Studies Towards the Synthesis of the C(9)–C(20) Lactone-Dipropionate Fragment of Calyculin C

Kaisa Karisalmi, Ari M. P. Koskinen*

Laboratory of Organic Chemistry, Helsinki University of Technology, PO Box 6100, 02015 Hut, Finland
Fax +358(94)512538; E-mail: Ari.Koskinen@hut.fi

Received 15 April 2004

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 77th birthday

Abstract: In this paper we describe the synthesis of a diastereomer of the C(9)–C(20) dipropionate-lactone fragment of Calyculin C. A short and enantioselective synthesis of the key intermediate **2** has been developed. This intermediate will play a critical role also in the synthesis of the correct diastereomer of C(9)–C(20) dipropionate-lactone fragment of Calyculin C.

Key words: aldol reactions, diastereoselectivity, dihydroxylations, natural products, stereoselective synthesis

Calyculins are a class of highly cytotoxic metabolites originally isolated from the marine sponge *Discodermia calyx* by Fusetani et al.[1] They have proven to be strong serine/threonine protein phosphatase inhibitors[2] and based on this property, calyculins might be potential anti-cancer agents.[3] Calyculin C (Figure 1) is one of the fourteen calyculins described so far, being among the most abundant ones in *D. calyx*.

The dipropionate-lactone fragment (boxed in Figure 1) contains seven of the total fifteen chiral centers of calyculin C. The synthesis of this C9–C20 segment demands strict stereocontrol and accurate planning. Our initial retrosynthetic analysis (Scheme 1) was based on (a) Sharpless asymmetric dihydroxylation,[4] (b) spontaneous lactonization, and (c) an *anti* aldol reaction via an (*E*)-Chx_2B-enolate.[5] This path has now been carried through

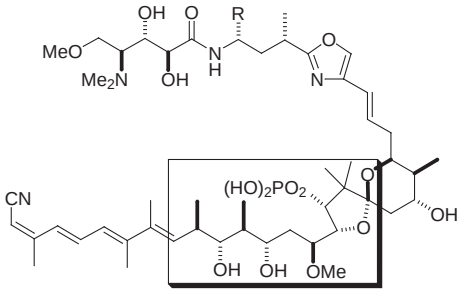
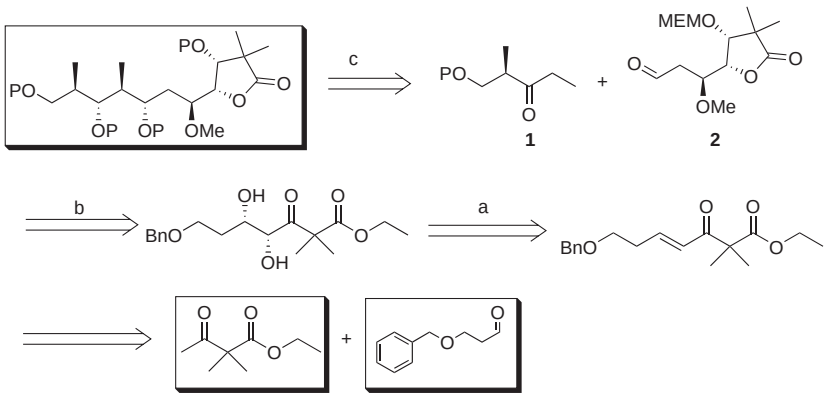


Figure 1 Calyculin A and C

and, unfortunately, it produced the wrong diastereomer. The results of this route will be discussed in this paper.

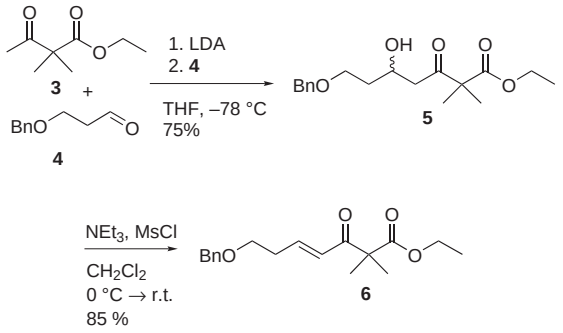
The synthesis started with an aldol addition followed by elimination to produce the intermediate enone **6** (Scheme 2). Both reactions gave the desired products with satisfactory yields (75 and 85%, respectively) and enone **6** was purified by simple filtration through a pad of silica gel (flash chromatography was not needed).

The enone **6** possesses the carbon skeleton of the key intermediate **2**. The next tasks were to simultaneously i) introduce the asymmetry into the molecule and ii) form the

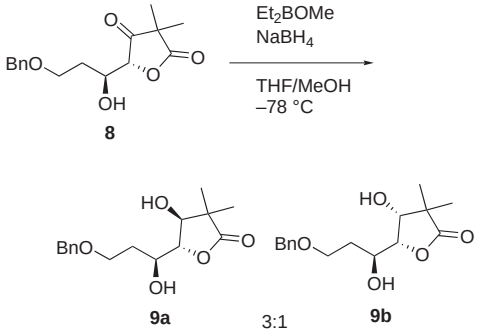


Scheme 1

SYNTHESIS 2004, No. 9, pp 1331–1342
Advanced online publication: 26.05.2004
DOI: 10.1055/s-2004-822389; Art ID: C02604SS



Scheme 2



Scheme 4

lactone structure. To achieve these goals, the enone **6** was subjected to Sharpless asymmetric dihydroxylation (Scheme 3). The dihydroxylation succeeded extremely well: the diol **7** lactonized spontaneously and the yield of the desired lactone **8** varied between 90% to quantitative. Two different ligands were tested for this reaction: $(DHQD)_2PHAL$ gave a disappointing enantiomeric excess (60%) while the 79% ee with $(DHQD)_2PYR$ was already satisfactory.[6]

On scale-up, lactone **8** turned out nicely crystalline. The crude lactone was recrystallized in the hope of enhancement of ee and we were fortunate to observe that it indeed improved the ee from 79 to 91%. The key lactone skeleton was produced in only three steps with reasonable yield and enantioselectivity from cheap and easily synthesized starting materials.

It was now time to start to shape the lactone towards the structure of the key intermediate **2**. The next decision was whether to perform first the methylation and then reduction of the ketone or vice versa. The ketone is in the 1,3 position to the hydroxyl group, hence the initial idea was to direct the stereochemistry of the reduction with the existing hydroxyl group by following the common *syn* 1,3-diol protocol.[7] Unfortunately, the diastereoselectivity was disappointingly low (3:1) (Scheme 4). The major diastereomer **9b** crystallized out as a racemate in the triclinic space group *P*-1. The X-ray crystal structure[8] reveals unambiguously the undesired isomer. Figure 2 shows an ORTEP-plot of the structure with thermal ellipsoids at 50% probability level. The molecular structure does not display any abnormal bond distance or angles.

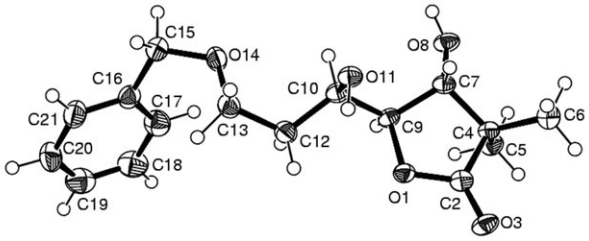
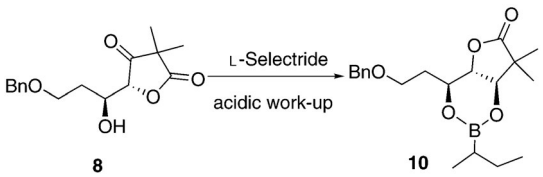


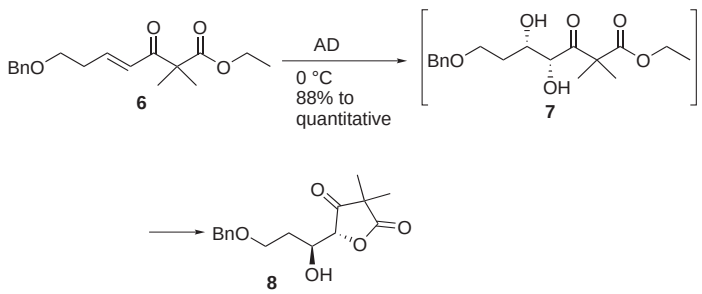
Figure 2 X-ray crystal structure of **9a** (shown as the enantiomer).

L-Selectride was next examined as the reducing agent (Scheme 5). The reaction was very diastereoselective but the product diol and the alkyl boron compound formed a stable complex **10**. An oxidative workup (H_2O_2/NaOH) resulted in the decomposition of the lactone.

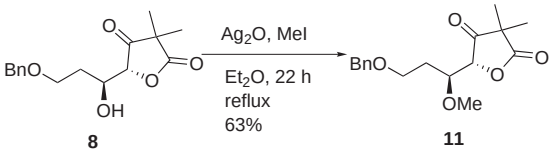


Scheme 5

We then decided to perform the methylation before the reduction so that the 1,3-diol-boron compound could not form. The standard procedure for methylation (KOH or some other base and MeX electrophile) was avoided because of possible epimerization. Ag_2O and MeI in diethyl ether produced the methylated product (Scheme 6), but the reaction was very slow and needed large excess of



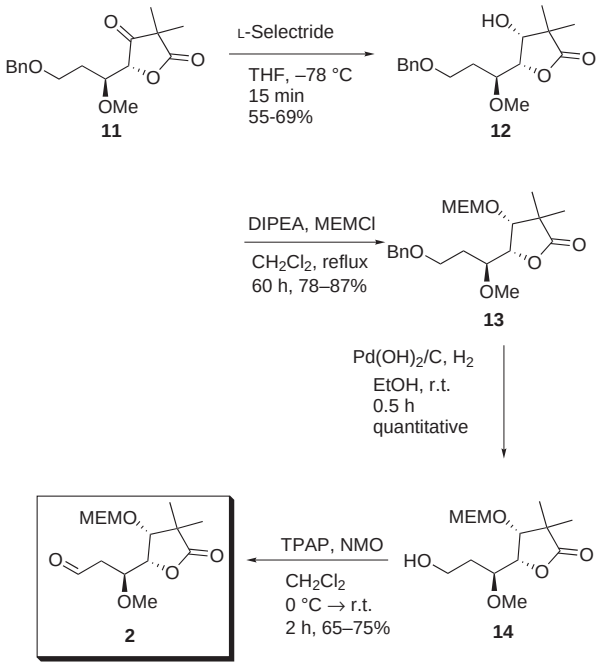
Scheme 3



Scheme 6

both reagents. The yield remained quite low (63%, 84% recycled) and 20–25% of the starting material was always recovered upon purification.

Since the formation of the *syn* 1,3-diol boron compound was blocked, it was time to realize the reduction with L-selectride. All starting material was consumed in 15 minutes. The reaction was also highly diastereoselective; based on ^{1}H NMR analysis of the crude product, only one diastereomer was obtained. The only problem with this reaction was the low yield. After purification by flash chromatography, pure **12** was obtained in 55–69% yield (Scheme 7).



Scheme 7

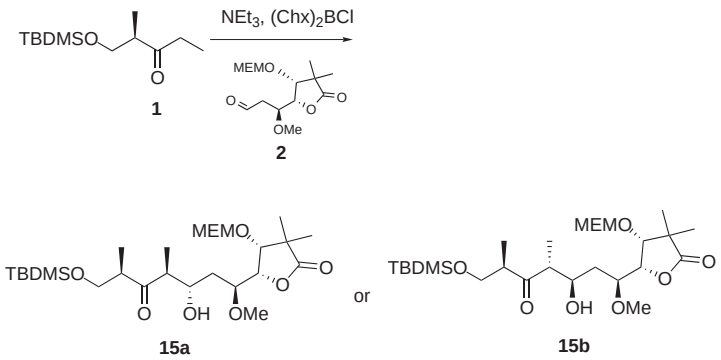
Last three steps in the synthesis of the lactone-aldehyde **2** were very straightforward (Scheme 7): the hydroxyl group was first protected with MEM protecting group, then the benzyl protecting group was removed with $Pd(OH)_2$/C and finally the free hydroxyl group was oxidized to aldehyde with TPAP[9] to produce the key intermediate **2**.

The next critical reaction in this route was the aldol reaction between **1** and **2**. A reaction of a boron enolate derived from $(Chx)_2BCl$ and a ketone with an aldehyde is known to produce an *anti* product.[10] When the reactants, ketone and aldehyde, are both chiral the situation becomes more complicated. Evans et al. have published an excellent study about diastereoselectivities of aldol reactions between chiral ketones and aldehydes.[11] The results of this study encouraged us to assume that under the reaction conditions shown in Scheme 8, the desired aldol product **15a** could be obtained as the major product. On the other hand, Paterson et al. have used the enol borinate [derived from $(Chx)_2BCl$] of the ketone **1** in a reaction with several different aldehydes to produce stereochemistry similar to **15b**.[12] Thus, in advance it remained ambiguous which one of these two aldol adducts (**15a** or **15b**) would be the major product in our case, and we hoped to shed some further light on this question.

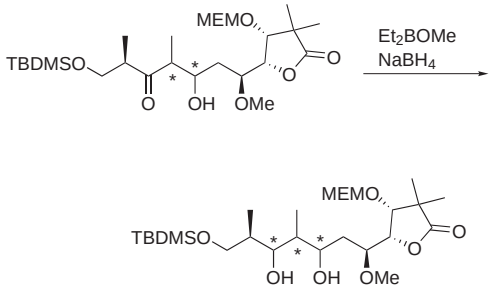
The enol borinate of the ketone **1** was first allowed to form at 0 °C for 1 hour, then the reaction mixture was cooled in a dry ice/acetone bath (–78 °C) and the aldehyde **2** was added. After 2.15 hours, the spot of the aldehyde had disappeared so the reaction was quenched, after which an oxidative workup (H_2O_2/NaOH) was performed to remove the boron. After purification with flash chromatography, only one aldol adduct was obtained in 28% yield.

Without further investigating the stereochemistry of the two new stereogenic centers (presuming that they are in *anti* relation to each other) the aldol product was allowed to undergo the *syn* 1,3-diol reduction[7] with Et_2BOMe/$NaBH_4$ (Scheme 9).

The reaction was very slow and two new spots on TLC (both less polar than the starting material) were obtained. The less polar one of those two new spots disappeared almost completely in the quench and a new one near the baseline appeared. Samples of pure boron-diol adduct **23**



Scheme 8



Scheme 9

(Figure 3) (upper spot) and a mixture of free *syn* and *anti* diols (spot near to baseline) were isolated by flash chromatography.

A gs-cosy spectrum helped us to assign the protons in the proton NMR spectrum. A closer look at the coupling constants of the boron-diol adduct (Figure 3) did not reveal the relative stereochemistry completely in the six-membered ring because of signal overlapping. However, one very important observation was made. H^2 has two coupling constants: 1.5 Hz has to be the coupling with the H^1 methine proton because only one coupling can be detected on H_1 (6.6 Hz, the coupling with methyl protons). The 10.3 Hz coupling is therefore the one between H^2 and H^3 corresponding to a coupling between two axial protons. This fact reinforces that the aldol reaction occurs in an *anti* manner.

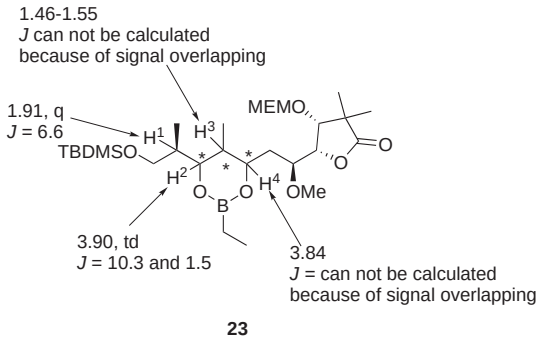
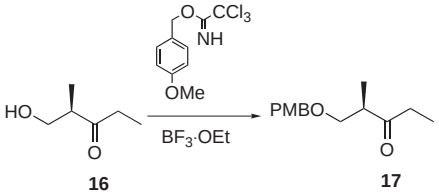


Figure 3 Coupling constants of H^1 to H^4 protons in **23**

The stereochemical relationship between the H^1 and H^2 protons (Figure 3) remained the biggest mystery in the stereotetrad prepared in Scheme 9. For resolving this problem the protecting group TBDMS was replaced with PMB: a PMB ether reacts with a free hydroxyl group under oxidative conditions to form a PMP acetal. Proton and ROESY NMR spectra of the PMP acetal could then reveal the relation (*anti* or *syn*) between H^1 and H^2.

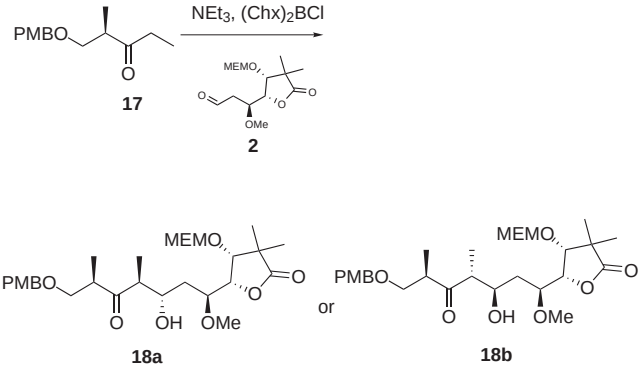
The PMB protected hydroxy ketone **17** was prepared from the free hydroxy ketone **16** using *p*-methoxybenzyltrichloroacetimidate and $BF_3{\cdot}OEt$ as the reagents (Scheme 11).[13] Basic reaction conditions were excluded to avoid epimerization. The reaction yielded the desired PMB protected alcohol in satisfactory yield (68%).



16 **17**

Scheme 10

The aldol reaction was then performed as with the TBDMS protected hydroxy ketone: the enol borinate was allowed to form for 1 hour at 0 °C, then the mixture was cooled to –78 °C and the aldehyde was added (Scheme 11). After a few hours the reaction flask was moved to cold room (–18 °C) and stirring was continued overnight. In this case the crude product was not allowed to undergo the oxidative workup. After flash chromatography, 33% of the aldol product (only one diastereomer) was obtained.



17 **2** **18a** **18b**

Scheme 11

The reduction was attempted in the same pot with the aldol addition by adding $NaBH_4$ to the reaction mixture after the aldol reaction was judged to be complete. Unfortunately the reduction did not succeed: after stirring overnight, quenching and flash chromatography the aldol adduct **18a**/**18b** was obtained as the main product. The reason for failure could have been inactivity of $NaBH_4$ or steric hindrance of the large cyclohexane rings in the boron-hydroxy ketone adduct (Figure 4).

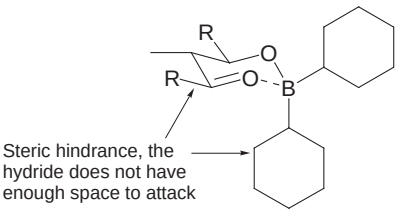
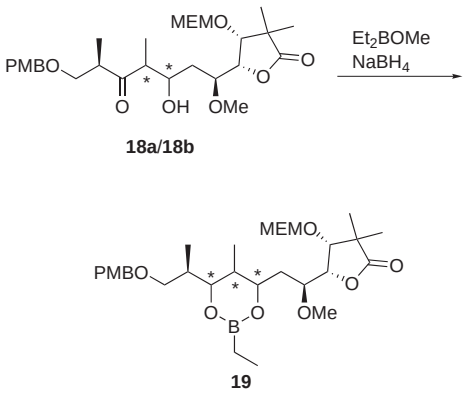


Figure 4 Structure of boron-hydroxy ketone adduct

The reduction was conducted as with the TBDMS aldol product: Et_2BOMe was allowed to react with the hydroxy ketone **18a**/**18b** first for one hour and 15 minutes (–70 to –78 °C) and then $NaBH_4$ was added in one portion

(Scheme 12). The reduction was complete in three hours (–65 to –78 °C). After purification a sample of pure boron-diol adduct **19** was obtained.



Scheme 12

The coupling constants in the proton NMR spectra did not give any new information about the stereochemistry of the boron-diol six-membered ring. The peaks of H^2 and H^4 overlap severely so that the coupling constants cannot be calculated (one proton from the MEM-group is in the same unresolved multiplet with H^2 and H^4). However, the chemical shifts and appearance of the multiplets is similar to the ones in compound **23**, suggesting the same facial preference in the aldol steps (Figure 5).

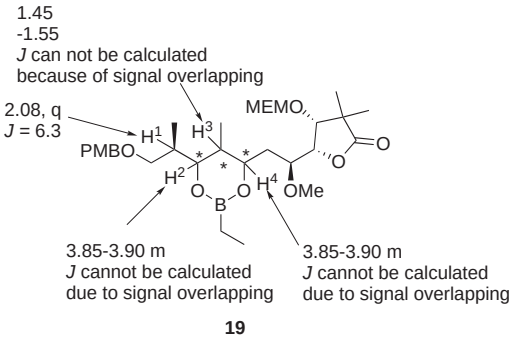
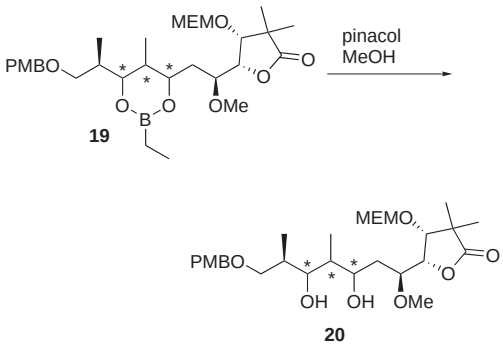


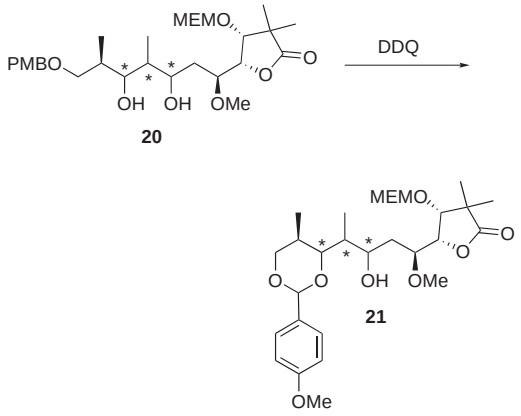
Figure 5 Coupling constants of H^1 to H^4 protons in **19**

The boron-diol adduct **19** proved to be exceptionally stable. It did not hydrolyze under mildly acidic conditions, and the deboronation (H_2O_2/NaOH) had to be avoided because of the PMB group. The idea of *trans* ketalization with excess of a diol, which could form a stable complex with the boron, seemed like an easy and mild way for removing the boron. The boron-diol adduct **19** was dissolved in MeOH and a large excess of pinacol was added (Scheme 13). The mixture was stirred at 40 °C overnight. A new spot near the baseline had appeared. After purification a sample of the free diol **20** was obtained. Hydrolysis of a larger sample took two days to go to completion.

The last reaction to be performed was the oxidative acetal formation of the PMB protected dipropionate-lactone fragment (Scheme 14).

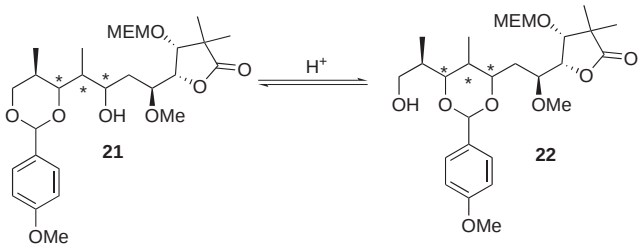


Scheme 13



Scheme 14

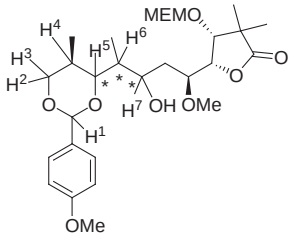
The reaction succeeded well and the PMP acetal product was obtained in quantitative yield. Attempted purification of the crude reaction mixture by filtration through a pad of silica gel led to migration of the newly formed acetal presumably catalyzed by the acidity of the silica gel (Scheme 15).[14]



Scheme 15

^{1}H, gs-cosy and ROESY NMR spectra were measured for the PMP acetal product **21**. The gs-cosy was used to identify the important peaks in the PMP acetal ring (Figure 6). Unfortunately the coupling between H^4 and H^5 was not detectable. However, the coupling constants of H^2 and H^3 revealed that H^4 has to be equatorial.

ROESY reinforced the conformation of the PMP acetal and positions of the substituents. All the important ROE



H^1: s, 5.51
H^2: dd, 4.08, *J* 11.2 2.0
H^3: dd, 4.03, *J* 11.2 1.3
H^4: m, 1.90–1.99
H^5: ?, 3.81–3.87
H^6: ?, 1.69
H^7: m, 4.13

Figure 6 Assignment of H^1 to H^7 protons in the ^1H NMR of **21**

couplings, which were detected from the spectrum are shown in Figure 7.

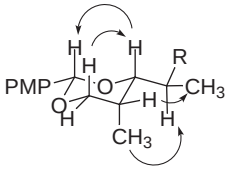


Figure 7 Conformation of PMP acetal **21**

These results lead to the disappointing conclusion: the leftward methyl and hydroxyl groups are *syn* to each other (Figure 8). ROESY data tells us also that the relation between the middle hydroxyl group and the rightward methyl is *anti*.

The following conclusions can be made from the NMR studies (Figure 9):

- The ^1H NMR spectrum of the diol-boron adduct **23** of the TBDMS protected stereotetrad-lactone fragment reveals that H^2 and H^3 are *anti*.

- ROESY spectrum of the PMP acetal **21** reinforces the *anti* relation between H^2 and H^3 and reveals the *syn* relation between H^1 and H^2.

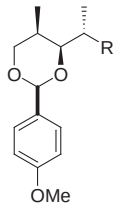


Figure 8 The wrong *syn*/*anti* relation of methyl and hydroxyl group found in **21**

- H^3–H^4 relation cannot be proven from the ^1H NMR spectra of the diol-boron adducts because of signal overlapping. However, it is safe to assume that $(Chx)_2B$-enolate leads to *anti* product and $Et_2BOMe/NaBH_4$ to *syn* 1,3-diol.

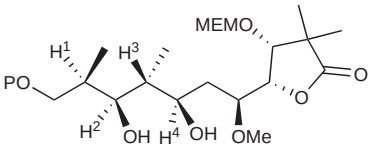


Figure 9 Relation of H^1, H^2, H^3 and H^4 protons in **21** and **23** as detected by NMR studies

These three points together lead to the following absolute stereochemistry of the products **15**, **23**, **18**, **19**, **20** and **21** (Figure 10).

The stereochemical results also reveal further insight to our original ambiguity concerning the facial selectivities. With both PMB and bulkier TBDMS ether enol borinates of **1** and **17**, we obtain products of the same relative configurations in the new stereogenic centers. For similar aldol reactions, Evans has evoked a model based on allylic strain,[11b] whereas Paterson has also involved electronic arguments to exclude alternative conformations.[15] How-

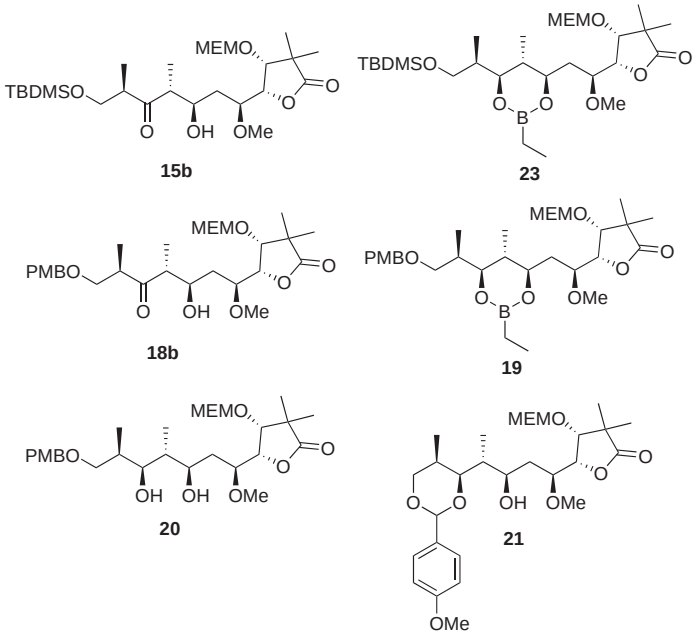
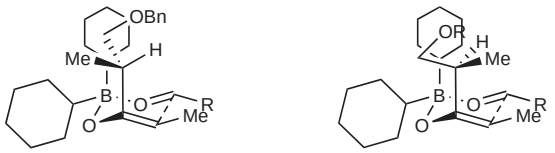


Figure 10 Absolute stereochemistry of **15**, **18**–**21**, **23**

ever, the presented model is not consistent with all results. Based on previous results and results presented here, we propose a common model to explain the observations. In this model, the previous presumptions hold, but we suggest that the transition state allow the allylic strain to be released later in the reaction path and thus avoid the severe steric interactions between the alkoxymethyl substituent and the boron–cyclohexyl substituent (Figure 11). In the Evans examples, this release of strain is not sufficient to overcome the increased strain caused by the (bulky) alkyl substituent on the alkoxymethyl carbon, and thus the opposite facial selectivity is necessarily obtained. However, further experiments and careful computational studies are needed to fully rationalize these observations.



Evans-Paterson *Present study*

Figure 11 Steric interactions between the alkoxymethyl substituent and the boron–cyclohexyl substituent in the transition state models of Evans–Paterson and our study

In this paper we have described a synthesis of a diastereomer of the C(9)–C(20) dipropionate-lactone fragment of Calyculin C. A short and enantioselective synthesis of the key intermediate **2** has been developed. This intermediate is going to play a critical role in the synthesis of the correct diastereomer of C(9)–C(20) dipropionate-lactone fragment of Calyculin C and the results will be reported in due course.

All reagents and solvents were purchased from commercial suppliers and used without further purification with the following exceptions: THF was refluxed over Na/benzophenone, CH_2Cl_2 was predried with $CaCl_2$ and refluxed over CaH_2, Et_2O was refluxed over Na and MeOH was refluxed over $Mg(OMe)_2$. All solvents were freshly distilled prior to use. Di-isopropylamine was distilled from NaOH, di-isopropyl ethylamine from KOH, Et_3N from CaH_2 and all of these reagents were stored under argon at r.t. Silica gel (230–400 mesh) for column chromatography as well as the corresponding TLC plates were purchased from Merck. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance-400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C measurements. Chemical shifts are reported in ppm on the δ scale from an internal standard of residual $CDCl_3$. HRMS spectra were recorded on Jeol JMS-DX 303 and Micromass LCT apparatus. Melting points were measured with a Fisher-Johns melting point apparatus. HPLC analyses were performed using a Waters 501 pump and Waters 486 detector. Separations were performed using a Daicel AS column.

Ethyl 7-(Benzyloxy)-5-hydroxy-2,2-dimethyl-3-oxoheptanoate (5)

LDA [prepared at 0 °C from DIPA (2.98 mL) and 2.5 M BuLi (8.18 mL)] in THF (69 mL) was cooled in an acetone/dry ice bath (–78 °C) under argon in a flame-dried flask and ethyl 2,2 dimethylacetoacetate (**3**; 2.71 g, 17.03 mmol) in THF (6 mL) was added dropwise. The enolate was allowed to form for 1 h at –78 °C and then the aldehyde **4** (3.75 g, 23 mmol) in THF (5 mL) was added. After 1 h, the reaction was quenched with aq sat. NH_4Cl (70 mL) and extracted with EtOAc (3 ×). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated to give the crude product as a yellow oil. The crude mixture was purified by flash chromatography (silica gel, 20% EtOAc–hexane) to give 4.1 g (75%) of the desired aldol adduct **5**; R_f = 0.20 (30% EtOAc–hexane).

IR (film): 3469, 1712 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (3 H, t, C*H*$_3$CH$_2$O$_2$CR, *J* = 7.1 Hz), 1.37 (3 H, s, RCOCC*H*$_3$CH$_3$CO$_2$Et), 1.38 (3 H, s, RCOCCH$_3$C*H*$_3$CO$_2$Et), 1.76–1.80 (2 H, m, BnOCH$_2$C*H*$_2$R), 2.67 (2 H, d, RCHOHC*H*$_2$COR, *J* = 6.0 Hz), 3.33 (1 H, d, OH, *J* = 3.0 Hz), 3.62–3.71 (2 H, m, BnOC*H*$_2$CH$_2$R), 4.18 (2 H, q, CH$_3$C*H*$_2$O$_2$CR, *J* = 7.1 Hz), 4.25–4.32 (1 H, m, RC*H*OHR), 4.52 (2 H, s, PhC*H*$_2$OR), 7.32–7.36 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 21.7, 21.8, 36.0, 44.9, 55.7, 61.4, 66.5, 67.9, 73.2, 127.6, 128.40, 128.43, 138.0, 173.3, 208.6.

HRMS: *m*/*z* calcd for $C_{18}H_{26}O_5$ + Na: 345.1678; found: 345.1684 (M + Na$^+$).

(*E*)-Ethyl 7-(Benzyloxy)-2,2-dimethyl-3-oxohept-4-enoate (6)

In a flame-dried flask, the aldol adduct **5** (4.1 g, 12.7 mmol) was dissolved in CH_2Cl_2 (220 mL) under argon and the mixture was cooled in an ice bath. Et_3N (45.9 mL, 0.33 mol) followed by MsCl (9.8 mL, 0.127 mol) were added through an addition funnel. The reaction mixture turned yellow and then orange. After 4.5 h, the reaction was quenched with aq $NaHCO_3$ (200 mL) and the phases were separated. The aqueous phase was extracted once with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated. The crude product was filtered through a silica gel pad using 10% EtOAc–hexane as eluent to afford 2.85g (85%) enone **6**; R_f = 0.41 (30% EtOAc–hexane).

IR (film): 1736, 1697, 1630 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (3 H, t, C*H*$_3$CH$_2$O$_2$CR, *J* = 7.1 Hz), 1.39 (6 H, s, RCOCC*H*$_3$C*H*$_3$CO$_2$Et), 2.52 (2 H, dq, BnOCH$_2$C*H*$_2$R, *J* = 6.5, 1.5 Hz), 3.59 (2 H, t, BnOC*H*$_2$CH$_2$R, *J* = 6.5 Hz), 4.16 (2 H, q, CH$_3$C*H*$_2$O$_2$CR, *J* = 7.1 Hz), 4.52 (2 H, s, PhC*H*$_2$OR), 6.32 (1 H, dt, C*H*=CHCOR, *J* = 15.4, 1.5 Hz), 7.01 (1 H, dt, RCH=C*H*COR, *J* = 15.4, 6.9 Hz), 7.30–7.38 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 22.2, 33.3, 54.8, 61.7, 68.7, 73.4, 126.6, 128.0, 128.8, 138.5, 145.5, 168.2, 174.3, 196.7.

HRMS: *m*/*z* calcd for $C_{18}H_{24}O_4$: 304.1675; found: 304.1719 (M$^+$).

(5*R*)-5-[(1*S*)-3-(Benzyloxy)-1-hydroxypropyl]-3,3-dimethylfuran-2,4(3*H*,5*H*)-dione (8)

$(DHQD)_2PYR$ (1.01 g, 1.15 mmol), $K_3Fe(CN)_6$ (16.2 g, 49.2 mmol), K_2CO_3 (6.79 g, 49.2 mmol), $NaHCO_3$ (4.13 g, 49.2 mmol) and $MeSO_2NH_2$ (1.56 mg, 16.4 mmol) were dissolved in H_2O–*t*-BuOH (75 + 75 mL) followed by OsO_4 (4.12 mL of 2.5 wt% in 2-methylpropan-2-ol) and the mixture was cooled in an ice bath. The enone **6** (5.0 g, 16.4 mmol) in toluene (10 mL) was added to the solution and the stirring was continued at 0 °C (in ice bath in a +4 °C room) overnight. Next morning (total reaction time 17 h), the reaction was quenched with aq Na_2SO_3, distilled H_2O was added and the mixture was extracted with EtOAc (4 ×). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated. The crude product was purified by filtering it through a silica gel pad to afford 4.2 g (88%) of the desired lactone **8** as yellowish crystals. The lactone was recrystallized from EtOAc–hexane; yield: 2.58 g of the lactone (91% ee) as white needle-like crystals; mp 73–74 °C; R_f = 0.37 (40% EtOAc–hexane); $[\alpha]_D$ –79.4 (*c* = 1.0, $CHCl_3$).

IR (film): 3468, 1800, 1751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (3 H, s, RCOCCH_3CH$_3$COO), 1.33 (3 H, s, RCOCCH$_3$CH_3COO), 1.83–1.89 (1 H, m, BnOCH$_2$CH_aH$_b$R), 2.12–2.22 (1 H, m, BnOCH$_2$CH$_a$$H_b$R), 3.27 (1 H, dd, OH, *J* = 3.5, 1.2 Hz), 3.69 (1 H, dt, BnOCH_aH$_b$R, *J* = 9.2, 3.3 Hz), 3.76–3.81 (1 H, m, BnOCH$_a$$H_b$R), 4.33–4.37 (1 H, m, RC*H*OHR), 4.52 (2 H, s, PhCH_2OR), 4.60 (1 H, t, RC*H*R$_2$, *J* = 1.4 Hz), 7.30–7.37 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 21.4, 32.1, 43.8, 68.1, 70.5, 73.1, 85.7, 127.4, 127.6, 128.2, 137.0, 177.8, 211.5.

HRMS: *m*/*z* calcd for $C_{16}H_{20}O_5$: 292.1310; found: 292.1266 (M^+).

(1*S*)-3-(Benzyloxy)-1-[(2*R*)-4,4-dimethyl-3,5-dioxotetrahydrofuran-2-yl]propyl Acetate

Racemic lactone **8** (25 mg, 0.08 mmol) was dissolved in CH_2Cl_2 (2.5 mL) under argon and the mixture was cooled in an ice bath. DMAP (cat.) and Ac_2O (96 mg, 0.088 mL) were added and the stirring was continued at 0 °C. After 1 h, the cooling bath was removed and the stirring was continued at r.t. for additional 3 h. Then H_2O was added and the mixture was extracted with CH_2Cl_2 (3 ×). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated giving the acetylated product in quantitative yield (34 mg); R_f = 0.28 (30% EtOAc–hexane).

IR (film): 1806, 1756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (3 H, s, RCOCCH_3CH$_3$COO), 1.30 (3 H, s, RCOCCH$_3$CH_3COO), 1.96 (3 H, s, CH_3CO$_2$R), 2.06–2.22 (2 H, m, BnOCH$_2$CH_2R), 3.59 (2 H, t, BnOCH_2R, *J* = 8.2 Hz), 4.49 (2 H, q, PhCH_2OR, *J* = 11.8 Hz), 4.95 (1 H, d, RC*H*R$_2$, *J* = 2.3 Hz), 5.43 (1 H, dt, CH$_3$CO$_2$C*H*R$_2$, *J* = 6.8, 2.3 Hz), 7.27–7.35 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 20.7, 22.0, 30.4, 44.2, 66.0, 70.7, 73.0, 83.8, 127.7, 127.8, 128.4, 137.9, 169.0, 177.0, 209.9.

HRMS: *m*/*z* calcd for $C_{18}H_{22}O_6$: 334.1416, found: 334.1449 (M^+).

(4*S*,5*S*)-5-[(1*S*)-3-(Benzyloxy)-1-hydroxypropyl]-4-hydroxy-3,3-dimethyldihydrofuran-2(3*H*)-one (9a) and (4*R*,5*S*)-5-[(1*S*)-3-(Benzyloxy)-1-hydroxypropyl]-4-hydroxy-3,3-dimethyldihydrofuran-2(3*H*)-one (9b)

Racemic lactone **8** (55 mg, 0.19 mmol) was dissolved in THF–MeOH (2 mL + 0.5 mL) in a flame-dried flask under argon and the mixture was cooled in dry ice/acetone bath (–78 °C). Et_2BOMe (0.21 mL of a 1 M solution in THF) was added and the mixture was stirred for 15 min before addition of $NaBH_4$ (8 mg, 0.21 mmol) in one portion. After 3 h 40 min, the reaction was quenched with AcOH (0.1 mL), diluted with EtOAc, and the EtOAc layer was washed with aq sat. Na_2CO_3. The aqueous phase was reextracted with EtOAc, the combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated. Purification with flash chromatography (50% EtOAc–hexane) gave 29 mg (53%) of a mixture of two diastereomers in a ratio of 3:1. The mixture was repurified by flash chromatography using 10% IPA–hexane as eluent and both diasteromers were obtained in pure form.

Major Diastereomer 9a

R_f = 0.30 (10% IPA–hexane).

IR (film): 3413, 1755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (3 H, s, RCHOHCCH_3CH$_3$COO), 1.23 (3 H, s, RCHOHCCH$_3$CH_3COO), 1.93–2.00 (2 H, m, BnOCH$_2$CH_2R), 3.02 (1 H, d, OH, *J* = 2.5 Hz), 3.20 (1 H, br s, OH), 3.71–3.79 (2 H, m, BnOCH_2R), 3.99–4.10 [3 H, m, (CH$_3$)$_2$CC*H*OHR, RC*H*OHR, RCHOHC*H*R$_2$], 4.53 (2 H, s, PhCH_2OR), 7.30–7.37 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 22.4, 32.4, 43.8, 67.3, 69.7, 73.5, 75.1, 83.2, 127.9, 128.0, 128.5, 137.3, 179.7.

HRMS: *m*/*z* calcd for $C_{16}H_{22}O_5$: 294.1467; found: 294.1480 (M^+).

Minor Diastereomer 9b

R_f = 0.20 (10% IPA–hexane).

IR (film): 3401, 1757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (3 H, s, RCHOHCCH_3CH$_3$COO), 1.27 (3 H, s, RCHOHCCH$_3$CH_3COO), 1.87–1.95 (1 H, m, BnOCH$_2$CH_aH$_b$R), 2.03–2.11 (1 H, m, BnOCH$_2$CH$_a$$H_b$R), 3.36 (1 H, d, OH, *J* = 4.1 Hz), 3.68–3.80 (2 H, m, BnOCH_2R), 4.01 (1 H, d, OH, *J* = 5.5 Hz), 4.12 [1 H, t, (CH$_3$)$_2$CC*H*OHR, *J* = 5.5, 4.3 Hz], 4.29–4.34 (1 H, m, RC*H*OHR), 4.38 (1 H, t, RCHOHC*H*R$_2$, *J* = 4.3 Hz), 4.54 (2 H, d, PhCH_2OR, *J* = 5.8 Hz), 7.31–7.36 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 23.3, 36.7, 45.6, 67.9, 69.8, 73.4, 76.7, 81.2, 127.8, 127.9, 128.5, 137.4, 180.9.

HRMS: *m*/*z* calcd for $C_{16}H_{22}O_5$: 294.1467; found: 294.1474 (M^+).

(5*R*)-5-[(1*S*)-3-(Benzyloxy)-1-methoxypropyl]-3,3-dimethylfuran-2,4(3*H*,5*H*)-dione (11)

Lactone **8** (2.2 g, 7.53 mmol) was dissolved in Et_2O (50 mL), and Ag_2O (8.7 g, 37.65 mmol) and MeI (10.6 g, 4.66 mL, 75.3 mmol) were added. The reaction flask was covered with aluminum foil and the mixture was refluxed for 22 h. Then the mixture was filtered through a silica gel pad, the solvent was evaporated and the crude product was purified by flash chromatography; yield: 1.45 g (62%) (474 mg of the starting material was recovered, recycled yield: 84%); R_f = 0.22 (30% EtOAc–hexane); $[\alpha]_D$ –37.9 (*c* = 1.0, $CHCl_3$).

IR (film): 1753, 1801, 2931 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (6 H, s, RCOCCH_3CH_3COO), 1.97–2.08 (2 H, m, BnOCH$_2$CH_2R), 3.26 (3 H, s CH_3OR), 3.55–3.64 (2 H, m, BnOCH_2R), 3.90 (1 H, dt, RC*H*OMeR, *J* = 1.8, 6.7 Hz), 4.51 (2 H, s, PhCH_2OR), 4.73 (1 H, d, RC*H*R$_2$, *J* = 1.8 Hz), 7.29-7.38 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 21.8, 29.8, 44.2, 58.5, 66.0, 73.0, 77.6, 85.0, 127.6, 127.7, 128.4, 137.9, 177.8, 212.0.

HRMS: *m*/*z* calcd for $C_{17}H_{22}O_5$ + Na: 329.1365; found: 329.1382 (M + Na^+).

(4*R*,5*S*)-5-[(1*S*)-3-(Benzyloxy)-1-methoxypropyl]-4-hydroxy-3,3-dimethyldihydrofuran-2(3*H*)-one (12)

The methylated lactone **11** (683 mg, 2.23 mmol) was dissolved in THF (15 mL) in a flame-dried flask under argon and the mixture was cooled in an acetone/dry ice bath (–78 °C). L-Selectride (2.34 mL of 1 M solution in THF) was added dropwise and after 15 min, the reaction was quenched with aq sat. NH_4Cl (15 mL). The mixture was allowed to reach r.t., then extracted with EtOAc (3 ×). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was dissolved in MeOH and the solvent was evaporated (this procedure was repeated several times) before purification with flash chromatography (silica gel, 10% IPA (isopropylamine)–hexane); yield: 442 mg (64%) of the desired alcohol **12** (only one diastereomer); R_f = 0.14 (10% IPA–hexane); $[\alpha]_D$ –21.4 (*c* = 2.0, $CHCl_3$).

IR (film): 1750, 2935, 3369 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (3 H, s, RCOCCH_3CH$_3$COO), 1.25 (3 H, s, RCOCCH$_3$CH_3COO), 1.87–2.01 (2 H, m, BnOCH$_2$CH_2R), 3.35 (1 H, d, OH, *J* = 4.1 Hz), 3.46 (3 H, s, CH_3OR), 3.59–3.66 (2 H, m, BnOCH_2R), 3.76 (1 H, dd, RC*H*OMeR, *J* = 5.5, 7.3 Hz), 4.02 [1 H, t, RC*H*OHC(CH$_3$)$_2$R, *J* = 3.8 Hz], 4.41 (1 H, dd, R$_2$C*H*OCOR, *J* = 3.8, 7.3 Hz), 4.51 (2 H, s, PhCH_2OR), 7.30–7.38 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 22.4, 30.9, 45.5, 58.6, 66.6, 73.3, 76.7, 77.7, 82.3, 127.90, 127.91, 128.5, 137.6, 180.6.

HRMS: *m*/*z* calcd for $C_{17}H_{24}O_5$: 308.1624; found: 308.1613 (M^+).

(4*R*,5*S*)-5-[(1*S*)-3-(Benzyloxy)-1-methoxypropyl]-4-[(2-methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (13)

Alcohol **12** (145 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (5 mL), DIPEA (0.49 mL, 2.82 mmol) and MEMCl (0.22 mL, 1.88 mmol) were added and refluxed. After refluxing for 17 h, there was still starting material left. Additional amounts of DIPEA (0.49 mL, 2.82 mmol) and MEMCl (0.22 mL, 1.88 mmol) were added. After 24 h, again DIPEA (0.49 mL, 2.82 mmol) and MEMCl (0.22 mL, 1.88 mmol) were added. The reaction was complete in 44.5 h. The mixture was poured into H_2O, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic phases were washed with aq sat. NH_4Cl and brine, dried (Na_2SO_4), filtered and the solvent was evaporated. The crude product was purified by flash chromatography (60% MTBE–hexane as eluent); yield: 137 mg (73%); R_f = 0.35 (60% EtOAc–hexane); $[\alpha]_D$ +14.2 (*c* = 1.0, $CHCl_3$).

IR (film): 1018, 1101, 1778, 2930 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (3 H, s, RCOCC*H*$_3$CH$_3$COO), 1.23 (3 H, s, RCOCCH$_3$C*H*$_3$COO), 1.70–1.79 (1 H, m, BnOCH$_2$C*H*$_a$H$_b$R), 1.92–1.98 (1 H, m, BnOCH$_2$CH$_a$*H*$_b$R), 3.34 (3 H, s, C*H*$_3$OCH$_2$CH$_2$R), 3.38–3.48 (2 H, m, CH$_3$OC*H*$_2$R), 3.46 (3 H, s, C*H*$_3$OR), 3.60–3.68 (3 H, m, BnOC*H*$_2$R + RC*H*OMeR), 3.72–3.81 (2 H, m, CH$_3$OCH$_2$C*H*$_2$OR), 3.97 (1 H, d, RC*H*OMEMR, *J* = 4.1 Hz), 4.48 (1 H, dd, R$_2$C*H*OCOR, *J* = 4.1 Hz), 4.48 (2 H, s, PhC*H*$_2$OR), 4.70 (1 H, d, OC*H*$_a$H$_b$O, *J* = 7.1 Hz), 4.76 (1 H, d, OCH$_a$*H*$_b$O, *J* = 7.1 Hz), 7.28–7.34 (5 H, m, ArH).

^1H NMR (100 MHz, $CDCl_3$): δ = 18.9, 22.9, 30.0, 45.4, 59.0, 59.5, 65.7, 68.4, 71.6, 73.2, 76.4, 76.6, 83.2, 96.9, 127.6, 127.7, 128.3, 138.3, 180.1.

HRMS: *m*/*z* calcd for $C_{21}H_{32}O_7$ + Na: 419.2046; found: 419.2024 ($M + Na^+$).

(4*R*,5*R*)-5-[(1*S*)-3-Hydroxy-1-methoxypropyl]-4-[(2-methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (14)

The benzyl protected alcohol **13** (408 mg, 1.03 mmol) was dissolved in EtOH (15 mL) and $Pd(OH)_2$ on carbon (82 mg, 20 wt%) was added. The black suspension was stirred at r.t. under H_2 for 40 min and then the mixture was filtered through Celite and the solvent was evaporated to give 309 mg (98%) of the deprotected alcohol **14**; R_f = 0.05 (60% EtOAc–hexane, PMA stain); $[\alpha]_D$ +32.9 (*c* = 2.0, $CHCl_3$).

IR (film): 3468, 1773 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (6 H, s, RCOCC*H*$_3$C*H*$_3$COO), 1.57–1.62 (1 H, m, HOCH$_2$C*H*$_a$H$_b$R), 1.92–1.95 (1 H, m, HOCH$_2$CH$_a$*H*$_b$R), 2.81 (1 H, dd, O*H*, *J* = 5.2 6.9 Hz), 3.40 (3 H, s, C*H*$_3$OCH$_2$CH$_2$R), 3.51–3.60 (3 H, m, CH$_3$OC*H*$_2$R, RC*H*OMeR), 3.56 (3 H, s, C*H*$_3$OR), 3.77–3.83 (3 H, m, HOC*H*$_2$R + CH$_3$OCH$_2$C*H*$_a$H$_b$OR), 3.89–3.94 (1 H, m, CH$_3$OCH$_2$CH$_a$*H*$_b$R), 3.95 (1 H, d, RC*H*OMEMR, *J* = 3.8 Hz), 4.43 (1 H, dd, R$_2$C*H*OCOR, *J* = 3.8, 8.6 Hz), 4.68 (1 H, d, OC*H*$_a$H$_b$O, *J* = 7.0 Hz), 4.78 (1 H, d, OCH$_a$*H*$_b$O, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 22.7, 32.8, 45.7, 59.05, 59.15, 60.1, 68.5, 71.8, 76.7, 83.6, 83.8, 97.1, 179.8.

HRMS: *m*/*z* calcd for $C_{14}H_{26}O_7$ + Na: 329.1576; found: 329.1586 ($M + Na^+$).

(3*S*)-3-Methoxy-3-{(2*R*,3*R*)-3-[(2-methoxyethoxy)methoxy]-4,4-dimethyl-5-oxotetrahydrofuran-2-yl}propanal (2)

Alcohol **14** (100 mg, 0.33 mmol) and NMO (66 mg, 0.49 mmol) were dissolved in CH_2Cl_2 (4 mL) in a reaction flask under argon and 4 Å MS powder (150 mg) was added. The mixture was cooled in an ice bath and TPAP (6 mg, 0.016 mmol) was added in one portion. The black suspension was then stirred in the ice bath for 10 min, the cooling bath was removed and stirring was continued at r.t. for another 2 h. Then the mixture was diluted with CH_2Cl_2 and filtered through a silica gel pad (eluent: EtOAc) to give 77 mg (78%) of the desired aldehyde **2** after evaporation of the solvent; R_f = 0.33 (EtOAc, PMA stain); $[\alpha]_D$ +5.8 (*c* = 2.0, $CHCl_3$).

IR (film): 1014, 1101, 1727, 1776, 2938 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (3 H, s, RCOCC*H*$_3$CH$_3$COO), 1.26 (3 H, s, RCOCCH$_3$C*H*$_3$COO), 2.65 (1 H, ddd, OHCC*H*$_a$H$_b$R, *J* = 2.0, 8.3, 17.0 Hz), 2.88 (1 H, dd, OHCHCH$_a$*H*$_b$R, *J* = 3.2, 17.0 Hz), 3.35 (3 H, s, C*H*$_3$OCH$_2$CH$_2$R), 3.47–3.53 (2 H, m, CH$_3$OC*H*$_2$R), 3.51 (3 H, s, C*H*$_3$OR), 3.57–3.62 (1 H, m, CH$_3$OCH$_2$C*H*$_a$H$_b$OR), 3.72–3.77 (1 H, m, CH$_3$OCH$_2$CH$_a$*H*$_b$OR), 4.00 (1 H, d, RC*H*OMEM, *J* = 4.4 Hz), 4.14 (1 H, dt, RC*H*OMeR, *J* = 3.2, 7.8 Hz), 4.49 (1 H, dd, R$_2$C*H*OCOR, *J* = 4.4, 7.8 Hz), 4.68 (1 H, d, OC*H*$_a$H$_b$O, *J* = 7.0 Hz), 4.78 (1 H, d, OCH$_a$*H*$_b$O, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 23.4, 44.3, 45.1, 59.0, 59.6, 68.4, 71.5, 74.4, 81.8, 82.6, 96.7, 179.7, 200.1.

HRMS: *m*/*z* calcd for $C_{14}H_{24}O_7$ + Na: 327.1420; found: 327.1455 ($M + Na^+$).

(4*R*,5*R*)-5-[(1*S*,3*R*,4*R*,6*R*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hydroxy-1-methoxy-4,6-dimethyl-5-oxoheptyl]-4-[(2-methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (15b)

Et_3N (35 mL, 0.25 mmol) was dissolved in anhyd Et_2O (1.5 mL) under argon in a flame-dried flask and the mixture was cooled in an ice bath. Then $(Chx)_2BCl$ (1 M in THF, 0.25 mL, 0.25 mmol) followed by ketone **1** (49 mg, 0.21 mmol) in Et_2O (0.7 mL) were added. This mixture was stirred at 0 °C for 1 h, then the ice bath was replaced with an acetone/dry ice bath (–78 °C) and the mixture was allowed to cool before the addition of aldehyde **2** (77 mg, 0.25 mmol) dissolved in Et_2O (0.8 mL). After 2 h 15 min, the reaction was quenched by pouring into Et_2O/pH 7 buffer solution (5 + 5 mL). The phases were separated, the aqueous phase was extracted with Et_2O (2 ×), and the combined organic phases were dried (Na_2SO_4). After filtration, the solvent was evaporated. The crude product (160 mg) was dissolved in MeOH/pH7 buffer (2 + 2 mL) and the mixture was cooled in an ice bath, then 30% H_2O_2 (0.5 mL) was added and the mixture was allowed to stir in the ice bath for 1 h at r.t. for 0.5 h. H_2O was added and the mixture was extracted with Et_2O (3 ×). The combined organic phases were washed with aq sat. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and the solvent evaporated to give 82 mg of crude product. The crude product was purified by flash chromatography (silica gel, 50% hexane–EtOAc) to afford 30 mg (28%) of the aldol product **15b**; R_f = 0.20 (50% EtOAc–hexane, PMA stain); $[\alpha]_D$ –4.0 (*c* = 1.0, $CHCl_3$).

IR (film): 1709, 1778, 3468 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 (3 H, s, C*H*$_3$Si), 0.03 (3 H, s, C*H*$_3$Si), 0.86 (9 H, s, *t*-C$_4$H$_9$), 0.99 (3 H, d, TBDMSOCH$_2$CHC*H*$_3$R, *J* = 7.0 Hz), 1.09 (3 H, d, C=OCHC*H*$_3$CHOHR, *J* = 7.1 Hz), 1.24 (6 H, s, RCOCC*H*$_3$C*H*$_3$COO), 1.57 (2 H, t, RCHHOC*H*$_2$CHOMeR, *J* = 5.9 Hz), 2.73 (1 H, dq, C=OC*H*CH$_3$CHOHR, *J* = 7.1, 7.1 Hz), 2.98 (1 H, tq, TBDMSOCH$_2$C*H*CH$_3$R, *J* = 7.0, 1.5 Hz), 3.27 (1 H, d, OH, *J* = 5.8 Hz), 3.38 (3 H, s, C*H*$_3$OR), 3.55 (3 H, s, RCH$_2$CHOC*H*$_3$CO$_2$R), 3.51–3.57 (2 H, m, CH$_3$OC*H*$_2$CH$_2$OR), 3.61–3.91 (5 H, m, TBDMSOC*H*$_2$R + CH$_3$OCH$_2$C*H*$_2$OR + RCH$_2$C*H*OMeCOO), 3.93 (1 H, d, RC*H*OMEM, *J* = 4.2 Hz), 4.00–4.08 (1 H, m, C=OCHCH$_3$C*H*OHR), 4.39 (1 H, dd, R$_2$C*H*OCOR, *J* = 4.2, 8.0 Hz), 4.70 (1 H, d, OC*H*$_a$H$_b$O, *J* = 7.0 Hz), 4.78 (1 H, d, OCH$_a$*H*$_b$O, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6, 12.8, 13.5, 18.3, 18.9, 23.2, 25.8, 35.3, 45.3, 47.4, 53.1, 59.0, 60.4, 65.5, 68.5, 69.3, 71.8, 76.0, 83.2, 83.6, 97.2, 180.0, 217.5.

HRMS: *m*/*z* calcd for $C_{30}H_{46}O_8$ + Na: 557.3090; found: 557.3099 ($M + Na^+$).

(4*R*,5*R*)-5-{(1*S*)-2-[(4*R*,5*R*,6*S*)-6-((1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-ethyl-5-methyl-1,3,2-dioxaborinan-4-yl]-1-methoxyethyl}4-[(2-methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (23)

The aldol adduct **15b** (25 mg, 0.047 mmol) was dissolved in THF–MeOH (0.75 + 0.1 mL) in a flame-dried flask under argon and the mixture was cooled in an acetone/dry ice bath (–78 °C). Et_2BOMe (1 M in THF, 51 mL, 0.051 mmol) was added dropwise and the mixture was stirred at –70 °C for 0.5 h. Then $NaBH_4$ (2 mg, 0.051 mmol) was added and the mixture was stirred for 4.5 h (–78 to –15 °C). Then an additional 0.05 mmol of both reagents (Et_2BOMe and $NaBH_4$) were added and stirring was continued (–15 °C) for another 2.5 h. Then the reaction was quenched with AcOH (0.1 mL) and the mixture was diluted with EtOAc. The organic layer was washed with aq sat. Na_2CO_3, dried (Na_2SO_4), filtered and the solvent was evaporated to give 24 mg of crude product. The crude product was purified by flash chromatography (silica gel, 40% EtOAc–hexane) to furnish 5 mg of the *syn* boron diol **23** adduct and 8 mg of a mixture of *syn* and *anti* diols.

23

R_f = 0.23 (40% EtOAc–hexane, PMA stain); $[\alpha]_D$ +5.0 (*c* = 0.3, $CHCl_3$).

IR (film): 1779 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 [6 H, s, $(CH_3)_2Si$], 0.62 (2 H, q, CH_3CH_2BR, *J* = 8.1 Hz), 0.74 (3 H, d, $TBDMSOCH_2CHCH_3R$, *J* = 6.9 Hz), 0.84 [3 H, d, $CHCH_3(CHOBR)_2$, *J* = 6.6 Hz], 0.86 (3 H, t, CH_3CH_2BR, *J* = 8.1 Hz), 0.90 (9 H, s, *t*-C_4H_9Si), 1.26 (3 H, s, $RCOCCH_3CH_3COO$), 1.29 (3 H, s, $RCOCCH_3CH_3COO$), 1.45–1.53 [2 H, m, $OBRCH_aH_bCHOMeR$ + $CHCH_3(CHOBR)_2$], 1.74 (1 H, dt, $CH_aH_bCHOMeR$, *J* = 12.1, 2.2 Hz), 1.91 (1 H, q, $TBDMSOCH_2CHCH_3R$, *J* = 6.6 Hz), 3.37 (s, 3 H, CH_3OR), 3.47–3.51 (3 H, m, $TBDMSOCH_2R$ + $CH_3OCH_aH_bCH_2OR$), 3.58 (3 H, s, $RCH_2CHOCH_3CO_2R$), 3.65 (1 H, ddd, $CH_3OCH_aH_bCH_2OR$, *J* = 10.9, 6.4, 3.1 Hz), 3.69 (1 H, dd, $CH_3OCH_2CH_aH_bOR$ *J* = 9.6, 8.6 Hz), 3.83 (1 H, dt, $CHCH_3CHOBRCHCH_3$, *J* = 10.3, 1.5 Hz), 3.89 (2 H, m, $CH_3OCH_2CH_aH_bOCH_2OR$ + $CHOBRCHCH_3CHOBCH_2$), 3.96 (1 H, d, RC*H*OMEM, *J* = 4.1 Hz), 4.04 (1 H, ddd, RC*H*OMeR, *J* = 10.4, 8.2, 2.2 Hz), 4.39 (1 H, dd, $R_2CHOCOR$, *J* = 8.2, 4.1 Hz), 4.74 (1 H, d, OCH_aH_bO, *J* = 7.4 Hz), 4.78 (1 H, d, OCH_aH_bO, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, 7.8, 8.4, 12.6, 18.3, 19.0, 23.1, 25.9, 35.8, 36.9, 37.8, 45.4, 59.1, 60.4, 65.2, 66.3, 68.5, 71.8, 71.9, 74.7, 75.0, 82.7, 84.1, 96.8, 180.0.

HRMS: *m*/*z* calcd for $C_{28}H_{55}BO_9Si$ + Na: 597.3606; found: 597.3604 ($M + Na^+$).

(4*R*,5*R*)-5-{(1*S*,3*R*,4*R*,6*R*)-3-Hydroxy-1-methoxy-7-[(4-methoxybenzyl)oxy]-4,6-dimethyl-5-oxoheptyl}-4-[(2-methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (18b)

$(Chx)_2BCl$ (1 M in THF, 0.19 mL, 0.185 mmol) was dissolved in anhyd Et_2O (1.0 mL) under argon in a flame-dried flask and Et_3N (28 mL, 0.19 mmol) was added dropwise. The mixture was cooled in an ice bath and then the ketone **17** (42 mg, 0.177 mmol) in Et_2O (1.0 mL) was added. This mixture was stirred at 0 °C for 1 h, then the ice bath was replaced with an acetone/dry ice bath (–78 °C) and the mixture was allowed to cool before the addition of the aldehyde **2** (56 mg, 0.18 mmol) in Et_2O (1.0 mL). After stirring for 3 h 15 min at –78 °C, the flask containing the reaction mixture was moved to a room cooled to –18 °C and allowed to stay there overnight. Next morning (total reaction time 21 h) the reaction was quenched with aq sat. NH_4Cl and the mixture was extracted with Et_2O (3 ×). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated to give 157 mg of crude product. The crude product was purified by flash chromatography (silica gel, 60% hexane–EtOAc) to afford 32 mg (33%) of the pure aldol **18b**; R_f = 0.23 (70% EtOAc–hexane, PMA stain); $[\alpha]_D$ +5.4 (*c* 0 1.0, $CHCl_3$).

IR (film): 1711, 1778, 3218 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (3 H, d, $PMBOCH_2CHCH_3R$, *J* = 7.0 Hz), 1.08 (3 H, d, $C{=}OCHCH_3CHOHR$, *J* = 7.1 Hz), 1.23 (3H, s, $RCOCCH_3CH_3COO$), 1.24 (3 H, s, $RCOCCH_3CH_3COO$), 1.55–1.59 (2 H, m, $RCHHOCH_2CHOMeR$), 2.65–2.72 (1 H, m, $C{=}OCHCH_3CHOHR$), 3.07–3.10 (1 H, m, $PMBOCH_2CHCH_3R$), 3.29 (1 H, br s, OH), 3.37 (3 H, s, CH_3OR), 3.51 (3 H, s, $RCH_2CHOCH_3CO_2R$), 3.51–3.56 (2 H, m, $CH_3OCH_2CH_2OR$), 3.62–3.77 (4 H, m, $CH_3OCH_2CH_2OR$ + $PMBOCH_2R$), 3.78 (3 H, s, CH_3OAr), 3.84–3.88 (1 H, m, RC*H*OMeR), 3.93 (1 H, d, RC*H*OMEM, *J* = 4.3 Hz), 3.98–4.02 (1 H, m, $C{=}OCHCH_3CHOHR$), 4.35–4.40 (1 H, m, $R_2CHOCOR$), 4.69 (1 H, d, OCH_aH_bO, *J* = 6.9 Hz), 4.76 (1 H, d, OCH_aH_bO, *J* = 6.9 Hz), 4.81 (2 H, s, $MeOArCH_2OR$), 6.84 (2 H, d, ArH, *J* = 8.6 Hz), 7.18 (2 H, d, ArH, *J* = 8.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 13.9, 18.9, 23.2, 35.1, 44.6, 45.2, 53.4, 55.2, 59.0, 67.4, 68.5, 69.1, 71.8, 72.2, 73.0, 75.9, 83.1, 83.5, 97.1, 113.7, 129.3, 129.7, 159.2, 180.0, 217.2.

HRMS: *m*/*z* calcd for $C_{28}H_{44}O_{10}$+ Na: 563.2841; found: 563.2832 ($M + Na^+$).

(4*R*,5*R*)-5-{(1*S*)-2-[(4*R*,5*R*,6*S*)-2-Ethyl-6-{(1*R*)-2-[(4-Methoxybenzyl)oxy-1-methylethyl]-5-methyl-1,3,2-dioxaborinan-4-yl}-1-methoxyethyl]}-4-[(methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (19)

The aldol adduct **18b** (42 mg, 0.078 mmol) was dissolved in THF–MeOH (0.7 + 0.1 mL) under argon in a flame-dried flask and the mixture was cooled in an acetone/dry ice bath (–78 °C). Then Et_2BOMe (1 M in THF, 0.156 mmol, 0.156 mL) was added dropwise and the mixture was stirred for 1 h 10 min (–70 to –78 °C) before the addition of $NaBH_4$ (3 mg, 0.086 mmol). After 2 h 50 min (–65 to –78 °C) the reaction was quenched with H_2O and the mixture was extracted with EtOAc (4 ×). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated to give 42 mg of crude product. After purification by flash chromatography, 16 mg of the *syn* boron diol adduct **19** was obtained; R_f = 0.41 (70% EtOAc–hexane, PMA stain); $[\alpha]_D$ +7.7 (*c* = 1.0, $CHCl_3$).

IR (film): 1778 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.60 (2 H, q, CH_3CH_2BR, *J* = 8.0 Hz), 0.80 (3 H, d, $PMBOCH_2CHCH_3R$, *J* = 6.8 Hz), 0.84 [3 H, d, $CHCH_3(CHOBR)_2$, *J* = 6.6 Hz], 0.86 (3 H, t, CH_3CH_2BR, *J* = 8.0 Hz), 1.26 (3 H, s, $RCOCCH_3CH_3COO$), 1.27 (3 H, s, $RCOCCH_3CH_3COO$), 1.45–1.55 [2 H, m, $CH_aH_bCHOMeR$ + $R_2CHCH_3(CHOBR)_2$], 1.74 (1 H, dt, $CH_aH_bCHOMeR$, *J* = 10.6, 2.4 Hz), 2.08 (1 H, q, $PMBOCH_2CHCH_3R$, *J* = 6.3 Hz), 3.36 (3 H, s, CH_3OR), 3.33–3.38 (1 H, m, $PMBOCH_aH_bR$), 3.47–3.51 (2 H, m, $PMBOCH_aH_bR$ + $CH_3OCH_aH_bCH_2OR$), 3.57 (3 H, s, $RCH_2CHOCH_3CO_2R$), 3.59 (1 H, t, $CH_3OCH_aH_bCH_2OR$, *J* = 8.9 Hz), 3.63 (1 H, ddd, $CH_3OCH_2CHCH_aH_bOR$, *J* = 3.2, 6.4, 11.1 Hz), 3.80 (3 H, s, CH_3OAr), 3.85–3.90 (3 H, m, $RBOCHCHMeCHOBR$ + $CH_3OCH_2CH_aH_bOR$), 3.97 (1 H, d, RC*H*OMEM, *J* = 4.1 Hz), 4.02 (1 H, dt, RC*H*OMeR, *J* = 8.1, 2.4 Hz), 4.38 (1 H, dd, $R_2CHOCOR$, *J* = 8.1 4.1 Hz), 4.74 (1 H, d, OCH_aH_bO, *J* = 7.4 Hz), 4.78 (1 H, d, OCH_aH_bO, *J* = 7.4 Hz), 4.81 (2 H, s, $MeOArCH_2OR$), 6.88 (2 H, d, ArH, *J* = 8.6 Hz), 7.27 (2 H, d, ArH, *J* = 8.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.8, 8.8, 12.5, 19.0, 23.2, 25.6, 34.5, 35.9, 37.9, 45.4, 55.3, 59.1, 60.5, 68.5, 71.8, 72.0, 72.6, 72.8, 75.0, 75.3, 82.7, 84.0, 96.8, 113.8, 129.1, 130.8, 159.1, 180.0.

HRMS: *m*/*z* calcd for $C_{30}H_{49}BO_{10}$ + Na: 603.3316; found: 603.3317 ($M + Na^+$).

(4*R*,5*R*)-5-{(1*S*,3*R*,4*R*,5*S*,6*R*)-3,5-Dihydroxy-1-methoxy-7-[(4-methoxybenzyl)oxy]-4,6-dimethylheptyl}-4-[(2-methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (20)

The boron diol adduct **19** (15 mg, 0.026 mmol) and pinacol (31 mg, 0.26 mmol) were dissolved in MeOH (1 mL) and the mixture was stirred at 40 °C over the weekend. Then CH_2Cl_2 was added, the organic phase was washed with H_2O, dried (Na_2SO_4), filtered and the solvent was evaporated to give 16 mg of crude product which, according to TLC, contained the starting material, pinacol and the free diol. After purification by flash chromatography (silica gel, 60% EtOAc–hexane) 4 mg of the desired free diol **20** and 8 mg of a mixture of starting material and pinacol were obtained.

20

R_f = 0.10 (60% EtOAc–hexane, PMA stain); $[\alpha]_D$ +5.0 (*c* = 0.2, $CHCl_3$).

IR (film): 1777, 3436 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.77 (3 H, d, CHOHCH-C*H*$_3$CHOH, *J* = 6.9 Hz), 0.98 (3 H, d, PMBOCH$_2$CHC*H*$_3$R, *J* = 7.0 Hz), 1.26 (3 H, s, RCOCC*H*$_3$CH$_3$COO), 1.27 (3 H, s, RCOCCH$_3$C*H*$_3$COO), 1.58–1.74 (3 H, m, CHOHC*H*CH$_3$CHOH + RCHHOC*H*$_2$CHOMeR), 1.92–1.96 (1 H, m, PMBOCH$_2$C*H*CH$_3$R), 3.39 (3 H, s, C*H*$_3$OR), 3.51–3.59 (4 H, m, PMBOC*H*$_2$R + CH$_3$OC*H*$_2$CH$_2$OR), 3.59 (3 H, s, RCH$_2$CHOC*H*$_3$COOR), 3.64 (1 H, m, CH$_3$OCH$_2$C*H*$_a$H$_b$OR), 3.80 (1 H, d, CHCH$_3$C*H*OHCHCH$_3$, *J* = 8.5 Hz), 3.82 (3 H, s, C*H*$_3$OAr), 3.91–4.0 (4 H, m, C*H*OHCH$_2$C*H*OMeR$_2$ + CH$_3$OCH$_2$CH$_a$*H*$_b$OR + MEMOC*H*R$_2$), 3.97 (1 H, d, RC*H*OMEM, *J* = 4.0 Hz), 4.44 (1 H, dd, R$_2$C*H*OCOR, *J* = 8.2, 4.0 Hz), 4.46 (2 H, s, OMeArC*H*$_2$OR), 4.71 (1 H, d, OC*H*$_a$H$_b$O, *J* = 6.9 Hz), 4.81 (1 H, d, OCH$_a$*H*$_b$O, *J* = 6.9 Hz), 6.89 (2 H, d, ArH, *J* = 8.6 Hz), 7.26 (2 H, d, ArH, *J* = 8.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.3, 12.6, 18.4, 18.9, 23.1, 35.0, 35.3, 41.4, 45.4, 55.3, 58.5, 59.0, 60.3, 68.5, 71.9, 72.1, 73.2, 75.5, 83.3, 83.8, 97.1, 113.9, 129.3, 130.0, 159.3, 180.1.

HRMS: *m*/*z* calcd for $C_{28}H_{46}O_{10}$+ Na: 565.2989; found: 565.2985 ($M + Na^+$).

(4*R*,5*R*)-5-{(1*S*,3*R*,4*R*)-3-Hydroxy-1-methoxy-4-[(4*S*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]pentyl}-4-[(2-methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (21)

To a solution of diol **20** (3 mg, 0.0055 mmol) in CH_2Cl_2 (0.2 mL) was added 4 Å MS-powder (3 mg). DDQ (3 mg, 0.013 mmol) was added and the mixture was stirred at r.t. for 1 h. Then Et_2O was added and the organic phase was washed with aq sat. $NaHCO_3$ (3 ×) dried (Na_2SO_4), filtered and the solvent was evaporated to give 3 mg of the crude acetal **21** as the desired product; R_f = 0.18 (60% EtOAc–hexane, PMA stain); $[\alpha]_D$ +13.5 (*c* = 0.2, $CHCl_3$).

IR (film): 1776 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (3 H, d, PMPCHOCH$_2$-CHC*H*$_3$R, *J* = 6.9 Hz), 1.20 (3 H, d, PMPCHOCHCHC*H*$_3$CHOH, *J* = 6.8 Hz), 1.25 (6 H, s, RCOCC*H*$_3$C*H*$_3$COO), 1.62–1.74 (3 H, m, RC*H*CH$_3$CHOHC*H*$_2$CHOMeR), 1.94 (1 H, m, PMPCHOCH$_2$-C*H*CH$_3$R), 3.39 (3 H, s, C*H*$_3$OR), 3.49–3.60 (3 H, m, CH$_3$C*H*$_2$C*H*$_a$H$_b$O), 3.54 (3 H, s, RCH$_2$CHOC*H*$_3$COOR), 3.72 (1 H, d, RC*H*OMEM, *J* = 3.9 Hz), 3.80 (3 H, s, C*H*$_3$OAr), 3.83–3.92 (3 H, m, PMPC*H*OCHCHCH$_3$CHOH + RC*H*OMeR + CH$_3$CH$_2$-CH$_a$*H*$_b$O), 4.02 (1 H, dd, PMPCHOC*H*$_a$H$_b$CHCH$_3$, *J* = 11.1, 1.3 Hz), 4.08 (1 H, dd , PMPCHOCH$_a$*H*$_b$CHCH$_3$, *J* = 11.1, 2.0 Hz), 4.10–4.14 (1 H, m, CHCH$_3$C*H*OHCH$_2$), 4.43 (1 H, dd, R$_2$C*H*OCOR, *J* = 8.4, 3.9 Hz), 4.57 (1 H, d, OC*H*$_a$H$_b$O, *J* = 7.2 Hz), 4.72 (1 H, d, OCH$_a$*H*$_b$O, *J* = 7.2 Hz), 5.51 [1 H, s, MeOArC*H*(OR)$_2$)] 6.88 (2 H, d, ArH, *J* = 8.8 Hz), 7.41 (2 H, d, ArH, *J* = 8.8 Hz).

HRMS: *m*/*z* calcd for $C_{28}H_{44}O_{10}$+ Na: 563.2832; found: 563.2823 ($M + Na^+$).

(4*R*,5*R*)-5-[(1*S*)-2-{(4*R*,5*R*,6*S*)-6-[(1*R*)-2-Hydroxy-1-methylethyl]-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl}-1-methoxyethyl]-4-[(2-methoxyethoxy)methoxy]-3,3-dimethyldihydrofuran-2(3*H*)-one (22)

R_f = 0.06 (60% EtOAc–hexane).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (3 H, d, PMPCHOCHC*H*$_3$R, *J* = 6.6 Hz), 1.06 (3 H, d, RC*H*$_3$CHOH, *J* = 7.0 Hz), 1.27 (6 H, s, RCOCC*H*$_3$C*H*$_3$COO), 1.69–1.83 (3 H, m, RCHCH$_3$C*H*OR-C*H*$_2$CHOMeR), 2.05 (1 H, m, HOCH$_2$C*H*CH$_3$R), 3.24, (1 H, t, OH, *J* = 4.4 Hz), 3.33 (s, 3 H, C*H*$_3$OR), 3.40–3.47 (2 H, m, CH$_3$OC*H*$_2$CH$_2$O), 3.55–3.61 (1 H, m, CH$_3$OCH$_2$C*H*$_a$H$_b$O), 3.59 (3 H, s, RCH$_2$CHOC*H*$_3$CO$_2$R), 3.73–3.97 (6 H, m, RC*H*OR-CHCH$_3$C*H*OR + CH$_3$OCH$_2$CH$_a$*H*$_b$O + HOC*H*$_2$CHCH$_3$R + CH$_2$C*H*OMeROR), 3.83 (3 H, s, C*H*$_3$OAr), 3.94 (1 H, d, MEMOC*H*R$_2$, *J* = 4.0 Hz), 4.38 (1 H, dd, R$_2$C*H*OCOR, *J* = 8.4, 4.0 Hz), 4.66 (1 H, d, OC*H*$_a$H$_b$O, *J* = 7.5 Hz), 4.71 (1 H, d, OCH$_a$*H*$_b$O, *J* = 7.5 Hz), 5.60 [1 H, s, MeOArC*H*(OR)$_2$], 6.89 (2 H, d, ArH, *J* = 8.8 Hz), 7.34 (2 H, d, ArH, *J* = 8.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 11.6, 18.9, 22.9, 34.3, 35.6, 45.6, 55.3, 59.0, 60.6, 66.8, 68.6, 71.8, 74.9, 77.2, 77.5, 82.9, 83.5, 84.1, 96.9, 99.8, 113.5, 126.9, 131.3, 159.7, 179.9.

Acknowledgment

We are grateful to professor Kari Rissanen, University of Jyväskylä, Finland, for the X-ray analysis, and Dr. Petri Pihko for helpful discussions. This project has been funded by a grant from the Finnish Academy.

References

(1) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 2780.
(2) Sheppeck, J. E. II; Gauss, C.-M.; Chamberlin, A. R. *Bioorg. Med. Chem.* **1997**, *5*, 1739.
(3) Bridges, A. J. *Chemtracts: Org. Chem.* **1995**, *8*, 73.
(4) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(5) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073.
(6) The separation of lactone or its derivatives (acetylated or benzylated lactone) were not successful with HPLC, but after methylation and reduction, the enantiomers of **12** were separable (Daicel AS column, 10% IPA–hexane, 0.5 mL/min, λ = 254 nm, retention times: 29 min and 39 min) and the ee was checked at this point.
(7) Chen, K.-M.; Hardtmann, G.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(8) Data collection with Enraf-Nonius kappa-CCD at 173.0(1) K, MoK_α radiation, λ = 0.71073 Å, triclinic, space group *P*-1, with *a* = 6.1216(4), *b* = 8.7954(8), *c* = 14.7365(14) Å, α = 100.224(3)°, β = 99.362(4)°, γ = 91.071(7)°, V = 769.52(11) Å^3, Z = 2, 278 parameters, *R*1 = 0.0405, *wR*2 = 0.0838. CCDC 212408 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21 EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).
(9) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(10) Fenzl, W.; Köster, R. *Liebigs Ann. Chem.* **1975**, 1322.
(11) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073. (b) Evans, D. A.; Ng, H. P.; Clarke, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.

(12) (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (c) Paterson, I.; Nowak, T. *Tetrahedron Lett.* **1996**, *37*, 8243. (d) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811.
(13) Clizbe, L. A.; Overman, L. E. *Org. Synth.* **1978**, *58*, 4.
(14) A similar rearrangement of a ketal to a more stable one occurred in the total synthesis of calyculin A: Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673.
(15) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.