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Solvent- and Structure-Dependent Regioselectivity in the Boron-Mediated Aldol Reaction of 2-(1,3-Dioxolan-2-yl)ethyl Ethyl Ketones

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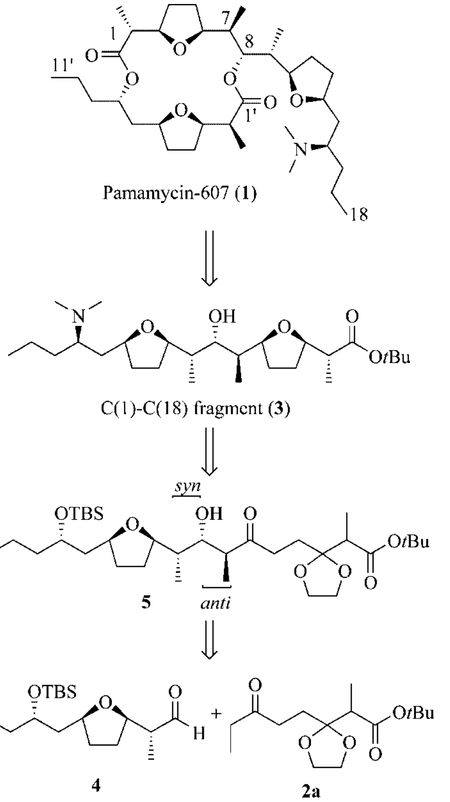
The regioselectivity of the Chx_2BCl/Et_3N-mediated (Chx = cyclohexyl) aldol reactions of ketones of general structure **2** has been studied and was shown to depend on both ketone structure and solvent. Useful levels of regioselectivity in favour of any of the two possible regioisomers were obtained in either pentane or diethyl ether. The relative configuration of the aldol products was assigned by ^{1}H NMR studies of six-membered-ring derivatives.

Introduction

During our synthetic studies on Pamamycin-607 (**1**)[1–3] we became interested in the study of ketone **2a** as a possible precursor of the C(1)–C(18) fragment (**3**) of Pamamycin-607, by an aldol reaction with the C(8)–C(18) fragment aldehyde **4**.[1] The desired aldol product **5** possesses a 2,3-*anti*-3,4-*syn* relationship between the newly formed stereogenic centres (Scheme 1).

This relative configuration arises from a Felkin–Anh[4–5] addition of the (*E*)-enolate of ketone **2a** to α-chiral aldehyde **4**. While some methods for the generation of lithium (*E*)-enolates are reported in the literature, they involve the use of strongly basic hindered lithium amides, and the lithium enolates generated by these methods often display moderate π-facial selectivities. On the other hand, boron enolates are known to react with high π-facial selectivities. Furthermore, the use of the Chx_2BCl/Et_3N (Chx = cyclohexyl) system developed by Brown,[6–7] which has been widely used in natural product synthesis,[8] is known to afford excellent (*E*) selectivity in the enolisation step. Furthermore, boron (*E*)-enolates display very high Felkin–Anh selectivity [in contrast with their (*Z*) isomers which lead to *anti*-Felkin–Anh products].[9] We thus decided to use the Chx_2BCl/Et_3N system for our synthetic purposes.

We reasoned that, in addition to the diastereoselectivity issues mentioned above, the substitution pattern of ketone **2a** might give rise to the formation of two regioisomeric enolates. Indeed, high to total regioselectivities are reported in the literature for the enolisation of α- or β-branched ethyl ketones, but little was known about ethyl ketones with more remote functionality (γ functionalisation in our case).



Scheme 1. Retrosynthetic analysis of Pamamycin-607.

In order to examine the behaviour of ketone **2a** during enolisation and subsequent aldol reaction, we decided to use aldehyde (*R*)-**6** as a model for the C(8)–C(18) aldehyde **4** (Figure 1).

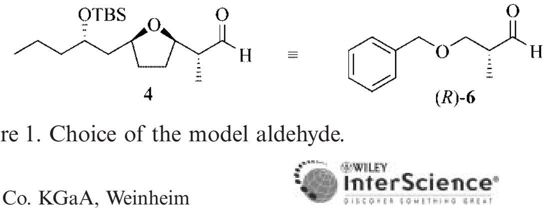


Figure 1. Choice of the model aldehyde.

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Indeed, (*R*)-**6** bears the same α-methyl group and Lewis-basic β-oxygen substitution pattern as aldehyde **4** and seems to be an ideal model to verify π-facial selectivity. Alternatively, the use of racemic aldehyde (±)-**6** was sufficient in many cases.

We describe the synthesis of ketone **2a** (Figure 2) and its analogues **2b–d**, and their behaviour in the boron-mediated aldol reaction with model aldehydes (*R*)-**6** or (±)-**6**.

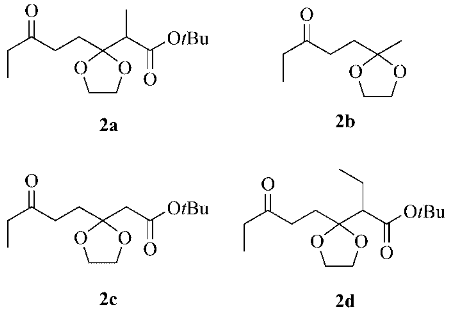
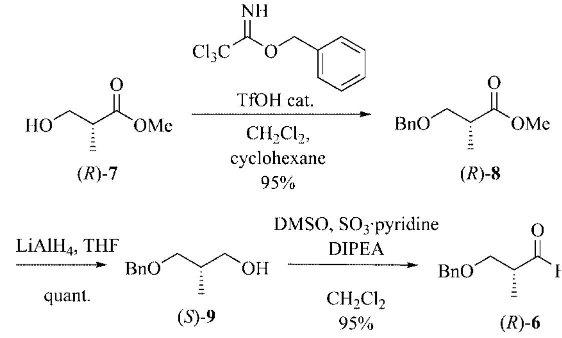


Figure 2. Structures of the studied ethyl ketones.

Results and Discussion

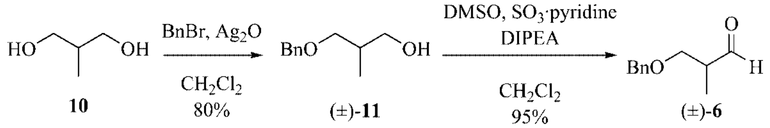
The chiral nonracemic aldehyde (*R*)-**6** was available in three steps from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate (**7**) according to literature procedures (Scheme 2). The use of the Parikh–Doering[10] oxidation in the last step was more convenient and reliable in our hands than the Swern oxidation used in previous syntheses of (*R*)-**6**.[11] The resulting crude aldehyde was used in the aldol reaction without further purification to avoid racemisation.



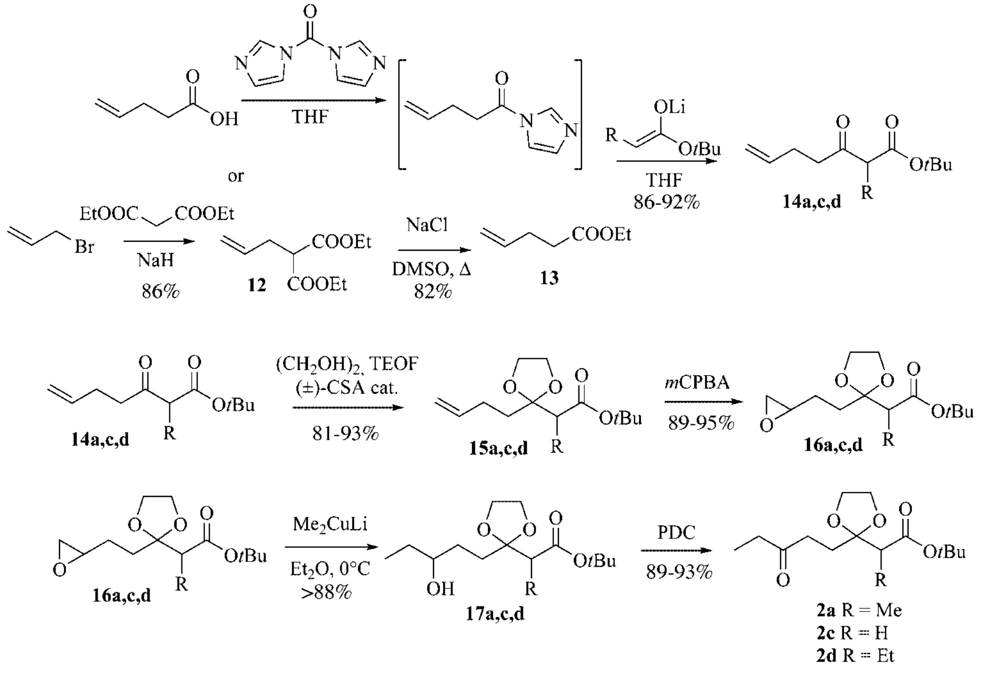
Scheme 2. Preparation of model aldehyde (*R*)-**6**.

The racemic aldehyde was easily prepared on a multigram scale from commercially available diol **10** by silver(I)-mediated monobenzylation[12] followed by a Parikh–Doering oxidation (Scheme 3).

While one possible approach to ketone **2a** relied on the ring opening of γ-caprolactone,[13] the most reliable and scalable synthesis of **2a** proved to be a 5-step procedure starting from commercially available 4-pentenoic acid (Scheme 4). Ketones **2c** and **2d** were prepared using the



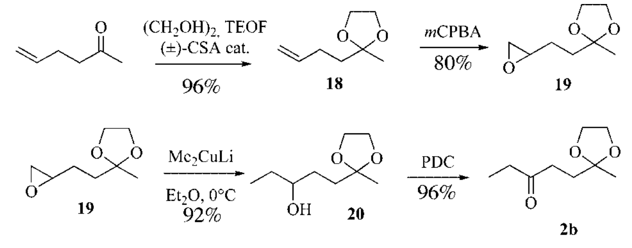
Scheme 3. Preparation of model aldehyde (±)-**6**.



Scheme 4. Preparation of ketones **2a**, **2c** and **2d**.

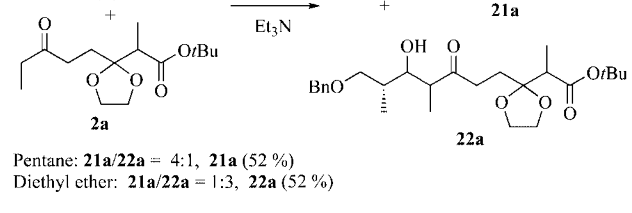
same sequence. The starting 4-pentenoic acid was converted into the corresponding *N*-acylimidazole which was treated in situ with the lithium enolate of *tert*-butyl propionate, *tert*-butyl acetate or *tert*-butyl butyrate to afford β-keto esters **14a**,**c**,**d** in good yield. Alternatively, β-keto esters **14a**,**c**,**d** were also available from diethyl malonate and allyl bromide[14] through ester **13**.[15] The ketone group was then protected as a dioxolane in compounds **15a**,**c**,**d** and the double bond was oxidised with *m*CPBA to afford epoxides **16a**,**c**,**d**. The secondary alcohols **17a**,**c**,**d** were obtained by opening of the epoxide using lithium dimethylcuprate, and subsequent oxidation afforded ketones **2a**,**c**,**d** in an overall yield of 49–67%.

Ketone **2b** was obtained in good overall yields from 5-hexen-2-one as illustrated in Scheme 5.



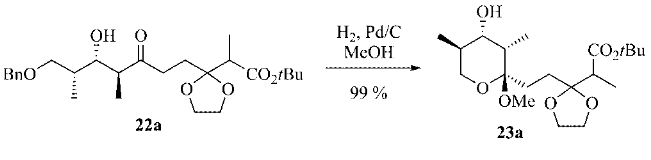
Scheme 5. Preparation of ketone **2b**.

With ketones **2a**–**d** and model aldehydes (±)-**6** and (*R*)-**6** in hand, we embarked on the study of the aldol reaction. Our first attempts using ketone **2a** employed the optimised conditions described by Brown;[6–7] the highest (*E*) selectivity during enolisation was obtained by using nonpolar solvents (of which pentane proved to be the best) at low concentrations (ideally 0.05 M). When ketone **2a** was enolised in pentane at 0 °C and subsequently treated with (*R*)-**6** at –78 °C, our first runs consistently afforded a mixture of two regioisomeric products in a combined yield of 65%. Surprisingly, aldol product **21a**, arising from the internal enolisation of **2a**, appeared to be the major product (**21a**/**22a** was approximately 4:1). On the other hand, when the enolisation and aldol reaction were conducted at the same temperatures and concentrations in diethyl ether, we were delighted to find that aldol product **22a**, arising from the enolisation of the ethyl group, was the major product (**21a**/**22a** = 3:1 in a combined yield of 78%, Scheme 6). Both aldol products **21a** and **22a** were isolated as pure diastereomers. At this stage, the use of the lithium enolate of ketone **2a** was investigated. However, the use of a strong amide base (LiTMP) led to the decomposition of the ketone by a competing deprotonation α to the ester group followed by ring opening of the dioxolane. On the other hand, the use of the milder base LiHMDS led to the same side reaction, albeit to a lesser extent. In view of these results, the use of lithium enolates was abandoned.



Scheme 6. Aldol reaction of ketone **2a** with aldehyde (*R*)-**6** (Chx = cyclohexyl).

The relative configuration of the desired aldol product **22a** has subsequently been ascertained by the debenzylation of **22a** using hydrogen gas and Pd/C in methanol (Scheme 7).



Scheme 7. Formation of ketal **23a**.

The ^1H NMR spectroscopic data of the cyclic ketal **23a** are in good agreement with those of a similar compound of the same relative configuration described by Gennari et al.[16] Furthermore, the selective decoupling and NOESY experiments are in agreement with the 2,3-*anti*-3,4-*syn* relative configuration in a chair configuration, as depicted in Figure 3.

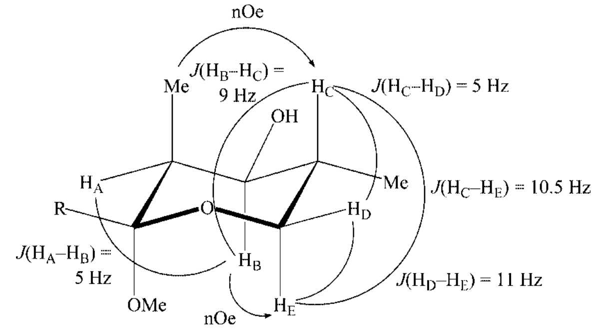


Figure 3. Characteristic NMR spectroscopic data for ketal **23a**.

Unfortunately, the determination of the relative configuration of regioisomer **21a** failed as its derivatization to cyclic compounds (i.e. the acetonide or cyclic ketal) was impossible in our hands. The Prasad–Narasaka reduction,[17–20] or catecholborane[21] reduction, which should give the corresponding 1,3-*syn*-diol, were ineffective. Access to 1,3-*anti*-diol using Evans–Carreira[22] or Evans–Tishchenko[23] conditions was also denied.

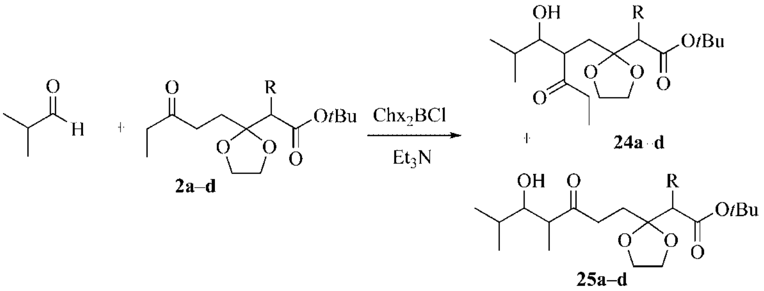
In order to examine the influence of the structure of the ketone, we extended the study to ketones **2a**, **2b**, **2c** and **2d** using the same reaction conditions described before. The use of isobutyraldehyde as the electrophile resulted in a significant simplification of the ^1H NMR signals and allowed a determination of the regioisomer ratios (**24**/**25**) by ^1H

NMR spectroscopy of the crude reaction mixture. The corresponding results are summarised in Table 1.

In this simplified case, the simple diastereoselectivity of the aldol reaction seemed slightly reduced, and small amounts of compounds assigned as diastereomers of each regioisomer could be detected in most reaction mixtures. In this case, the use of more polar solvents (MTBE, DME, or THF) was also examined, but generally resulted in the complete loss of regio- and diastereoselectivity, and the latter solvents were considered unsuitable. However, the major diastereomers of compounds **24b–d** and **25b–d** could be isolated. We did not succeed in the separation of **24a** and **25a** as pure samples; nevertheless, the regio- and diastereomeric ratio was determined from characteristic signals in the ^{1}H NMR spectra (C*H*-OH, and CH_2-H) by comparison with those of isolated and fully characterised **24b**,**c** and **25b**,**c**. In contrast with aldol products **21a**, **24b–d** and **25b–d** could now be smoothly reduced to the corresponding 1,3-*syn*-diols. Whereas **21a** required the use of catecholborane,[21] **24b–d** and **25b–d** reacted smoothly under Narasaka–Prasad conditions[17–20] (Scheme 8). In both cases, the corresponding acetonides **26b–d** and **27b–d** were obtained using standard reaction conditions.

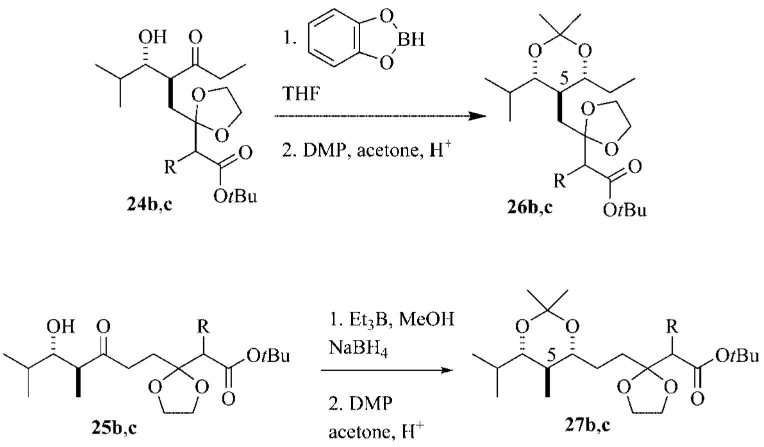
The relative configuration of the cyclic derivatives can be determined by ^{1}H NMR spectroscopy. For all compounds **26b–d** and **27b–d**, the signal of the proton in position 5 of the dioxane ring is split by the coupling with two other protons, giving coupling constants of 11–12 Hz each. These compounds are known to exist predominantly in a chair conformation which explains the characteristic ^{13}C chemi-

Table 1. Boron-mediated aldol reaction of ketones **2a–d** with isobutyraldehyde.[a]



Entry	Ketone	R	Solvent	Relative amount			
				Regioisomer 24		Regioisomer 25	
				syn[b]	*anti*	*syn*[b]	*anti*
1	**2a**	Me	pentane	7	63	10	20
2	**2a**	Me	diethyl ether	4	25	12	59
3	**2b**	–	pentane	8	38	11	43
4	**2b**	–	diethyl ether	6	34	12	48
5	**2c**	H	pentane	0	69	0	31
6	**2c**	H	diethyl ether	0	46	8	46
7	**2d**	Et	pentane	6	35	15	44
8	**2d**	Et	diethyl ether	4	18	16	62

[a] A solution of the ketone was added to a mixture of borane and triethylamine at 0 °C, followed by cooling to –78 °C and the addition of the aldehyde (0.33 equiv.). [b] The diastereomeric ratios were determined by integration of characteristic signals of the ^{1}H NMR spectra of the crude reaction mixtures.



Scheme 8. *syn*-Selective reduction and acetonide formation.

cal shift of the acetonide methyl groups.[24,25] Assuming this chair conformation, the splitting of the signal of the proton in position 5 is consistent with an axial position and two axial-axial couplings with the protons in positions 4 and 6 on the ring. This allows us to assign a 2,3-*anti* relationship to all the major aldol products **24b–d** and **25b–d**. Thus, the simple diastereoselectivity of the aldol reaction was not altered by changing the solvent, allowing the assumption that the (*E*)-enol borinate was formed predominantly in all the reactions.

The regioselectivities observed with ketone **2d** (Table 1, Entries 5 and 6) confirmed the surprising solvent effect previously described with ketone **2a** (Scheme 6 and Table 1, Entries 1 and 2). This effect was clearly structure-dependent. Ketone **2b** which was not substituted with a propionate or a butyrate unit gave similar ratios of regioisomers **24b** and **25b** in either solvent (Table 1, Entries 3 and 4). An acetate substituent α to the dioxolane (ketone **2c**) led to a stronger preference for regioisomer **24c** when the aldolisation was performed in pentane (Table 1, Entry 5). This preference dropped significantly in diethyl ether (Table 1, Entry 6).

Finally, we confirmed these results by performing the aldolisation between the racemic aldehyde (±)-**6** and ketone **2b** or **2d** (Table 2).

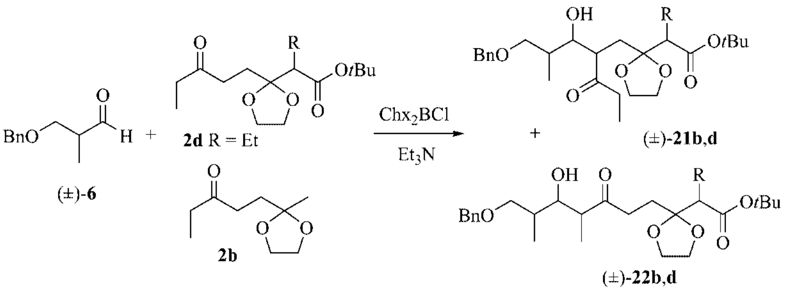
The 2,3-*anti*-3,4-*syn* relative configuration of aldol **22d** was confirmed by the preparation of the corresponding cyclic ketal **23d** using the previously described conditions (Scheme 7 and Figure 3).

These results are in agreement with those observed in Table 1 and confirm the solvent effect on the regioselectivity of the reaction. The more bulky ethyl group of ketone **2d** compared to the methyl group in **2a** increases slightly the regioselectivity of the aldol reaction in diethyl ether but decreases the regioselectivity in pentane (see also Table 1, Entries 1, 2 7, and 8).

This surprising solvent effect, by which the intrinsic regiochemical preference of a ketone for enolisation is inverted, is, to the best of our knowledge, unprecedented in the literature. While a strong influence of remote substitution on aldol regioselectivity has been mentioned in one example by Heathcock,[26] we found no reports on relevant changes of regioselectivity in different solvents.

The regio- and stereoselectivity observed during the formation of enol borinates is commonly rationalised by the model proposed by Paterson and Goodman.[27] This model is based on the conformational preference of the ketone–borane adduct, governed by a strong anomeric effect and the ability of the α-carbon atom to stabilise a negative charge. For the ketones examined in our study, we reckoned that there should be no significant difference in the ability of either α position to stabilise a negative charge. However, steric interactions based on the remote substitution should favour complexation of the borane on the least-hindered side and thus trigger deprotonation of the ethyl substituent. This seems to apply only to the simplest substrate, ketone **2b**, which shows a slight preference for enolate formation on the least-hindered side in all cases. In the case of the more complex substrates (ketones **2a**, **2c** and **2d**) and in pentane, the deprotonation of the internal position is favoured. As in all cases the (*E*)-enol borinate is still formed selectively; we assume that the Paterson–Goodman model is still applicable, but that the complexation of the borane takes place preferentially on the internal position. This preference is unlikely to be governed by steric factors, but could be controlled by dipole interactions which are in turn, of course, determined by the orientation of the dioxolane and ester substituents (i.e. the conformation of the ketone substrate). We propose that it is the change of this conformation in a more polar solvent like diethyl ether that is the cause for the reversal of regioselectivity that is observed when the latter solvent is used.

Table 2. Boron-mediated aldol reaction of ketones **2b**,**d** with model aldehyde (±)-**6**.[a]



Entry	Ketone	Solvent	Combined isolated yield [%]	Relative amount Regioisomer **21**[b]	Regioisomer **22**
1	**2b**	pentane	75	40	60
2	**2b**	diethyl ether	79	35	65
3	**2d**	pentane	72	55	45
4	**2d**	diethyl ether	75	22	78

[a] A solution of the ketone was added to a mixture of borane and triethylamine at 0 °C, followed by cooling to –78 °C and the addition of the aldehyde (0.33 equiv.). [b] Attempts to determine the relative configuration of the major diastereomer of **21** failed.

Conclusions

We have studied the regioselectivity of the aldol reaction of 2-(1,3-dioxolan-2-yl)ethyl ethyl ketones. This regioselectivity seems to be influenced strongly by remote substitution and by the nature of the solvent used. The experimental results lead us to propose that it is likely to be controlled by polar interactions. More importantly, we have observed that the conformational changes induced by a change of solvent can have a significant influence on the regioselectivity of enol formation. While the influence of the solvent on the stereoselectivity of enol borinate formation has been examined most thoroughly in the past,[6,7] our results show that it is important to consider its influence on regioselectivity as well. This solvent-mediated regiochemical control has also enabled us to develop a viable aldol-based approach to the convergent assembly of the C(1)–C(18) fragment of Pamamycin-607 (**1**) using ketone **2a**.

Experimental Section

General: Unless otherwise stated, reagents and solvents were purchased as reagent grade and used without further purification. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. Column chromatography was performed with silica gel 60 (230–400 mesh, 0.040–0.063 mm), purchased from E. Merck. Thin-layer chromatography (TLC) was performed with glass sheets coated with silica gel 60 F_{254} (unless otherwise stated), purchased from E. Merck, and visualization was effected by UV light and/or appropriate staining reagents. IR (cm^{-1}) spectra were recorded using Universal ATR sampling accessories with a Perkin–Elmer Spectrum One spectrometer. NMR spectra (^1H and ^{13}C) were recorded with a Bruker AC200 (200 MHz) or a Bruker Avance (300 MHz or 400 MHz) spectrometer. Chemical shifts are reported in ppm relative to the residual solvent ($CHCl_3$) resonance at δ = 7.26 ppm in the ^1H spectra and relative to the central $CDCl_3$ resonance at δ = 77.0 ppm in the ^{13}C spectra. Data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. s = broad singlet; integration; coupling constant(s) in Hz.

Preparation of Ketones 2a–d

Preparation of β-Keto Esters 14a,c,d from Allyl Bromide

Diethyl Allylmalonate (12): To a suspension of NaH (0.92 g, 55% in oil, 21.0 mmol) in THF (50 mL) was added dropwise diethyl malonate (3.20 g, 20.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Allyl bromide (2.90 g, 24.0 mmol) was added, and the resulting solution was stirred overnight. After the addition of H_2O (100 mL) and extraction with diethyl ether, the organic layer was washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/diethyl ether, 10:1) to afford **12** (3.44 g) in 86% yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.71 (m, 1 H), 5.16–5.03 (m, 2 H), 4.20 (q, J = 7.17 Hz, 2 H), 4.19 (q, J = 7.17 Hz, 2 H), 3.42 (t, J = 7.7 Hz, 1 H), 2.67–2.61 (m, 2 H), 1.26 (t, J = 7.17 Hz, 6 H) ppm.

Ethyl 4-Pentenoate (13): To a solution of diethyl allylmalonate (**12**) (5 g, 25 mmol, 1 equiv.) in DMSO (25 mL) was added NaCl (2.19 g, 37 mmol, 1.5 equiv.) and H_2O (20 mL). The reaction mixture was refluxed (160–180 °C) for 8 h. The ester was isolated by the addition of H_2O to the reaction mixture and separation of the ester-containing layer. The aqueous layer was extracted with diethyl ether, and the organic phases were purified by distillation to afford a colourless oil (2.6 g) in 82% yield. B.p. 40 °C/25 Torr. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.81–5.67 (m, 1 H), 5.00–4.86 (m, 2 H), 4.05 (t, J = 7.2 Hz, 2 H), 2.32–2.27 (m, 4 H), 1.17 (t, J = 7.17 Hz, 3 H) ppm.

General Procedure for the Preparation of *tert*-Butyl β-Keto Esters 14a,c,d: To a stirred solution of diisopropylamine (11.4 mL, 81.2 mmol) in dry THF (80 mL) and HMPA (30 mL) under argon was added dropwise *n*-butyllithium (55.8 mL of a 1.6 M solution in hexane, 89.3 mmol) at –78 °C. The solution was stirred for 30 min, and then a solution of *tert*-butyl acetate, propionate or butyrate (74.9 mmol) in dry THF (20.0 mL) was added dropwise. After the addition, the solution was stirred for 1 h, and a solution of ethyl 4-pentanoate (**13**) (4.0 g, 31.2 mmol) in dry THF (50 mL) was added. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction was quenched by the addition of saturated aq. NH_4Cl (200 mL). The mixture was extracted with AcOEt (3 × 100 mL), the combined organic layers were washed with brine and dried with $MgSO_4$, and the solvents were removed in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/AcOEt, 5:1) to afford the *tert*-butyl β-keto esters **14a**,**c**,**d** as colourless oils in 82–86% yield.

Preparation of β-Keto Esters 14a,c,d from 4-Pentenoic Acid: To a stirred solution of 4-pentenoic acid (4.94 g, 49.3 mmol, 1 equiv.) in dry THF (50 mL) under argon, was added slowly carbonyldiimidazole (8 g, 49.3 mmol, 1 equiv.). The mixture was stirred at room temperature for 1 h. To a stirred solution of diisopropylamine (20 g, 197.3 mmol, 4 equiv.) in dry THF (20 mL) under argon was added dropwise *n*-butyllithium (123 mL of a 1.6 M solution in hexane, 197.4 mmol, 4 equiv.) at –78 °C. The solution was stirred at –78 °C for 30 min, and then a solution of *tert*-butyl acetate, propionate or butyrate (98.65 mmol, 2 equiv.) in dry THF (15.0 mL) was added dropwise. After stirring at 78 °C for another 30 min, this solution was transferred by cannula to the imidazolide solution and the mixture cooled to –78 °C. After 15 min at –78 °C, the reaction mixture was then warmed to room temperature and stirred for 2 h. A white precipitate appeared, and the reaction was quenched by the addition of saturated aq. NH_4Cl (300 mL). The mixture was extracted with diethyl ether (2 × 100 mL), the combined organic layers were washed with brine and dried with $MgSO_4$, and the solvents were removed in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/MTBE, 15:1) to afford the *tert*-butyl β-keto esters **14a**,**c**,**d** as colourless oils in 86–92% yield.

***tert*-Butyl 2-Methyl-3-oxohept-6-enoate (14a):** Pale yellow oil; R_f = 0.42 (hexane/AcOEt, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.88–5.27 (m, 1 H), 5.09–4.94 (m, 2 H), 3.42 (q, J = 7.1 Hz, 1 H), 2.70–2.45 (m, 2 H), 2.40–2.26 (m, 2 H), 1.45 (s, 9 H), 1.28 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9, 172.1, 136.2, 117.6, 81.6, 56.4, 40.0, 28.6, 28.0, 12.9 ppm.

***tert*-Butyl 3-Oxohept-6-enoate (14c):** Pale yellow oil; R_f = 0.44 (hexane/AcOEt, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.88–5.75 (m, 1 H), 5.01–4.97 (m, 2 H), 3.35 (s, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.38–2.31 (m, 2 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.4, 166.4, 136.7, 115.5, 50.7, 41.9, 27.96, 27.42 ppm.

***tert*-Butyl 2-Ethyl-3-oxohept-6-enoate (14d):** Colourless oil; R_f = 0.40 (hexane/AcOEt, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.87–5.74 (m, 1 H), 5.07–4.96 (m, 2 H), 3.26 (t, J = 7.3 Hz, 1 H), 2.67–2.51 (m, 2 H), 2.38–2.31 (m, 2 H), 1.84 (m, 2 H), 1.45 (s, 9 H), 0.92 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.8, 168.9, 136.9, 115.3, 81.7, 61.8, 40.9, 27.9, 26.9, 21.5, 11.9 ppm.

Preparation of 2-(1,3-Dioxolan-2-yl) Esters 15a,c,d and Dioxolane 18: To a solution of β-oxo esters **14a**,**c**,**d** or 2-oxo-1-hexene (20 mmol, 1 equiv.) in dry CH_2Cl_2 (200 mL) under argon was added ethylene glycol (200 mmol, 10 equiv.). Ethyl orthoformate (30 mmol, 1.5 equiv.) and camphorsulfonic acid (2 mmol, 0.1 equiv.) were then added, and the reaction mixture was stirred at room temperature for 1 d. The reaction was quenched with saturated aq. $NaHCO_3$ (200 mL). The mixture was extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and the solvent was evaporated in vacuo. The products were purified by flash chromatography.

***tert*-Butyl 2-[2-(But-3-enyl)-1,3-dioxolan-2-yl]propanonate (15a):** Yield: 4.5 g (88%). Colourless oil obtained by chromatography (hexane/diethyl ether, 10:1). R_f = 0.38 (hexane/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.77 (m, 1 H), 5.07–4.94 (m, 2 H), 4.06–3.95 (m, 4 H), 2.73 (q, J = 7.1 Hz, 1 H), 2.25–2.05 (m, 2 H), 2.0–1.65 (m, 2 H), 1.46 (s, 9 H), 1.16 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 139.4, 122.6, 114.6, 77.9, 64.4, 45.2, 33.0, 31.0, 29.5, 12.1 ppm.

***tert*-Butyl 2-[2-(But-3-enyl)-1,3-dioxolan-2-yl]acetate (15c):** Yield: 4.5 g (93%). Colourless oil obtained by chromatography (cyclohexane/AcOEt, 2:1). R_f = 0.41 (hexane/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.77 (m, 1 H), 5.06–4.92 (m, 2 H), 4.04–3.94 (m, 4 H), 2.56 (s, 2 H), 2.21–2.14 (m, 2 H), 1.94–1.88 (m, 2 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 138.3, 114.3, 109.2, 80.6, 65.0, 43.8, 36.8, 28.1, 27.9 ppm.

***tert*-Butyl 2-[2-(But-3-enyl)-1,3-dioxolan-2-yl]butanoate (15d):** Yield: 4.37 g (81%). Colourless oil obtained by chromatography (hexane/diethyl ether, 10:1). R_f = 0.39 (hexane/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87–5.74 (m, 1 H), 5.07–4.96 (m, 2 H), 3.26 (t, J = 7.3 Hz, 1 H), 2.67–2.51 (m, 2 H), 2.38–2.31 (m, 2 H), 1.84 (m, 2 H), 1.45 (s, 9 H), 0.92 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.8, 168.9, 136.9, 115.3, 81.7, 61.8, 40.9, 27.9, 26.9, 21.5, 11.9 ppm.

2-(But-3-enyl)-2-methyl-1,3-dioxolane (18): Yield: 2.35 g (96%). Viscous yellow oil obtained by chromatography (hexane/AcOEt, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.68 (m, 1 H), 4.99 (dd, J = 10.5, 2 Hz, 1 H), 4.92 (dd, J = 18, 2 Hz, 1 H), 3.95 (m, 4 H), 2.19 (m, 2 H), 1.96 (m, 2 H), 1.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 114.5, 110.5, 64.6, 35.6, 29.6, 23.8 ppm.

Preparation of Epoxides 16a,c,d and 19: To a solution of *tert*-butyl ester **15a**,**c**,**d** or dioxolane **18** (16.5 mmol, 1 equiv.) in dry CH_2Cl_2 (400 mL) was added *m*-CPBA (77%, 19.8 mmol, 1.2 equiv. of active oxygen). The reaction mixture was stirred at room temperature overnight. Saturated aq. K_2CO_3 (100 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The products were purified by flash column chromatography (cyclohexane/AcOEt, 10:3).

***tert*-Butyl 2-{2-[2-(Oxiran-2-yl)ethyl]-1,3-dioxolan-2-yl}propanoate (16a):** Yield: 4.23 g (95%). Colourless oil. R_f = 0.44 (hexane/AcOEt, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.05–3.95 (m, 4 H), 2.98–2.90 (m, 1 H), 2.78–2.72 (m, 1 H), 2.72 (q, 1 H), 2.3 (m, 1 H), 2.09–1.53 (m, 4 H) 1.46 (s, 9 H), 1.17 (d, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 122.8, 77.9, 64.4, 59.7, 46.5, 44.9, 30.9, 30.1, 29.5, 12.1 ppm.

***tert*-Butyl 2-{2-[2-(Oxiran-2-yl)ethyl]-1,3-dioxolan-2-yl}acetate (16c):** Yield: 3.88 g (92%). Colourless oil. R_f = 0.40 (hexane/AcOEt, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95–3.84 (m, 4 H), 2.89–2.83 (m, 1 H), 2.66 (dd, J = 4.9, 3.3 Hz, 2 H), 2.39 (dd, J = 4.9, 3.3 Hz, 2 H), 1.93–1.86 (m, 2 H), 1.61–1.53 (m, 2 H), 1.37 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 108.9, 80.7, 65.1, 52.1, 47.1, 43.7, 38.7, 33.6, 28.0, 26.7 ppm.

***tert*-Butyl 2-{2-[2-(Oxiran-2-yl)ethyl]-1,3-dioxolan-2-yl}butanoate (16d):** Yield: 4.17 g (89%). Colourless oil. R_f = 0.44 (hexane/AcOEt, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.05–3.94 (m, 4 H), 2.96–2.88 (m, 1 H), 2.75–2.71 (m, 1 H), 2.51–2.44 (m, 2 H), 2.09–1.51 (m, 7 H), 1.46 (s, 9 H), 0.89 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 110.7, 80.4, 65.3, 55.9, 52.2, 47.2, 30.6, 27.9, 25.9, 21.0, 12.4 ppm.

2-Methyl-2-[2-(oxiran-2-yl)ethyl]-1,3-dioxolane (19): Yield: 1.8 g (80%). Viscous colourless oil obtained by chromatography (hexane/AcOEt, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (m, 4 H), 2.85 (m, 1 H), 2.54 (dd, J = 5.6, 2.8 Hz, 2 H), 1.69 (m, 4 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.5, 64.7, 52.2, 47.2, 35.1, 27.1, 23.9 ppm.

Preparation of Alcohols 17a,c,d and 20: To a suspension of CuI (41 mmol, 2 equiv.) in dry diethyl ether (100 mL) at 0 °C under argon, was added dropwise MeLi (52 mL, 1.6 M in diethyl ether, 82 mmol, 4 equiv.). A solution of epoxides **16a**,**c**,**d** (20 mmol, 0.95 equiv.) in diethyl ether (50 mL) was then added dropwise. The reaction was monitored by TLC until the disappearance of the starting material (50–60 min). Saturated aq. NH_4Cl (75 mL) was then added, and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine and dried with $MgSO_4$, and the solvent was evaporated in vacuo. The products were purified by flash column chromatography (cyclohexane/AcOEt, 2:1).

***tert*-Butyl 2-[2-(3-Hydroxypentyl)-1,3-dioxolan-2-yl]propanoate (17a):** Yield: 4.2 g (90%). Colourless oil. R_f = 0.32 (hexane/AcOEt, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.10–3.92 (m, 4 H), 3.54–3.43 (m, 1 H), 2.74 (q, J = 7.1 Hz, 0.5 H, diastereomer A), 2.73 (q, J = 7.1 Hz, 0.5 H, diastereomer B), 2.1–1.65 (m, 4 H), 1.53–1.33 (m, 2 H), 1.44 (s, 9 H), 1.14 (d, J = 7.1 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 122.7, 77.9, 72.0, 64.4, 44.9, 31.6, 30.7, 30.2, 29.5, 12.1, 9.7 ppm.

***tert*-Butyl 2-[2-(3-Hydroxypentyl)-1,3-dioxolan-2-yl]acetate (17c):** Yield: 3.9 g (88%). Colourless oil. R_f = 0.3 (hexane/AcOEt, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.06–3.96 (m, 4 H), 3.57–3.49 (m, 1 H), 2.58 (s, 2 H), 2.06–1.88 (m, 3 H), 1.71–1.59 (m, 1 H), 1.57–1.48 (m, 3 H), 1.46 (s, 9 H), 0.95 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 109.5, 80.7, 73.1, 65.0, 64.9, 43.6, 33.7, 30.7, 30.2, 28.0, 9.9 ppm.

***tert*-Butyl 2-[2-(3-Hydroxypentyl)-1,3-dioxolan-2-yl]butanoate (17d):** Yield: 4.45 g (90%). Colourless oil. R_f = 0.35 (hexane/AcOEt, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.05–3.94 (m, 4 H), 3.51–3.43 (m, 1 H), 2.50 (dd, J = 3.6, 11.5 Hz, 1 H), 2.1 (br. s, 1 H), 2.06–1.96 (m, 1 H), 1.83–1.47 (m, 7 H), 1.44 (s, 9 H), 0.91 (t, J = 7.4 Hz, 3 H), 0.87 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 111.3, 80.4, 73.1, 65.2, 65.1, 55.9, 30.7, 30.2, 29.9, 28.0, 21.0, 12.3, 9.8 ppm.

1-(2-Methyl-1,3-dioxolan-2-yl)pentan-3-ol (20): Yield: 2.3 g (92%). Yellow oil obtained by chromatography (hexane/AcOEt, 4:1). R_f = 0.53 (hexane/AcOEt, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.9 (m, 4 H), 3.45 (m, 1 H), 2.5 (m, 1 H), 1.7 (m, 2 H), 1.6 (m, 2 H), 1.55 (m, 2 H), 1.3 (s, 3 H), 0.85 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.1, 73.24, 64.6, 35.3, 31.1, 30.1, 23.7, 10 ppm.

Preparation of Ketones 2a,b,c,d: To a solution of alcohols **17a**,**c**,**d** (3.2 mmol, 1 equiv.) in DMF was added PDC (pyridinium dichromate) portionwise (3.66 g, 9.73 mmol, 3 equiv.). The reaction mixture was stirred at room temperature under argon overnight. H_2O (20 mL) and diethyl ether (20 mL) were then added. The reaction mixture was stirred at 0 °C for 15 min and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aq. NH_4Cl (2 × 50 mL) and then with brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated in vacuo, and the product was purified by flash column chromatography (cyclohexane/EtOAc, 3:1).

***tert*-Butyl 2-[2-(3-Oxopentyl)-1,3-dioxolan-2-yl]propanoate (2a):** Yield: 0.82 g (91%). Colourless oil. R_f = 0.32 (hexane/AcOEt, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04–3.92 (m, 4 H), 2.74 (q, J = 7.1 Hz, 1 H), 2.55–2.39 (m, 4 H), 2.19 (A part of ABXY, J_{AB} = 14.8, J_{AX} =, J_{AY} = 6.5, $\Delta\nu$ = 47 Hz, 1 H), 2.08 (B part of ABXY, J_{AB} = 14.8, J_{BX} = 6.2, J_{BY} = 6.2, $\Delta\nu$ = 47 Hz, 1 H), 1.46 (s, 9 H), 1.17 (d, J = 7.1 Hz, 3 H), 1.05 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.5, 174.0, 122.3, 77.9, 64.4, 43.9, 38.2, 36.0, 30.5, 29.5, 12.1, 7.8 ppm. $C_{15}H_{26}O_5$ (286.36): calcd. C 62.91, H 9.15; found C 62.57, H 9.19.

1-(2-Methyl-1,3-dioxolan-2-yl)pentan-3-one (2b): Yield: 0.83 g (96%). Colourless oil. R_f = 0.51 (hexane/AcOEt, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4 (m, 4 H), 2.46 (t, J = 7.4 Hz, 2 H), 2.25 (q, J = 8 Hz, 2 H), 1.75 (t, J = 7.5 Hz, 2 H), 1.35 (s, 3 H), 0.93 (t, J = 8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5, 109.4, 64.7, 36.9, 35.8, 32.8, 23.9, 7.8 ppm. $C_9H_{16}O_3$ (172.2): calcd. C 62.77, H 9.36; found C 62.87, H 9.29.

***tert*-Butyl 2-[2-(3-Oxopentyl)-1,3-dioxolan-2-yl]acetate (2c):** Yield: 0.89 g (93%). Colourless oil. R_f = 0.31 (hexane/AcOEt, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.03–3.92 (m, 4 H), 2.55 (s, 2 H), 2.50 (t, J = 6.9 Hz, 2 H), 2.43 (q, J = 7.3 Hz, 2 H), 2.19–2.15 (m, 2 H), 1.45 (s, 9 H), 1.06 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7, 168.5, 108.8, 80.8, 65.0, 43.9, 36.6, 35.6, 31.6, 7.8 ppm. $C_{14}H_{24}O_5$ (272.3): calcd. C 61.74, H 8.88; found C 61.89, H 8.99.

***tert*-Butyl 2-[2-(3-Oxopentyl)-1,3-dioxolan-2-yl]butanoate (2d):** Yield: 0.43 g (89%). Colourless oil. R_f = 0.33 (hexane/AcOEt, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.04–3.91 (m, 4 H), 2.50–2.39 (m, 5 H), 2.22 (ddd, J = 7, 8.15, 14.9 Hz, 1 H), 2.04 (ddd, J = 7, 8.15, 14.7 Hz, 1 H), 1.83–1.67 (m, 1 H), 1.61–1.46 (m, 1 H), 1.46 (s, 9 H), 1.04 (t, J = 7 Hz, 3 H), 0.89 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.1, 171.7, 110.7, 80.5, 65.2, 65.1, 55.9, 36.3, 35.4, 29.7, 28.1, 21.0, 12.4, 7.9 ppm. $C_{16}H_{28}O_5$ (300.4): calcd. C 63.97, H 9.40; found C 63.79, H 9.19.

General Procedure for the Aldol Reactions: To a stirred solution of Chx_2BCl (1.31 mmol, 290 µL, 1.3 equiv.) in pentane or diethyl ether (15 mL) at 0 °C under argon, was added dropwise a solution of ketones **2a**–**d** (1 mmol, 1 equiv.) in the same solvent (10 mL), and the enolate was generated rapidly with concurrent formation and precipitation of $Et_3N·HCl$. The reaction mixture was stirred at 0 °C for 2 h. To this mixture was added dropwise the aldehyde [0.82 mmol, neat in the case of isobutyraldehyde and dissolved in the reaction solvent (5 mL) for aldehyde **6**] at –78 °C. The reaction mixture was stirred at this temperature for 3 h, and then tightly sealed and stored in the freezer (–23 °C) overnight. Then a pH = 7 phosphate buffer solution (10 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The organic layers were combined and concentrated, and methanol (20 mL), pH = 7 phosphate buffer (5 mL) and finally H_2O_2 (35% in H_2O, 10 mL) were added at 0 °C. The mixture was stirred at room temperature for 2 h. Thereafter, distilled H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), and dried with $MgSO_4$. The solvent was evaporated, and the crude product was subjected to flash chromatography (gradient elution).

Aldol Adduct 21a: Obtained from a reaction in pentane and a purification using a cyclohexane → cyclohexane/diisopropyl ether (2:1) gradient. Yield: 240 mg (52%). Colourless oil. R_f = 0.12 (hexane/diethyl ether, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 4.53 (A of AB system, both diastereomers, J_{AB} = 11.9, $\Delta\nu$ = 10 Hz, 1 H), 4.48 (B of AB system, one diastereomer, J_{AB} = 11.9, $\Delta\nu$ = 10 Hz, 0.5 H), 4.47 (B of AB system, one diastereomer, J_{AB} = 11.9, $\Delta\nu$ = 12 Hz, 0.5 H), 4.01–3.85 (m, 5 H), 3.60–3.48 (m, 2 H), 2.91 (d, one diastereomer, J = 3.8 Hz, 0.5 H), 2.84 (d, one diastereomer, J = 4.2 Hz, 0.5 H), 2.87–2.72 (m, 1 H), 2.70 (q, one diastereomer, J = 7.1 Hz, 0.5 H), 2.69 (q, one diastereomer, J = 7.2 Hz, 0.5 H), 2.61–2.49 (m, 2 H), 2.50–2.24 (m, 1 H), 2.06–1.79 (m, 1 H), 1.95–1.85 (m, 1 H), 1.46 (s, 9 H), 1.16 (d, one diastereomer, J = 7.4 Hz, 1.5 H), 1.14 (d, one diastereomer, J = 7.4 Hz, 1.5 H), 1.04 (t, one diastereomer, J = 7.3 Hz, 1.5 H), 1.02 (t, one diastereomer, J = 7.1 Hz, 1.5 H), 1.01 (d, one diastereomer, J = 7.1 Hz, 1.5 H), 1.01 (d, one diastereomer, J = 7.2 Hz, 1.5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.4, 215.0, 172.7, 172.5, 138.3, 128.8, 128.1, 128.0, 111.1, 110.9, 81.0, 80.9, 77.6, 76.2, 75.8, 75.7, 75.5, 65.4, 65.3, 65.2, 65.1, 50.0, 49.6, 47.8, 47.3, 37.4, 36.4, 36.0, 35.8, 33.9, 33.6, 28.4, 28.4, 13.2, 12.9, 10.6, 10.4, 7.9, 7.8 ppm.

Aldol Adduct 21b: Obtained from a reaction in pentane and a purification using a cyclohexane → cyclohexane/diisopropyl ether (2:1) gradient. Yield: 98 mg (28%). Colourless oil. R_f = 0.26 (hexane/diethyl ether, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.17 (m, 5 H), 4.48 (AB, J = 12.06, $\Delta\upsilon$ = 13.72 Hz, 2 H), 3.97–3.86 (m, 5 H), 3.58–3.48 (m, 2 H), 2.88–2.79 (m, X part of ABX system, 1 H), 2.62–2.47 (m, 4 H), 2.33 (dd, A part of ABX system, J_{AX} = 10.3, J_{AB} = 14.5 Hz, 1 H,), 2.00 (dd, B part of ABX system, J_{BX} = 2.4, J_{AB} = 14.5, $\Delta\upsilon$ = 103.7 Hz, 1 H), 1.94–1.87 (m, 1 H), 1.02 (t, J = 7.5 Hz, 3 H), 1.00 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.9, 168.4, 137.9, 128.4, 127.7, 108.4, 80.8, 75.7, 73.5, 64.8, 64.6, 43.9, 37.1, 36.6, 35.4, 28.0, 10.1, 7.4 ppm.

Aldol Adduct 21d: Obtained from a reaction in pentane and a purification using a cyclohexane → cyclohexane/diisopropyl ether (2:1) gradient. Yield: 190 mg (40%). Colourless oil. R_f = 0.14 (hexane/diethyl ether, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 5 H), 4.51 (A of AB system, both diastereomers, J_{AB} = 12, $\Delta\nu$ = 10 Hz, 1 H), 4.47 (B of AB system, one diastereomer, J_{AB} = 12, $\Delta\nu$ = 10 Hz, 0.5 H), 4.46 (B of AB system, one diastereomer, J_{AB} = 12, $\Delta\nu$ = 12 Hz, 0.5 H), 4.07–3.88 (m, 5 H), 3.61–3.5 (m, 2 H), 2.9 (m, one diastereomer, J = 6 Hz, 0.5 H), 2.87 (m, one diastereomer, J = 6 Hz, 0.5 H), 2.87–2.72 (m, 1 H), 2.74 (t, one diastereomer, J = 7.5 Hz, 0.5 H), 2.71 (t, one diastereomer, J = 7.5 Hz, 0.5 H), 2.6–2.47 (m, 2 H), 2.52–2.2 (m, 1 H), 2.1–1.82 (m, 1 H), 1.96–1.83 (m, 1 H), 1.44 (s, 9 H), 1.68 (td, one diastereomer, J = 7.5, 7.2 Hz, 1 H), 1.64 (td, one diastereomer, J = 7.5, 7.2 Hz, 1 H), 1.06 (t, one diastereomer, J = 7 Hz, 1.5 H), 1.04 (t, one diastereomer, J = 7.3 Hz, 1.5 H), 1.02 (d, one diastereomer, J = 7 Hz, 1.5 H), 1.01 (d, one diastereomer, J = 7.2 Hz, 1.5 H), 0.99 (t, one diastereomer, J = 7.2 Hz, 1.5 H), 0.97 (t, one diastereomer, J = 7.2 Hz, 1.5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.4, 213.0, 174.5, 173.5, 138.3, 128.8, 128.1, 128.0, 110.1, 110.0, 81.0, 80.9, 75.6, 75.2, 74.9, 74.7, 74.5, 65.4, 65.3, 65.2, 65.1, 50.2, 49.6, 48.8, 48.3, 37.3, 36.4, 36.0, 35.6, 33.9, 33.6, 28.4, 28.4, 12.2, 11.9, 11.6, 11.4, 8.0, 7.9 ppm.

Aldol Adduct 22a: Obtained from a reaction in diethyl ether and a purification using a cyclohexane → cyclohexane/diisopropyl ether (1:1) gradient. Yield: 243 mg (52%). Colourless oil. R_f = 0.10 (hexane/diethyl ether, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H), 4.56–4.48 (m, 2 H), 4.15–3.85 (m, 5 H), 3.62–3.54 (m, 2

H), 2.93 (d, one diastereomer, J = 2.5 Hz, 0.5 H), 2.92 (d, one diastereomer, J = 2.5 Hz, 0.5 H), 2.90–2.50 (m, 3 H), 2.72 (q, J = 7.2 Hz, 1 H), 2.24–2.02 (m, 2 H), 1.98–1.85 (m, 1 H), 1.46 (s, 9 H), 1.18 (d, J = 7.3 Hz, 3 H), 1.17 (t, one diastereomer, J = 7.1 Hz, 1.5 H), 1.05 (t, one diastereomer, J = 7.0 Hz, 1.5 H), 1.03 (d, one diastereomer, J = 7.1 Hz, 1.5 H), 0.98 (d, one diastereomer, J = 7.0 Hz, 1.5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.3, 215.2, 172.7, 138.5, 128.8, 128.1, 128.0, 111.3, 110.9, 80.9, 77.9, 76.6, 75.6, 75.5, 75.2, 75.2, 65.8, 65.6, 49.5, 49.3, 47.9, 47.8, 37.4, 37.3, 37.1, 37.0, 36.4, 35.4, 28.4, 15.8, 19.4, 14.2, 12.9, 10.3 ppm.

Aldol Adduct 22b: Obtained from a reaction in pentane and a purification using a cyclohexane → cyclohexane/diisopropyl ether (2:1) gradient. Yield: 173 mg (47%). Colourless oil. R_f = 0.19 (hexane/diethyl ether, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 4.5 (s, 2 H), 4.02–3.92 (m, 5 H), 3.62–3.52 (m, 2 H), 2.90–2.68 (m, 1 H), 2.65–2.57 (m, 2 H), 2.55 (d, 1 H), 2.18–2.12 (m, 2 H), 1.95–1.86 (m, 1 H), 1.46 (s, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 211, 137.4, 128.8, 127.4, 109.1, 76.5, 71.2, 70.3, 49.3, 35.5, 35.3, 26.9, 26.3, 10.2, 9.3 ppm.

Aldol Adduct 22d: Obtained from a reaction in diethyl ether and a purification using a cyclohexane → cyclohexane/diisopropyl ether (1:1) gradient. Yield: 158 mg (32%). Colourless oil. R_f = 0.12 (hexane/diethyl ether, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 4.53–4.49 (m, 2 H), 4.1–3.83 (m, 5 H), 3.63–3.55 (m, 2 H), 2.91 (d, one diastereomer, J = 2.5 Hz, 0.5 H), 2.89 (d, one diastereomer, J = 2.5 Hz, 0.5 H), 2.90–2.50 (m, 3 H), 2.75 (t, J = 7 Hz, 1 H), 2.21–2.05 (m, 2 H), 1.98–1.86 (m, 1 H), 1.45 (s, 9 H), 1.15 (t, one diastereomer, J = 6.9 Hz, 1.5 H), 1.06 (t, one diastereomer, J = 7.0 Hz, 1.5 H), 1.04 (d, one diastereomer, J = 7 Hz, 1.5 H), 0.96 (d, one diastereomer, J = 7.0 Hz, 1.5 H), 0.95 (t, one diastereomer, J = 7.1 Hz, 1.5 H), 0.94 (t, one diastereomer, J = 7.1 Hz, 1.5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.8, 215.4, 173.1, 138.5, 128.8, 128.0, 127.9, 111.3, 110.9, 80.9, 77.9, 76.7, 75.6, 75.5, 75.2, 75.1, 65.8, 65.6, 65.5, 65.4, 49.5, 49.3, 47.4, 47.3, 37.4, 37.2, 37.1, 37.0, 36.4, 35.4, 28.4, 15.8, 14.2, 14.1, 11.2, 10.0 ppm.

Aldol Adduct 24b (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97–3.83 (m, 4 H), 3.39–3.43 (m, 1 H), 2.96 (ddd, X part of ABX system, J = 3.1, 5.9, 9.9 Hz, 1 H), 2.69–2.46 (m, 2 H), 2.42 (br. s, 1 H), 2.30 (dd, A part of ABX system, J_{AX} = 9.9, J_{AB} = 14.8 Hz, 1 H), 1.86 (dd, B part of ABX system, J_{BX} = 3.1, J_{AB} = 14.8, $\Delta\upsilon$ = 182.6 Hz, 1 H), 1.63 (m, 1 H), 1.36 (s, 3 H), 1.06 (t, J = 7.4 Hz, 3 H), 0.98 (d, J = 5.4 Hz, 3 H), 0.96 (d, J = 5.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.3, 109.0, 78.8, 64.3, 48.9, 39.3, 38.0, 31.4, 23.9, 19.8, 16.6, 7.3 ppm.

Aldol Adduct 24c (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.91–3.81 (m, 4 H), 3.31 (dd, J = 6, 6.1 Hz, 1 H), 2.83 (ddd, X part of ABX system, J = 3, 6.42, 9.42 Hz, 1 H), 2.56–2.42 (m, 4 H), 2.35 (dd, A part of ABX system, J_{AX} = 9.9, J_{AB} = 14.9 Hz, 1 H), 2.06 (dd, B part of ABX system, J_{BX} = 3, J_{AB} = 14.9, $\Delta\upsilon$ = 93.1 Hz, 1 H), 1.65–1.50 (m, 1 H), 1.38 (s, 3 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.0, 168.4, 108.5, 80.9, 78.7, 67.7, 64.6, 48.7, 43.8, 37.7, 37.3, 31.4, 28.0, 19.9, 16.7, 7.4 ppm.

Aldol Adduct 24d (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.10–3.86 (m, 8 H), 3.40–3.34 (m, 2 H), 2.95–2.88 (m, X part of ABX system of one diastereomer, 1 H), 2.84–2.78 (m, X part of ABX system of the other diastereomer, 1 H), 2.62–2.42 (m, 8 H), 2.36–2.25 (m, 3 H), 2.12 (dd, B part of ABX system of one diastereomer, J_{BX} = 2.6, J_{AB} = 15 Hz, 1 H), 1.93 (dd, B part of ABX system of the other diastereomer, J_{BX} = 3, J_{AB} = 14.9 Hz, 1 H), 1.81–1.56 (m, 6 H), 1.47 (s, 9 H), 1.46 (s, 9 H), 1.05–0.86 (m, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.3, 170.4, 109.5, 78.9, 76.7, 69.7, 68.6, 49.7, 37.7, 37.3, 31.4, 29.0, 19.9, 16.7, 11.2, 7.4 ppm.

Aldol Adduct 25b (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98–3.91 (m, 4 H), 3.51–3.45 (m, 1 H), 2.84–2.74 (m, 1 H), 2.67–2.56 (m, 2 H), 2.53 (d, 1 H, OH), 2.03–197 (m, 2 H), 1.82–1.71 (m, 1 H), 1.34 (s, 3 H), 1.12 (d, J = 7.2 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.6, 109.3, 78.3, 64.6, 48.7, 37.4, 32.2, 30.4, 23.9, 20.0, 15.7, 14.4 ppm.

Aldol Adduct 25c (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.00–3.95 (m, 4 H), 3.46 (dd, J = 7, 4.5 Hz, 1 H), 2.82–2.73 (m, 1 H), 2.66–2.51 (m, 4 H), 2.19–2.13 (m, 2 H), 2.03–1.97 (m, 2 H), 1.80–1.71 (m, 1 H), 1.45 (s, 9 H), 1.11 (d, J = 7.3 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.4, 168.5, 108.7, 80.8, 78.2, 65.0, 64.6, 48.3, 43.9, 37.1, 30.9, 30.4, 28.0, 20.0, 15.8, 14.4 ppm.

Aldol Adduct 25c (*syn*): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04–3.96 (m, 4 H), 3.54 (dd, J = 6.4, 2.6 Hz, 1 H), 2.78 (dq, J = 7.3, 2.6 Hz,1 H), 2.64–2.59 (m, 1 H), 2.57 (s, 2 H), 2.54–2.42 (m, 1 H), 2.23–2.15 (m, 2 H), 1.69 (dd, J = 6.7, 2.0 Hz, 1 H), 1.47 (s, 9 H), 1.14 (d, J = 7.3 Hz, 3 H), 1.04 (d, J = 6.4 Hz, 3 H), 0.87 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.7, 168.9, 109.1, 81.3, 76.7, 65.4, 65.3, 47.8, 44.2, 36.1, 30.9, 28.4, 19.6, 19.4, 14.1 ppm.

Aldol Adduct 25d (*anti*, two diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.11–3.92 (m, 4 H), 3.49–3.44 (m, 1 H), 2.83–2.74 (m, 1 H), 2.66–2.46 (m, 4 H), 2.29–1.99 (m, 2 H), 1.83–1.53 (m, 3 H), 1.48 (s, 9 H), 1.12 (d, J = 7.1 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.91 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.8, 172.1, 111.8, 78.5, 77.0, 64.8, 51.1, 48.2, 37.2, 29.6, 29.1, 28.1, 19.3, 18.1, 17.7, 14.2 ppm.

Aldol adduct 25d (*syn*, two diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11–3.92 (m, 4 H), 3.52 (dd, J = 8.5, 2.5 Hz, 1 H), 2.83–2.75 (m, 1 H), 2.64–2.47 (m, 4 H), 2.31–2.0 (m, 2 H), 1.83–1.63 (m, 3 H), 1.48 (s, 9 H), 1.45 (s, 9 H), 1.13 (d, J = 7 Hz, 3 H), 1.12 (d, J = 7 Hz, 3 H), 1.04 (d, J = 6.5 Hz, 3 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.92 (t, J = 7 Hz, 3 H), 0.9 (t, J = 7 Hz, 3 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.2, 173.1, 113.8, 77.9, 76.9, 64.2, 51.0, 48.8, 36.9, 29.9, 29.3, 28.8, 19.4, 18.0, 17.3, 14.6 ppm.

Cyclic Ketals 23a,d: To a rapidly stirred solution of **22a**,**d** (0.07 mmol) in dry MeOH (0.5 mL) was added Pd/C (5 mg, 5% w/w). The flask was purged with hydrogen gas and stirred at room temperature under hydrogen overnight. The reaction mixture was then filtered through Celite, which was copiously washed with diethyl ether. The solvents were removed in vacuo. The residue was purified by flash column chromatography (hexane/diethyl ether, 2:3) to afford a colourless oil. R_f = 0.15 (hexane/diethyl ether, 2:3). **23a**: Yield: 20 mg (99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09–3.95 (m, 4 H), 3.89–3.81 (m, 1 H), 3.54 (dd, J = 11, 5.4 Hz, 1 H), 3.17 (t, J = 10.5 Hz, 1 H), 3.15 (s, 3 H), 2.71 (q, one diastereomer, J = 7.2 Hz, 0.5 H), 2.70 (q, one diastereomer, J = 7.2 Hz, 0.5 H), 2.02–1.93 (m, 1 H), 1.90–1.74 (m, 3 H), 1.71–1.51 (m, 2 H), 1.47 (s, 9 H), 1.17 (d, 3 H), 0.97 (d, J = 7.1 Hz, 3 H,), 0.90 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 111.3, 111.2, 104.1, 104.0, 80.3, 80.2, 77.2, 65.8, 65.7, 65.6, 65.6, 65.5, 48.2, 48.0, 47.2, 47.2, 39.7, 39.6, 31.9, 31.9, 28.0, 27.8, 27.6, 25.2, 13.2, 12.7, 12.6, 8.0 ppm. **23d**: Yield: 22 mg (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09–3.95 (m, 4 H), 3.9–3.8 (m, 1 H), 3.55 (dd, J = 11, 5.6 Hz, 1 H), 3.2 (t, J = 10.5 Hz, 1 H), 3.16 (s, 3 H), 2.68 (t, one diastereomer, J = 5.2 Hz, 0.5 H), 2.68 (t, one diastereomer, J = 5.2 Hz, 0.5 H), 2.04–1.98 (m, 1 H), 1.90–1.75 (m, 3 H), 1.7–1.51 (m, 2 H), 1.65 (m, 2 H), 1.49 (s, 9 H), 1.05 (d, J = 6.5 Hz, 2 H), 0.97 (d, J = 7.0 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 111.8, 111.6, 104.0, 104.0, 80.9, 80.7, 77.2, 65.8, 65.7, 65.6, 65.6, 65.5, 49.4, 49.1, 48.8, 48.8, 39.6, 39.5, 31.9, 31.9, 28.5, 27.7, 27.5, 25.2, 19.4, 14.5, 13.2, 8.3 ppm.

Catecholborane Reduction of 24b–d and Acetonide 26b–d Formation: A typical experimental procedure is as follows. The hydroxy ketone **24b**,**c** (1 mmol) was dissolved in anhydrous THF (10.0 mL) in a dry round-bottomed flask under argon. The solution was chilled in an MeOH/ice bath (–10 °C) and charged with catecholborane (1 M solution in THF, 5.1 mL, 5.1 mmol, 5 equiv.). After 24 h, the reaction was quenched by the addition of anhydrous MeOH (2.0 mL) and saturated aq. sodium potassium tartrate (2.0 mL). This mixture was stirred at 25 °C for 2 h, and the desired product was isolated by a standard extractive isolation procedure. The crude mixture was placed in acetone (5 mL) in the presence of dimethoxypropane (2 mmol) and of camphorsulfonic acid (0.1 mmol). The mixture was stirred overnight, neutralised with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The resulting oils were purified by flash chromatography (diethyl ether/cyclohexane, 1:1) to give pure acetonides **26b**,**c**.

Acetonide 26b (*anti-anti*): ^1H NMR (400 MHz, $CDCl_3$): δ = 3.99–3.95 (m, 4 H), 3.39–3.34 (m, 1 H), 3.32 (dd, J = 1.56, 10.84 Hz, 1 H), 2.02 (dd, J = 1.60, 7.0 Hz, 1 H), 1.91–1.81 (m, 1 H), 1.50 (d, J = 3.52 Hz, 2 H), 1.47–1.40 (m, 2 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.30 (s, 3 H), 0.96 (d, J = 6.96 Hz, 3 H), 0.94 (t, J = 7.32 Hz, 3 H), 0.86 (d, J = 6.69 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.4, 109.2, 76.3, 64.3, 48.7, 36.3, 35.5, 31.0, 23.9, 19.2, 18.3, 7.5 ppm.

Acetonide 26c (*anti-anti*): ^1H NMR (400 MHz, $CDCl_3$): δ = 4.04–4.00 (m, 4 H), 3.46–3.41 (m, 1 H), 3.31 (dd, J = 2.5, 10.5 Hz, 1 H), 2.58 (s, 2 H), 2.13–2.05 (m,1 H), 1.87 (dd, J = 2.5, 7.05 Hz, 1 H), 1.82–1.73 (m, 1 H), 1.48 (s, 9 H), 1.46–1.40 (m, 2 H), 1.39–1.36 (m, 1 H), 1.38 (s, 3 H), 1.34 (s, 3 H), 0.95 (d, J = 7.05 Hz, 3 H), 0.85 (d, J = 7.05 Hz, 3 H), 0.77 (d, J = 7.05 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 109.7, 97.6, 80.5, 77.7, 74.2, 65.0, 43.9, 35.8, 33.2, 30.1, 28.1, 28.0, 27.1, 20.1, 19.6, 14.3, 11.8 ppm.

Prasad-Narasaka Reduction of 25b–d and Acetonide Formation: A typical experimental procedure is as follows. The hydroxy ketones **25b**,**c** (1 mmol) were dissolved in a mixture of anhydrous THF/MeOH (8:2, 10.0 mL) in a dry round-bottomed flask under argon. The solution was charged at –78 °C with diethyl(methoxy)borane (1 M solution in THF, 1.1 mmol, 1 equiv.) and stirred for 45 min, at which time $NaBH_4$ (1.1 mmol, 1.1 equiv.) was added portionwise. The reaction mixture was stirred at –78 °C for 5 h, quenched with aq. acetic acid (1 M, 6 mL), and allowed to warm to room temperature. The mixture was neutralised with saturated aq. $NaHCO_3$, and AcOEt (20 mL) was added. The mixture was stirred for 30 min, the aqueous phase was acidified by the addition of aq. sulfuric acid (10% w/w), and the mixture was extracted with AcOEt (3×50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. Finally, boronic ester hydrolysis was achieved by adding MeOH and distilling the resulting MeOH/Et_2BOMe azeotrope. The crude mixture was placed in acetone (5 mL) in the presence of dimethoxypropane (2 mmol) and camphorsulfonic acid (0.1 mmol). The mixture was stirred overnight, neutralised with saturated aq. $NaHCO_3$, and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine and dried with $MgSO_4$ and concentrated in vacuo. The resulting oils were purified by flash chromatography (diethyl ether/cyclohexane, 1:1) to give pure acetonides **27b**,**c**.

Acetonide 27b (*anti-anti*): ^1H NMR (300 MHz, $CDCl_3$): δ = 3.89–3.84 (m, 4 H), 3.38–3.31 (m, 1 H), 3.22 (dd, J = 2.28, 10.17 Hz, 1 H), 1.87–1.35 (m, 6 H), 1.29 (s, 3 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.76 (d, J = 6.8 Hz, 3 H), 0.67 (d, J = 6.75 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.2, 97.6, 77.7, 74.2, 64.6, 35.8, 34.5, 30.1, 28.2, 27.7, 26.9, 23.8, 20.1, 19.6, 14.3, 11.8 ppm.

Acetonide 27c (*anti-anti*): ^1H NMR (400 MHz, $CDCl_3$): δ = 4.04–4.00 (m, 4 H), 3.40–3.35 (m, 1 H), 3.33 (dd, J = 1.52, 10.68 Hz, 1 H), 2.49 (s, 2 H), 2.03 (dd, J = 1.52, 7.04 Hz, 1 H), 1.92–1.82 (m, 1 H), 1.74–1.72 (m, 2 H), 1.47 (s, 9 H), 1.45–1.42 (m, 1 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.34–1.32 (m, 1 H), 0.96 (d, J = 6.52 Hz, 3 H), 0.93 (t, J = 7.52 Hz, 3 H), 0.84 (d, J = 6.52 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 108.9, 97.2, 80.7, 77.8, 75.6, 64.7, 64.6, 45.1, 35.5, 34.9, 30.0, 29.7, 28.0, 27.6, 25.8, 20.9, 19.5, 14.5, 10.1 ppm.

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