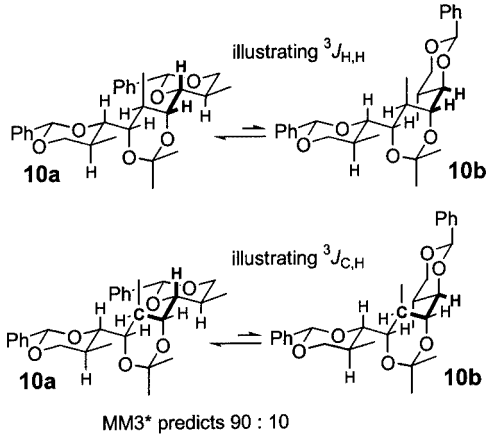
Conversion of the aldehyde **38** into the ketone **40** was effected as described for the generation of the ketone **24**. The *Z* lithium enolate of the ketone **40** was generated by deprotonation with lithium diisopropylamide and then added to the aldehyde *ent*-**38**, resulting in a single aldol **41** or **42** in 62% yield. The fact that neither ketone **40** nor the aldehyde **38** were enantiomerically pure was not a problem in the coupling reaction, because due to the principle of Horeau[35] the *ee* of the coupling product should have increased in our case to 97%, if a somewhat lower yield were accepted. The resulting aldol is a *syn* aldol, on the basis of a $^3J_{H,H}$ coupling constant of 4.0 Hz and a ^{13}C NMR chemical shift of the methyl group of $\delta = 8$ ppm. As before, however, we could not determine the relative configurations (**41** or **42**) of the newly formed stereogenic centres with respect to the resident stereocentres in the aldehyde and ketone, respectively. The intended conversion of the aldol (presumably **42**) into the diol **43** could not, however, be achieved. Repeated attempts at reduction with DIBAH resulted in a product that lacked any plane of symmetry. One of the (labile) *p*-methoxybenzylidene acetals was probably reductively opened in parallel with the formation of the 1,3-diol unit. Thus, our approach to compound **44** was abandoned at this point.



Overall, these results demonstrate that a highly efficient and stereoselective construction of *meso* compounds such as **10** or **11** is possible by use of the convergent approach starting from the two enantiomeric "ends" of the molecule. The high levels of asymmetric induction inherent to various variants[9,31] of the aldol addition were certainly a key to the success of this approach.

While the main emphasis of this paper rests on the convergent synthesis of *meso* compounds with multiple stereogenic centres, the conformational preferences of the compounds **8**−**11** nevertheless merit some comments:

The $^3J_{H,H}$ coupling constants of 5.1 and 6.4 Hz at the inter-ring bonds of **8** and **9** show that these compounds display no conformational preference whatsoever. The effect of the methyl groups in the corresponding compounds **10** and **11** becomes increasingly evident: compound **10**, for instance, has a coupling constant of 1.3 Hz at the inter-ring bond. This does not by itself prove a high conformational preference, though, because both low-energy conformers **10a** and **10b** should have small $^3J_{H,H}$ coupling constants at their inter-ring bonds, as both conformers have the relevant hydrogen atoms in a *gauche* arrangement. Evidence that **10a** is indeed the predominant conformer (as predicted by the force-field calculations) is provided by the determination of the indicated $^3J_{C,H}$ coupling constant to 3.0 Hz, characteristic[36] of a **C**−C−C−**H** *gauche* arrangement. The behaviour of compound **10** is thus in line with the analogues **3** and **4**;[3] that is, with expectations and calculations.



General considerations would not, however, have given rise to the expectation that compound **11** should show a significant conformer preference at all, because each of the diamond-lattice type conformations should suffer from some kind of a *syn*-pentane interaction.[37] We were therefore surprised that the MM3* calculations predicted a 99% preference for conformer **11a**, despite the presence of two CH/O *syn*-pentane interactions and two *anti* O−C−C−O arrangements, which are energetically less favourable than *gauche* O−C−C−O arrangements.[38,39] An explanation for the preference of conformation **11a** has to take into account that any rotation at one of the inter-ring bonds of **11** creates two CH/CH *syn*-pentane interactions, which are much more destabilising than the corresponding CH/O *syn*-pentane interactions.[40]

Experimental Section

General Remarks: All temperatures quoted are uncorrected. ^{1}H NMR, ^{13}C NMR: Bruker ARX 200, AC 300, WH 400, AM 400, AMX 500. $^3J_{H,H}$ coupling constants were taken directly from the 500 MHz NMR spectra, $^3J_{C,H}$ coupling constants were determined by Bax's method.[41] Boiling range of petroleum ether: 40−60 °C. Flash chromatography: Silica gel SI 60, E. Merck KGaA, Darmstadt, 40−63 μm. pH7-buffer: $NaH_2PO_4 \cdot 2H_2O$ (56.2 g) and $Na_2HPO_4 \cdot 4H_2O$ (213.6 g), made up to 1 L with water. Conformer populations were estimated by force-field calculations with the MM3* force-field implemented in the MACROMODEL[16] program, versions 4.5 and 6.5. 1500 starting structures were generated with a Monte Carlo procedure and energy-minimised (gas phase environment). Conformers with energies of less than 6 kcal·mol^{-1} above the minimum energy conformer were subjected to Boltzmann averaging for 298 K to predict the conformer population.

1. (2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxane-4-carbaldehyde (14): Dess−Martin periodinane[13] (4.05 g, 9.54 mmol) and pyridine (823 μL, 10.2 mmol) were added to a solution of the alcohol **13** (1.43 g, 6.36 mmol) in dichloromethane (60 mL). After the mixture had been stirred for 4 h at room temperature it was poured into saturated aqueous $K_2CO_3/Na_2S_2O_3$ (100 mL). After stirring for 10 min the layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (2 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. This provided the aldehyde **14** (989 mg, 70%), which was used immediately, due to its tendency to polymerise. ^{1}H NMR (200 MHz, C_6D_6): δ = 1.45−2.00 (m, 2 H), 3.47−3.60 (m, 3 H), 5.45 (s, 1 H), 6.72−6.76 (m, 2 H), 7.19−7.25 (m, 2 H), 9.89 (s, 1 H) ppm.

2. (1*RS*)-1-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-1-ethanol (15): A solution of ethylmagnesium bromide (2.5 M in ether, 4.0 mL, 10 mmol) was added dropwise at 0 °C to a solution of the aldehyde **14** (1.35 g, 6.05 mmol) in ether (60 mL). After stirring for 2 h the mixture was poured onto ice and was neutralised with aqueous 2 N hydrochloric acid. The mixture was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography with pentane/*tert*-butyl methyl ether, 1:1 (containing 1% of triethylamine) furnished a 1.5:1-diastereomeric mixture (1.03 g, 71%) of the alcohol **15** as a colourless oil. ^{1}H NMR (200 MHz, C_6D_6): δ = 0.90 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.90−0.99 (m, 2 H), 1.40 (tdd, *J* = 13.3, 11.5, 5.2 Hz, 1 H), 1.70 (tdd, *J* = 13.0, 11.5, and 5.0 Hz, 1 H), 3.14 (s, 6 H), 3.19−3.29 (m, 3 H), 3.35 (td, *J* = 11.5, 2.7 Hz, 1 H), 3.50 (quin, *J* = 6.5 Hz, 1 H), 3.59 (qd, *J* = 6.5, 4.4 Hz, 1 H), 3.80 (ddd, *J* = 11.4, 5.2, 1.3 Hz, 1 H), 3.88 (ddd, *J* = 11.5, 5.3, and 1.3 Hz, 1 H), 5.18 (s, 1 H), 5.24 (s, 1 H), 6.66−6.74 (m, 4 H), 7.37−7.48 (m, 4 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): major isomer δ = 18.3, 25.6, 54.9, 66.9, 69.4, 80.9, 101.5, 113.8, 128.1, 132.3, 160.5 ppm; minor isomer δ = 18.2, 27.3, 54.9, 66.6, 70.3, 81.8, 101.6, 113.9, 128.3, 132.1, 160.6 ppm. $C_{13}H_{18}O_4$: calcd. 238.1205; found. (HRMS EI) 238.1199.

3. 1-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-1-ethanone (16): Powdered molecular sieves (4 Å, 100 mg), *N*-methylmorpholine *N*-oxide (62 mg, 0.53 mmol) and tetrapropylammonium perruthenate

(7 mg, 0.02 mmol) were added to a solution of the alcohol **15** (83 mg, 0.35 mmol) in dichloromethane (1.5 mL). After stirring for 30 min at room temperature the mixture was separated by flash chromatography with pentane/*tert*-butyl methyl ether, 2:1 (containing 1% of triethylamine) to give the ketone **16** (76 mg, 91%) as a colourless oil, which later solidified (m.p. 74 °C). $[\alpha]_D^{20} = -55.6$ (c = 1.08, $CHCl_3$). ^1H NMR (200 MHz, C_6D_6): δ = 1.31 (dtd, J = 13.4, 2.8, and 1.4 Hz, 1 H), 1.57 (dtd, J = 13.4, 11.8, and 5.0 Hz, 1 H), 1.91 (s, 3 H), 3.21 (s, 3 H), 3.30 (td, J = 11.8, 2.8 Hz, 1 H), 3.66 (dd, J = 11.8, 2.8 Hz, 1 H), 3.78 (ddd, J = 11.8, 5.0, and 1.4 Hz, 1 H), 5.13 (s, 1 H), 6.73−6.80 (m, 2 H), 7.42−7.49 (m, 2 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 25.5, 27.6, 54.9, 66.7, 81.8, 101.2, 113.9, 128.0, 131.7, 160.7, 206.7 ppm. $C_{13}H_{16}O_4$ (236.2): calcd. C 66.06, H 6.83; found C 66.06, H 6.92.

4. (3*RS*)-3-Hydroxy-3-[(2*R*,4*R*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-1-[(2*S*,4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-1-propanone (17,18): *n*-Butyllithium (1.53 M in hexane, 1.96 mL, 3.00 mmol) was added dropwise at 0 °C to a solution of diisopropylamine (492 mg, 3.00 mmol) in THF (10 mL). After stirring for 15 min, the solution was cooled to −78 °C and a solution of the ketone **16** (588 mg, 2.50 mmol) in THF (3 mL) was added dropwise. After the mixture had been stirred for a further 20 min, a solution of the aldehyde *ent*-**14** (444 mg, 2.00 mmol) in THF (3 mL) was added dropwise. After stirring for 40 min at −78 °C, the mixture was poured onto pH7 buffer solution (20 mL). The layers were separated and the aqueous layer was extracted with ether (4 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1:1 (+ 1% of triethylamine) furnished the aldol **17** (420 mg, 46%) and the aldol **18** (123 mg, 46%) as colourless oils.

Aldol 17: $[\alpha]_D^{20} = -62.1$ (c = 0.98, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ = 1.26 (d, J = 12.5 Hz, 1 H), 1.38 (d, J = 12.2 Hz, 1 H), 1.65−1.76 (m, 4 H), 2.73 (br. s, 1 H), 3.27 (s, 6 H), 3.34 (td, J = 12.4, 1.9 Hz, 1 H), 3.46 (td, J = 12.2, 2.3 Hz, 1 H), 3.55 (ddd, J = 11.2, 6.0, and 2.2 Hz, 1 H), 3.80−3.86 (m, 2 H), 3.96 (dd, J = 11.6, 4.9 Hz, 1 H), 4.18−4.22 (m, 1 H), 5.20 (s, 1 H), 5.31 (s, 1 H), 6.80−6.84 (m, 4 H), 7.52−7.54 (m, 4 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 27.3, 27.4, 41.2, 54.8, 66.6, 66.7, 70.2, 79.4, 81.6, 101.2, 101.3, 113.7, 113.9, 127.9, 128.0, 131.4, 132.0, 160.4, 160.5, 209.0 ppm. $C_{25}H_{30}O_8$, [M + Na]: calcd. 481.1838; found (HRMS ESI) 481.1842.

Aldol 18: $[\alpha]_D^{20} = -43.6$ (c = 1.12, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ = 1.18−1.22 (m, 1 H), 1.24−1.27 (m, 1 H), 1.33−1.37 (m, 1 H), 1.70−1.82 (m, 3 H), 2.64 (s, 1 H), 3.27−3.29 (m, 1 H), 3.28 (s, 3 H), 3.29 (s, 3 H), 3.36 (td, J = 12.2, 2.5 Hz, 1 H), 3.49 (td, J = 11.9, 2.5 Hz, 1 H), 3.72 (dd, J = 11.5, 2.3 Hz, 1 H), 3.81−3.85 (m, 2 H), 4.00 (ddd, J = 11.1, 4.9, and 1.1 Hz, 1 H), 5.20 (s, 1 H), 5.33 (s, 1 H), 6.75−6.81 (m, 4 H), 7.50−7.54 (m, 4 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 23.2, 25.4, 44.6, 54.8, 66.0, 66.9, 73.3, 81.9, 82.6, 101.2, 101.4, 113.7, 113.9, 127.8, 127.9, 131.2, 132.0, 160.3, 160.5, 210.6 ppm.

5. (4*S*,6*R*)-4-[(2*R*,4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-6-[(2*S*,4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-2,2-dimethyl-1,3-dioxane (9): A solution of DIBAH (1 M in petroleum ether, 1.29 mL, 1.3 mmol) was added at −100 °C to a solution of the aldol **18** (196 mg, 0.43 mmol) in THF (7 mL). After stirring for 5 h, the mixture was poured into saturated aqueous sodium potassium tartrate solution (20 mL) and stirred for 1 h. The layers were separated and the aqueous layer was extracted with ether (5 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1:9, (containing 1% of triethylamine) furnished the diol **20** (194 mg, 98%) as a colourless solid (m.p. 164 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.53 (q, J = 13.7 Hz, 1 H), 1.61 (dq, J = 13.3, 1.2 Hz, 2 H), 1.95 (qd, J = 12.1, 4.9 Hz, 2 H), 2.00 (dt, J = 14.5, 2.2 Hz, 1 H), 3.42 (br. s, 2 H), 3.74 (ddd, J = 11.3, 5.2, and 2.3 Hz, 2 H), 3.79 (s, 6 H), 3.90−3.94 (m, 2 H), 4.29 (ddd, J = 11.6, 4.0, and 1.0 Hz, 2 H), 5.47 (s, 2 H), 6.86−6.91 (m, 4 H), 7.37−7.43 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9, 33.3, 55.2, 66.7, 74.2, 79.4, 100.9, 113.5, 127.3, 130.9, 159.9 ppm.

The diol **20** (40 mg, 90 μmol) was dissolved in THF (1 mL). 2-Methoxypropene (17 μL, 0.174 mmol) and *p*-toluenesulfonic acid (ca. 5 mg) were added. The mixture was stirred for 30 min and poured into saturated aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with ether (4 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 2:1 (containing 1% of triethylamine) furnished the product **9** (32 mg, 72%) as a colourless solid of m.p. 191 °C. ^1H NMR (200 MHz, C_6D_6): δ = 1.26 (s, 3 H), 1.43 (dq, J = 13.3, 1.4 Hz, 2 H), 1.51 (s, 3 H), 1.58 (q, J = 11.6 Hz, 1 H), 1.75 (qd, J = 12.7, 4.9 Hz, 2 H), 2.14 (dt, J = 13.0, 2.5 Hz, 1 H), 3.24 (s, 6 H), 3.58 (td, J = 11.5 2.5 Hz, 2 H), 3.62 (ddd, J = 11.2, 6.4, and 2.4 Hz, 2 H), 3.76 (ddd, J = 11.5, 6.4, and 2.5 Hz, 2 H), 4.04 (ddd, J = 11.3, 4.9, and 1.3 Hz, 2 H), 5.39 (s, 2 H), 6.77−6.79 (m, 4 H), 7.57−7.62 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.8, 28.0, 29.9, 30.2, 55.3, 66.9, 71.5, 79.8, 98.8, 101.0, 113.6, 127.4, 131.3, 159.9 ppm. $C_{28}H_{36}O_8$: calcd. 500.2410; found (HRMS EI) 500.2410.

6. (4*R*,6*S*)-4-[(2*R*,4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-6-[(2*S*,4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-2,2-dimethyl-1,3-dioxane (8): A solution of the aldol **17** (51 mg, 0.11 mmol) was converted into the ter-dioxane **8** (67%) as described under 5. m.p. 180 °C. ^1H NMR (500 MHz, C_6D_6): δ = 1.03 (dq, J = 13.1, 1.4 Hz, 2 H), 1.32 (s, 3 H), 1.38 (dt, J = 12.5, 2.5 Hz, 1 H), 1.53 (s, 3 H), 1.58 (q, J = 12.1 Hz, 1 H), 1.81 (qd, J = 12.5, J = 5.0 Hz, 2 H), 3.24 (s, 6 H), 3.56 (td, J = 11.2, 2.3 Hz, 2 H), 3.73 (ddd, J = 11.2, 5.1, and 2.2 Hz, 2 H), 3.93 (ddd, J = 11.2, 5.1, and 2.3 Hz, 2 H), 4.03 (ddd, J = 11.4, 4.0, 0.9 Hz, 2 H), 5.43 (s, 2 H), 6.78−6.80 (m, 4 H), 7.60−7.65 (m, 4 H) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 19.7, 26.0, 26.9, 30.4, 54.8, 66.9, 71.1, 80.3, 98.7, 101.9, 113.8, 128.5, 132.2, 160.4 ppm. $C_{28}H_{36}O_8$, [M + H]: calcd. 501.2488, found (HRMS ESI) 501.2538.

7. (1*RS*)-1-[(2*S*,4*S*,5*S*)-5-Methyl-2-phenyl-1,3-dioxan-4-yl]-1-propanol (23): Pyridine (194 μL, 2.40 mmol) and Dess−Martin periodinane[13] (1.02 g, 2.40 mmol) were added at room temperature to a solution of (2*S*,4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-ylmethanol[21] (312 mg, 1.50 mmol) in dichloromethane (10 mL). After stirring for 3 h the mixture was poured into a solution of potassium carbonate (4 g) in saturated aqueous $Na_2S_2O_3$ (20 mL). After the mixture had been stirred for 10 min, the layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The resulting crude aldehyde **22** (271 mg, 87%) was used as obtained for the next step. $[\alpha]_D^{20} = -43.1$ (c = 1.37, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.7 Hz, 3 H), 2.08−2.19 (m, 1 H), 3.56 (t, J = 11.3 Hz, 1 H), 3.89 (d, J = 10.8 Hz, 1 H), 4.20 (dd, J = 11.3, 4.9 Hz, 1 H), 5.55 (s, 1 H), 7.37−7.42 (m, 3 H), 7.48−7.52 (m, 2 H), 9.67 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.4, 29.4, 72.5, 85.5, 100.5, 126.1, 128.3, 129.1, 137.5, 199.5 ppm.

A solution of ethylmagnesium bromide (2.5 M in ether, 1.60 mL, 3.90 mmol) was added at 0 °C to a solution of the aldehyde **22** (538 mg, 2.61 mmol) in ether (15 mL) After stirring for 2 h the mixture was poured onto ice and neutralised by addition of hydrochloric acid (2N). The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 3:1 (containing 1% of triethylamine) furnished a 2:1 diastereomer mixture of alcohols **23** (441 mg, 72%) as a colourless oil. A small sample was rechromatographed to give the pure diastereomers.

Major Diastereomer: $[\alpha]_D^{20}$ = +4.2 (*c* = 1.67, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.7 Hz, 3 H), 1.00 (t, *J* = 7.4 Hz, 3 H), 1.45−1.60 (m, 2 H), 2.10−2.34 (m, 1 H), 3.39 (dd, *J* = 10.0, 1.2 Hz, 1 H), 3.52 (t, *J* = 11.2 Hz, 1 H), 3.53−3.57 (m, 1 H), 4.18 (dd, *J* = 11.2, 4.9 Hz, 1 H), 5.56 (s, 1 H), 7.25−7.37 (m, 3 H), 7.45−7.50 (m, 2 H) ppm, the OH signal was obscured. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.4, 12.1, 27.2, 29.4, 71.4, 72.9, 84.0, 100.7, 126.0, 128.2, 128.7, 138.5 ppm. $C_{14}H_{20}O_3$ (236.3): calcd. C 71.16, H 8.53; found C 71.02, H 8.75.

Minor diastereomer: $[\alpha]_D^{20}$ = +10.3 (*c* = 1.15 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.5 Hz, 3 H), 1.04 (t, *J* = 7.2 Hz, 3 H), 1.51−1.76 (m, 2 H), 1.92−2.01 (m, 1 H), 3.50 (t, *J* = 11.3 Hz, 1 H), 3.53−3.58 (m, 3 H), 4.10 (dd, *J* = 11.3, 4.8 Hz, 1 H), 5.48 (s, 1 H), 7.34−7.40 (m, 3 H), 7.45−7.50 (m, 2 H) ppm, the OH signal was obscured. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.6, 12.0, 24.0, 30.5, 71.4, 72.6, 85.6, 101.5, 126.2, 128.0, 128.6, 138.4 ppm. $C_{14}H_{20}O_3$: calcd. 236.1412; (HRMS EI) found 236.1404.

8. 1-[(2*S*,4*S*,5*S*)-5-Methyl-2-phenyl-1,3-dioxan-4-yl]-1-propanone (24): Powdered molecular sieves (4 Å, 2.4 g), *N*-methylmorpholine *N*-oxide (829 mg, 7.08 mmol) and tetrapropylammonium perruthenate (84 mg, 0.24 mmol) were added to a solution of the alcohols obtained under 7. (1.115 g, 4.72 mmol) in dichloromethane (20 mL). After stirring for 2 h at room temperature, the mixture was concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 4:1 (containing 1% of triethylamine) furnished the ketone **24** (989 mg, 90%) as a colourless oil, which solidified on storage at 5 °C. M.p.: 33 °C. $[\alpha]_D^{20}$ = −57.4 (*c* = 1.29, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.6 Hz, 3 H), 1.07 (t, *J* = 7.5 Hz, 3 H), 1.97−2.19 (m, 1 H), 2.74 (q, *J* = 7.4 Hz, 2 H), 3.54 (t, *J* = 11.3 Hz, 1 H), 3.92 (d, *J* = 10.5 Hz, 1 H), 4.16 (dd, *J* = 11.3, 4.8 Hz, 1 H), 5.53 (s, 1 H), 7.35−7.40 (m, 3 H), 7.49−7.52 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 6.9, 12.0, 30.9, 31.2, 72.8, 87.4, 100.6, 125.9, 128.2, 128.9, 152.8, 208.8 ppm. $C_{14}H_{18}O_3$ (234.3): calcd. C 71.77, H 7.74; found C 71.64, H 7.52.

9. (2*S*,3*S*)-3-Hydroxy-2-methyl-3-[(2*R*,4*R*,5*R*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]-1-[(2*S*,4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]propan-1-one (25): A solution of *n*-butyllithium (1.53 M in hexane, 915 μL, 1.40 mmol) was added at 0 °C to a solution of 2,2,6,6-tetramethylpiperidine (253 μL, 1.50 mmol) in THF (3 mL). After stirring for 15 min the mixture was cooled to −78 °C and a solution of the ketone **24** (327 mg, 1.40 mmol) in THF (3 mL) was added. After stirring for 20 min a solution of the aldehyde *ent*-**22** (280 mg, 1.30 mmol) in THF (2 mL) was added and stirring was continued for 1 h. The mixture was poured into aqueous buffer (pH 7, 15 mL) and the layers were separated. The aqueous layer was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 4:1 (containing 1% of triethylamine) furnished the aldol **25** (single stereoisomer, 366 mg, 64%) as a colourless oil. $[\alpha]_D^{20}$ = −45.8 (*c* = 1.04, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ =0.70 (d, *J* = 6.8 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H), 1.15 (d, *J* = 7.1 Hz, 3 H), 1.83−1.91 (m, 1 H), 2.10−2.21 (m, 1 H), 2.79 (d, *J* = 6.1 Hz, 1 H), 3.48 (t, *J* = 11.5 Hz, 1 H), 3.55 (t, *J* = 11.5 Hz, 1 H), 3.57 (dd, *J* = 10.0, 5.9 Hz, 1 H), 3.63 (qd, *J* = 7.1, 2.9 Hz, 1 H), 3.97 (d, *J* = 10.2 Hz, 1 H), 3.98 (dd, *J* = 11.5, 4.7 Hz, 1 H), 4.10 (dd, *J* = 11.5, 4.9 Hz, 1 H), 4.26 (td, *J* = 6.1, 2.9 Hz, 1 H), 5.36 (s, 1 H), 5.46 (s, 1 H), 7.23−7.25 (m, 6 H), 7.34−7.40 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.0, 12.3, 12.4, 30.7, 32.8, 42.6, 71.8, 72.8, 73.1, 83.5, 86.2, 101.0, 101.2, 125.9 (2 C), 126.0 (2 C), 128.1 (2 C), 128.2 (2 C), 128.7, 128.9, 137.4, 138.1, 211.6 ppm. $C_{26}H_{32}O_6$: calcd. 440.2199; found (HRMS EI) 440.2218.

10. (4*S*,5*R*,6*R*)-2,2,5-Trimethyl-4-[(2*R*,4*R*,5*R*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]-6-[(2*S*,4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]-1,3-dioxane (11): A solution of DIBAH (1.0 M in petroleum ether, 1.0 mL, 1.0 mmol) was added dropwise at −100 °C to a solution of the aldol **25** (129 mg, 0.29 mmol) in THF (5 mL). After stirring for 3 h the mixture was poured into saturated aqueous potassium sodium tartrate (10 mL). After this mixture had been stirred for a further 1 h, the layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (5 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 2:1 (containing 1% of triethylamine) furnished the *syn*-diol **27** (93 mg, 71%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.8 Hz, 6 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 1.96−2.10 (m, 2 H), 2.39−2.46 (m, 1 H), 3.23 (d, *J* = 4.4 Hz, 2 H), 3.52 (t, *J* = 11.2 Hz, 2 H), 3.59 (dd, *J* = 10.0, 6.1 Hz, 2 H), 4.04−4.08 (m, 2 H), 4.10 (dd, *J* = 11.3, 4.6 Hz, 2 H), 5.45 (s, 2 H), 7.34−7.36 (m, 6 H), 7.43−7.47 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.4, 12.5, 32.8, 33.2, 73.1, 78.1, 83.6, 101.4, 125.9, 128.2, 128.8, 138.3 ppm.

2-Methoxypropene (31 μL, 0.32 mmol) and *p*-toluenesulfonic acid (ca 5 mg) were added to a solution of the diol **27** (72 mg, 0.16 mmol) in THF (1 mL). After the mixture had been stirred for 2 h at room temperature, saturated aqueous $NaHCO_3$ (2 mL) was added. The layers were separated and the aqueous layer was extracted with ether (4 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 7:1 (containing 1% of triethylamine) furnished the acetonide **11** (51 mg, 69%) as a colourless solid of m.p. 190 °C. ^{1}H NMR (500 MHz, C_6D_6): δ = 0.85 (d, *J* = 6.7 Hz, 6 H), 1.28 (s, 3 H), 1.40 (d, *J* = 6.7 Hz, 3 H), 1.50 (s, 3 H), 1.95−2.02 (m, 2 H), 2.56 (qt, *J* = 6.7, 2.2 Hz, 1 H), 3.35 (t, *J* = 11.2 Hz, 2 H), 3.50 (dd, *J* = 9.3, 8.3 Hz, 2 H), 3.96 (dd, *J* = 8.3, 2.3 Hz, 2 H), 4.05 (dd, *J* = 11.3, 4.7 Hz, 2 H), 5.46 (s, 2 H), 7.30−7.32 (m, 2 H), 7.37−7.41 (m, 4 H), 7.81−7.84 (m, 4 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 6.2, 13.0, 19.4, 29.1, 29.9, 35.4, 73.0, 77.1, 80.2, 98.5, 100.2, 126.0, 128.4, 128.9, 139.5 ppm. $C_{29}H_{38}O_6$: calcd. 482.2668; found (HRMS EI) 482.2662.

11. (2*S*,3*R*)-3-Hydroxy-2-methyl-3-[(2*R*,4*R*,5*R*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]-1-[(2*S*,4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]propan-1-one (30): Triethylamine (904 μL, 6.52 mmol) was added at 0 °C to a solution of chlorodicyclohexylborane (1.26 mL, 5.83 mmol) in ether (13 mL). After the mixture had been stirred for 5 min, a solution of the ketone **24** (801 mg, 3.43 mmol) in ether (3 mL) was added, resulting in the formation of a white precipitate. After stirring for further 2 h the mixture was cooled to −78 °C. A

solution of the aldehyde *ent*-**22** (541 mg, 2.62 mmol) in ether (3 mL) was added slowly. The mixture was kept for 48 h at −18 °C and was subsequently poured into a combination of buffer solution (pH7, 10 mL), water (10 mL) and methanol (10 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined extracts were concentrated and the residue was taken up in a mixture of buffer solution (pH7, 10 mL) and methanol (20 mL). Aqueous hydrogen peroxide (30%, 5 mL) was added slowly and the mixture was stirred for 1 h. The mixture was extracted with ether (5 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 3:1 (containing 1% of triethylamine) furnished the aldol **30** (1.032 g, 89%) as a single diastereomer. $[\alpha]_D^{20} = -54.7$ (c = 1.54, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.59 (d, J = 6.8 Hz, 3 H), 0.72 (d, J = 6.8 Hz, 3 H), 1.22 (d, J = 7.1 Hz, 3 H), 1.63 (br. s, 1 H), 1.75−1.79 (m, 1 H), 1.82−1.94 (m, 2 H), 3.16 (t, J = 11.2 Hz, 1 H), 3.37 (t, J = 11.3 Hz, 1 H), 3.53 (d, J = 10.5 Hz, 1 H), 3.54 (dd, J = 10.3, 3.4 Hz, 1 H), 3.71 (dt, J = 10.3, 3.2 Hz, 1 H), 3.91 (dd, J = 11.3, 4.9 Hz, 1 H), 3.94 (dd, J = 11.3, 4.9 Hz, 1 H), 5.15 (s, 1 H), 5.35 (s, 1 H), 7.21−7.23 (m, 4 H), 7.26−7.30 (m, 2 H), 7.33−7.36 (m, 2 H), 7.42−7.45 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 12.2, 16.0, 31.1, 31.4, 37.9, 72.7, 72.8, 76.9, 86.0, 86.1, 100.6, 100.7, 125.9, 126.0, 127.9, 128.0, 128.6, 128.7, 137.9, 138.2, 214.5 ppm. $C_{26}H_{32}O_6$: calcd. 440.2199; found (HRMS EI) 440.2220.

12. (1*R*,2*r*,3*S*)-2-Methyl-1-[(2*R*,4*R*,5*R*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]-3-[(2*S*,4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]propane-1,3-diol (32): The ketone **30** (187 mg, 0.425 mmol) was reduced as described under 10. to give the *syn*-diol **32** (128 mg, 73%) as a colourless oil. ^1H NMR (300 MHz, C_6D_6): δ = 0.83 (d, J = 6.8 Hz, 6 H), 1.48 (d, J = 7.1 Hz, 3 H), 2.21−2.37 (m, 2 H), 2.79−2.84 (m, 1 H), 3.42 (t, J = 11.2 Hz, 2 H), 3.87 (dd, J = 10.0, 3.7 Hz, 2 H), 4.15 (dd, J = 11.2, 4.7 Hz, 4 H), 4.22 (br. s, 2 H), 5.65 (s, 2 H), 7.42−7.56 (m, 6 H), 7.91−7.99 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.6, 19.2, 31.1, 34.6, 73.0, 76.6, 86.4, 101.3, 126.0, 128.1, 128.8, 138.0 ppm. $C_{26}H_{34}O_6$: calcd. 442.2355; found (HRMS EI) 442.2353.

13. (4*R*,5*R*,6*S*)-2,2,5-Trimethyl-4-[(2*R*,4*R*,5*R*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]-6-[(2*S*,4*S*,5*S*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]-1,3-dioxane (10): The diol **32** (102 mg, 0.230 mmol) was converted into the acetonide as described under 10. to give **10** (86 mg, 78%) as a colourless solid of m.p. 100 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (d, J = 6.6 Hz, 6 H), 1.09 (d, J = 6.3 Hz, 3 H), 1.41 (s, 3 H), 1.46 (s, 3 H), 2.07 (tq, J = 10.7, 6.3 Hz, 1 H), 2.21−2.32 (m, 2 H), 3.52 (t, J = 11.2 Hz, 2 H), 3.57 (dd, J = 12.3, 1.3 Hz, 2 H), 3.77 (dd, J = 10.7, 1.3 Hz, 2 H), 4.11 (dd, J = 11.2, 4.8 Hz, 2 H), 5.48 (s, 2 H), 7.34−7.39 (m, 6 H), 7.49−7.52 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8, 13.6, 19.0, 29.9, 31.6, 31.8, 73.3, 76.4, 85.2, 98.0, 101.0, 126.0, 128.0, 128.7, 138.6 ppm. $C_{29}H_{38}O_6$: calcd. 482.2668; found (HRMS EI) 482.2695.

14. (2*R*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-methylbutane-1,3-diol (36): A solution of methylmagnesium bromide (2.7 M in THF, 2.70 mL, 7.4 mmol) was added dropwise at −20 °C to a suspension of copper(I) iodide (141 mg, 0.74 mmol) in THF/ether (5:1 v/v, 25 mL) The resulting suspension was cooled to −40 °C and a solution of the epoxide **35**[32] (539 mg, 2.47 mmol) in ether (3 mL) was added. After the mixture had been stirred for 3.5 h, saturated aqueous NH_4Cl (20 mL) and aqueous ammonia (32%, 5 mL) were added. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1:1 furnished the 1,3-diol **36** (405 mg, 70%) as well as the 1,2-diol (56 mg, 10%) as colourless oils.

Compound 36: $[\alpha]_D^{20} = -17.2$ (c = 2.47, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.83 (s, 9 H), 0.88 (d, J = 7.0 Hz, 3 H), 1.76−1.82 (m, 1 H), 3.02 (d, J = 3.4 Hz, 1 H), 3.22−3.30 (m, 1 H), 3.54−3.60 (m, 4 H), 3.73−3.77 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.3, 11.1, 18.3, 25.9, 37.2, 65.1, 66.1, 73.8 ppm. $C_{11}H_{26}O_3Si$ (234.4): calcd. C 56.36, H 11.18; found C 56.06, H 11.40.

The 1,2-diol: $[\alpha]_D^{20} = -25.7$ (c = 1.50, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.83 (s, 9 H), 0.86 (d, J = 7.2 Hz, 3 H), 1.70−1.74 (m, 1 H), 3.51−3.69 (m, 5 H). The signal of the OH groups was obscured. ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.4, 11.6, 18.0, 25.7, 37.6, 64.4, 66.3, 74.4.

15. (2*S*,4*S*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-ylmethanol (37): A solution of the diol **36** (954 mg, 4.07 mmol), anisaldehyde diethyl acetal (1.03 g, 4.88 mmol), and camphorsulfonic acid (ca. 5 mg) in dichloromethane (5 mL) was heated at 15 mbar to 40 °C for 30 min in a rotary evaporator. THF (20 mL) and a solution of tetrabutylammonium fluoride (1 M in THF, 5.0 mL, 5.0 mmol) were added and the mixture was stirred for 20 min. The mixture was concentrated in vacuo. Flash chromatography of the residue with pentane/ether, 1:1 furnished the acetal **37** as a colourless oil; $[\alpha]_D^{20} = -18.9$ (c = 1.72, $CHCl_3$). ^1H NMR (300 MHz, C_6D_6): δ = 1.04 (d, J = 7.0 Hz, 3 H), 1.22−1.29 (m, 1 H), 1.85 (br. s, 1 H), 3.26 (s, 3 H), 3.30 (dd, J = 11.4, 4.4 Hz, 1 H), 3.59 (dd, J = 11.4, 8.0 Hz, 1 H), 3.64 (dd, J = 11.2, 2.0 Hz, 1 H), 3.68 (dd, J = 11.2, 1.0 Hz, 1 H), 3.76 (ddd, J = 8.0, 4.4, and 2.0 Hz, 1 H), 5.35 (s, 1 H), 6.81−6.84 (m, 2 H), 7.53−7.56 (m, 2 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 11.6, 30.2, 54.8, 63.9, 73.6, 80.5, 102.1, 113.8, 128.1, 132.1, 160.5 ppm. $C_{13}H_{18}O_4$ (238.1): calcd. C 65.53, H 7.61; found C 65.14, H 7.48.

16. (1*RS*)-1-[(2*S*,4*S*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-1-propanol (39): Dess−Martin periodinane[13] (1.10 g, 2.60 mmol) was added to a solution of the alcohol **37** (310 mg, 1.30 mmol) in dichloromethane (6 mL). The mixture was stirred for 4 h and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1:1 (containing 1% of triethylamine) furnished the aldehyde **38** (225 mg, 73%) as a colourless oil. $[\alpha]_D^{20} = -52.8$ (c = 1.04, $CHCl_3$). ^1H NMR (300 MHz, C_6D_6): δ = 1.03 (d, J = 6.8 Hz, 3 H), 1.49−1.55 (m, 1 H), 3.27 (s, 3 H), 3.43 (dd, J = 11.2, 2.5 Hz, 1 H), 3.55 (dd, J = 11.2, 1.2 Hz, 1 H), 3.66 (d, J = 2.7 Hz, 1 H), 5.23 (s, 1 H), 6.82−6.94 (m, 2 H), 7.49−7.56 (m, 2 H), 9.46 (s, 1 H) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 11.9, 30.7, 54.8, 72.8, 83.5, 101.8, 113.9, 128.4, 131.3, 160.7, 201.5 ppm.

A solution of ethylmagnesium bromide (2.5 M in ether, 1.0 mL, 2.5 mmol) was added at −10 °C to a solution of the aldehyde **38** (556 mg, 2.09 mmol) in ether (10 mL). After the mixture had been stirred for 30 min, saturated aqueous NH_4Cl (15 mL) was added. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (4 × 10 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1:1 (containing 1% of triethylamine) furnished a 4:1 mixture of the diastereomeric alcohols **39**. A small sample was rechromatographed to give the pure diastereomers.

Major Diastereomer: $[\alpha]_D^{20} = -15.7$ (c = 2.13, $CHCl_3$). ^1H NMR (300 MHz, C_6D_6): δ = 0.95 (t, J = 7.3 Hz, 3 H), 1.28 (d, J =

6.8 Hz, 3 H), 1.33−1.45 (m, 1 H), 1.63−1.65 (m, 1 H), 1.67−1.70 (m, 1 H), 3.29 (s, 3 H), 3.48−3.50 (m, 2 H), 3.77 (dd, J = 11.0, 2.4 Hz, 1 H), 3.87 (dd, J = 11.0, 1.2 Hz, 1 H), 5.38 (s, 1 H), 6.80−6.85 (m, 2 H), 7.54−7.56 (m, 2 H) ppm. The OH signal was obscured. ^{13}C NMR (75 MHz, C_6D_6): δ = 9.9, 12.0, 27.2, 29.7, 54.9, 71.9, 74.1, 82.2, 102.1, 113.8, 128.0, 132.4, 160.5 ppm. $C_{15}H_{22}O_4$: calcd. 266.1518; found (HRMS EI) 266.1516.

Minor Diastereomer: $[\alpha]_D^{20}$ = −17.2 (c = 1.43, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6): δ = 1.04 (d, J = 6.8 Hz, 3 H), 1.11 (t, J = 7.6 Hz, 3 H), 1.20−1.27 (m, 3 H), 3.30 (s, 3 H), 3.28−3.35 (m, 1 H), 3.68 (dd, J = 8.6, 2.0 Hz, 1 H), 3.55 (dd, J = 8.6, 2.9 Hz, 1 H), 3.60 (q, J = 2.2 Hz, 1 H), 3.68 (dd, J = 11.2, 0.7 Hz, 1 H), 5.33 (s, 1 H), 6.82−6.86 (m, 2 H), 7.61−7.70 (m, 2 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 10.1, 11.7, 24.2, 29.9, 54.9, 72.4, 73.7, 83.6, 102.4, 113.9, 128.1, 132.1, 160.7 ppm.

17. 1-[(2*S*,4*S*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-1-propanone (40): The mixture of alcohols **39** (208 mg, 0.782 mmol) was oxidized as described under 8. Flash chromatography with pentane/*tert*-butyl methyl ether, 2:1 (containing 1% of triethylamine) furnished the ketone **40** (174 mg, 85%) as a colourless oil. $[\alpha]_D^{20}$ = −44.1 (c = 2.01, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.09 (t, J = 7.3 Hz, 3 H), 1.14 (d, J = 7.1 Hz, 3 H), 1.90−1.95 (m, 1 H), 2.43−2.56 (m, 2 H), 3.41 (s, 3 H), 3.67 (dd, J = 11.2, 2.4 Hz, 1 H), 3.74 (dd, J = 11.2, 1.5 Hz, 1 H), 4.01 (d, J = 2.7 Hz, 1 H), 5.32 (s, 1 H), 6.93−6.98 (m, 2 H), 7.62−7.67 (m, 2 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 6.9, 12.9, 31.2, 32.9, 54.8, 73.0, 84.4, 101.6, 113.8, 128.3, 131.7, 160.6, 210.0 ppm. $C_{15}H_{20}O_4$: calcd. 264.1362; found (HRMS EI) 264.1370.

18. Aldol Addition between 40 and *ent*-38: *n*-Butyllithium (1.53 M in hexane, 1.40 mL, 2.15 mmol) was added at 0 °C to a solution of diisopropylamine (302 μL, 2.15 mmol) in THF (3 mL). The mixture was stirred for 15 min and cooled to −78 °C. A solution of the ketone **40** (378 mg, 1.43 mmol) in THF (3 mL) was added, followed by 15 min stirring. A solution of the aldehyde *ent*-**38** (549 mg, 2.32 mmol) in THF (3 mL) was added dropwise at −78 °C. After the mixture had been stirred for 30 min, buffer solution (pH 7, 10 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (4 × 7 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1:1 (containing 1% of triethylamine) furnished an aldol (446 mg, 62%) as a colourless oil. $[\alpha]_D^{20}$ = −10.3 (c = 1.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (d, J = 6.9 Hz, 3 H), 1.15 (d, J = 7.1 Hz, 3 H), 1.23 (d, J = 6.9 Hz, 3 H), 1.88−1.91 (m, 1 H), 2.05−2.09 (m, 1 H), 3.49 (qd, J = 7.0, 4.1 Hz, 1 H), 3.76 (dd, J = 9.2, 2.2 Hz, 1 H), 3.78 (s, 6 H), 3.89 (dd, J = 11.2, 2.1 Hz, 1 H), 3.96 (d, J = 11.1 Hz, 1 H), 4.02−4.04 (m, 2 H), 4.05 (dd, J = 9.5, 4.0 Hz, 1 H), 4.23 (d, J = 2.8 Hz, 1 H), 5.33 (s, 1 H), 5.42 (s, 1 H), 6.87−6.90 (m, 4 H), 7.35−7.38 (m, 2 H), 7.44−7.46 (m, 2 H) ppm. The OH signal was obscured. ^{13}C NMR (75 MHz, C_6D_6): δ = 8.0, 9.3, 11.7, 29.6, 31.0, 43.3, 54.8, 70.2, 73.2, 74.0, 80.2, 84.0, 102.0, 102.4, 114.1, 114.2, 128.3, 128.4, 131.2, 132.4, 160.8, 213.9 ppm. $C_{28}H_{36}O_8$: calcd. 500.2410; found (HRMS EI) 500.2424.

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