Studies on C18–C20 Aldol Couplings of Rhizopodin

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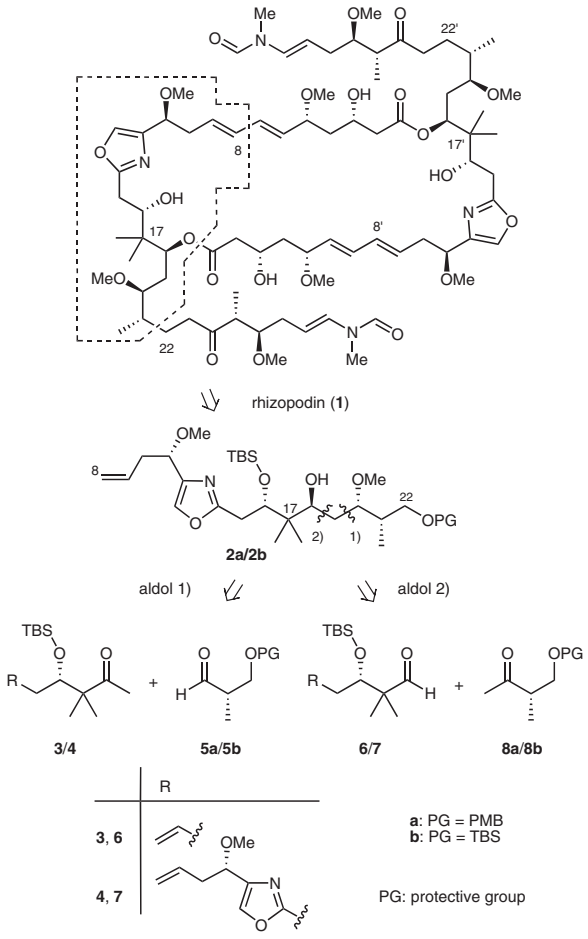
Received: 09.04.2013; Accepted after revision: 17.05.2013

Abstract: The aldol addition of an enol(ate) to a carbonyl compound is one of the most powerful and versatile C–C bond forming reactions. In complex target synthesis the coupling of two chiral partners may complicate the stereochemical outcome by multiple stereoinductions. Here, we report studies on pivotal aldol couplings employed in the rhizopodin synthesis, detailing the various directing effects exerted by the stereogenic centers present in this sterically hindered connection.

Key words: natural products, aldol reaction, asymmetric synthesis, methyl ketone, Felkin product

Myxobacteria are an extremely proliferative source of novel polyketides and an impressive number of structurally unique and biosynthetically diverse representatives have been reported from these soil-living organisms, in particular by the pioneering work of Höfle and Reichenbach.[1] In 1993 they reported rhizopodin as the main metabolite from *Myxococcus stipitatus* (strain Mx f164).[2,3] Being originally considered to be monomeric, the structure was more recently revised to be a C_2-symmetric dimer (**1**), as shown in Scheme 1.[4] The full configuration was independently assigned in our group by extensive NMR studies in combination with modeling and chemical derivatization[5] and in the group of Schubert by an X-ray structure analysis of actin-bound rhizopodin.[6] The unique architecture of rhizopodin is characterized by a 38-membered macrolide ring with two conjugated diene systems and two disubstituted oxazole systems in combination with two enamide side chains and contains in total 18 stereogenic centers.

Rhizopodin presents a highly potent antiproliferative agent that inhibits the growth of various cancer cell lines in low nanomolar concentrations.[2] This potency has been attributed to its ability to disrupt actin cytoskeleton formation by binding specifically to a few critical sites of G-actin.[7] The important biological properties and its natural scarcity, coupled with its intriguing molecular architecture have attracted high interest from the synthetic community[8] and so far two total syntheses have been accomplished by our group and by Paterson et al.[9] A concise preparative approach to the central C8–C22 subunit **2** proved to be particularly challenging. To enable convergent access to this key fragment, our synthetic plan relied on pivotal aldol reactions[10] to set the C18–C20 segment, either by a coupling along the C19–C20 bond (aldol coupling 1) or along the C18–C19 bond (aldol coupling 2), by union of aldehyde **5** with ketones **3/4** or ketone **8** with aldehydes **6/7**, respectively. Herein, we report in detail the subtle stereoselective contributions of the various stereogenic centers of the methyl ketones and aldehydes in these pivotal aldol reactions under various enolization conditions with different protective groups. This fundamental study enabled high-yielding access to the central C8–C22 fragment **2** of rhizopodin.



Scheme 1 Pivotal C18–C20 aldol couplings in the synthesis of rhizopodin

SYNTHESIS 2013, 45, 2305–2315
Advanced online publication: 12.07.2013
DOI: 10.1055/s-0033-1338493; Art ID: SS-2013-T0198-OP
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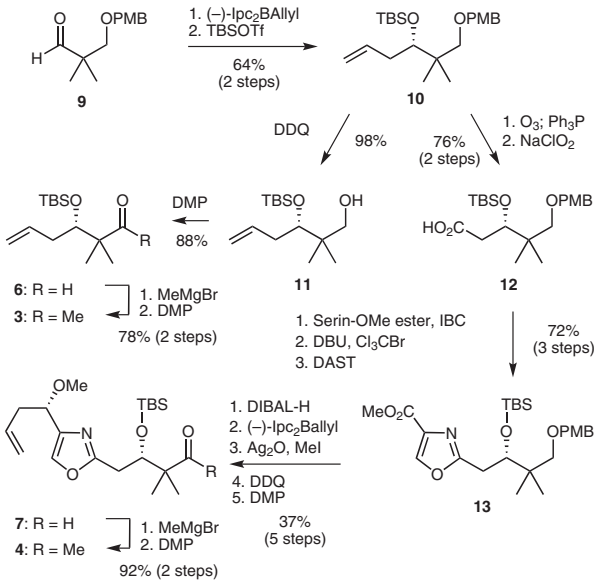
As shown in Scheme 2, a joint synthesis of the required ketones (**3** and **4**) and aldehydes (**6** and **7**) was effected by a late-stage diversification strategy starting from readily available aldehyde **9**.[11,12] Brown allylation[13] and protection of the newly generated alcohol as a TBS ether gave homoallylic ether **10**, which was further derivatized to either primary alcohol **11** by deprotection of the PMB group or acid **12** by oxidative cleavage of the double bond. Oxidation of **11** then gave the target aldehyde **6**, which was transformed into methyl ketone **3** through a two-step sequence (addition of MeMgBr and oxidation). Acid **12**, in turn, was condensed with serine methyl ester to oxazole **13**, which was then transformed into aldehyde **7** in a five-step sequence, involving reduction of the terminal ester to the aldehyde, asymmetric Brown allylation, methylation of the newly generated alcohol, PMB deprotection, and subsequent oxidation of the terminal alcohol. The corresponding methyl ketone **4** was obtained in an analogous sequence as before.



Scheme 2 Joint synthesis of required ketones **3** and **4** and aldehydes **6** and **7**

Having established an efficient route to the required building blocks, we first turned our attention to aldol coupling of type 1 and studied the union of methyl ketones **3**/**4** with aldehydes **5a**/**5b** bearing different protective groups (Table 1). As shown in Figure 1, a Felkin–Anh induction exerted by the aldehyde was expected to favor the desired 1,2′-*syn* product **16**. In contrast, high 1,5-*anti* inductions in the coupling of methyl ketones have been observed in boron and alkali-metal-mediated aldol couplings.[14] According to a model developed by Goodman,[15] this selectivity may be rationalized by a boat-type transition state involving an H-bond between the formyl-H of the aldehyde and the β-alkoxy substituent of the ketone. In agreement with this model, substituents favoring such a coordination (e.g., PMB, Bn, MOM) led to high selectivities, while only a moderate or no selectivity has been observed with bulky silyl groups and, in one case, a high 1,5-*syn* selectivity which would also be required here was reported for a substrate with a β-OTBS-substituent.[16] Consequently, a TBS protective group was chosen for the β-alkoxy-substituent of the methyl ketones studied herein (**3**/**4**).

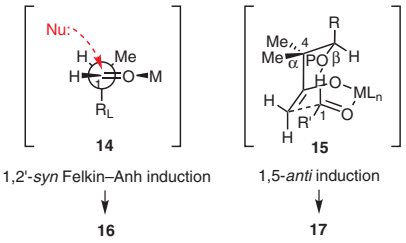


Figure 1 Transitions states for aldol couplings of type 1

As shown in Table 1 for selected examples, a variety of reaction conditions with various metal counter ions and bases were evaluated. However, in all cases, either the undesired isomer **17** was obtained preferentially or no selectivity was observed. This unfavorable facial bias could also not be overturned by the use of chiral Ipc ligands (entries 4 and 5) or by using Mukaiyama type conditions.[17] Similar results were obtained with the simplified ketone **3** as well as with the more elaborate analogue **4**. In addition, yields remained low in all cases, presumably due to the high steric hindrance exerted by the neopentylic center of the methyl ketone.

Faced with these unpromising results, we turned our attention to an inversion of the coupling partners and studied the coupling of aldehydes **6**/**7** with methyl ketones **8a**/**8b**, giving the two possible aldol products **18** and **19**. As shown in Table 2 for selected reactions with simplified aldehyde **6**,[18] a strong facial bias towards the undesired product **19** was again observed. This preference could again not be overturned by the use of chiral Ipc ligands (entries 4 and 5). Only Mukaiyama type aldol couplings enabled preferential formation of the desired epimer **18** (entry 6). However, very low conversion was observed, which could not be further increased. In general, the observed yields remained initially moderate under conventional conditions, again presumably due to the high steric hindrance exerted by the geminal dimethyl-substituents of the aldehyde. However, in contrast to the studies described above, higher degrees of conversion could be obtained by modification of the reaction conditions (entry 7), which could be further optimized (Table 4).

As shown in Figure 2, this inherent facial bias towards **19** may be explained by a 1,4-*syn* induction exerted by the methyl ketone. In analogy to the model developed by Goodman,[14] this selectivity may result from either formation of a hydrogen bond between the β-alkoxy-substituent and the formyl hydrogen in a similar fashion to that described above, or a coordination of the metal center with this β-substituent, as schematically shown for structures **20** and **21**. This facial bias could not be reversed by using

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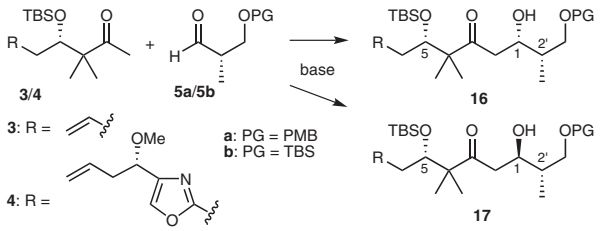
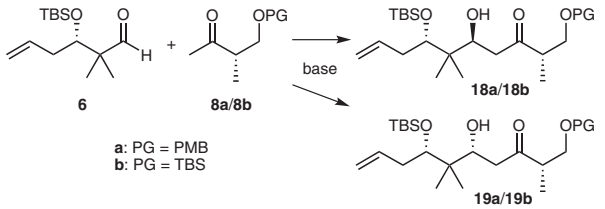
Table 1 Aldol Couplings of Ketones **3**/**4** with Aldehydes **6a**/**6b**



Entry	Ketone	PG	Conditions	Solvent	dr **16**/**17**	Yield (%)
1	**3**	PMB	LiHMDS, –78 °C	THF	1:1.6	36
2	**3**	PMB	NaHMDS, –78 °C	THF	1:1.6	17
3	**3**	PMB	KHMDS, –78 °C	THF	1:1.6	19
4	**3**	TBS	(+)-Ipc$_2$BCl, Et$_3$N, –78 to –20 °C	Et$_2$O	1.1.7	23
5	**3**	TBS	(–)-Ipc$_2$BCl, Et$_3$N, –78 to –20 °C	THF	1:1.2	12
6	**4**	PMB	LiHMDS, –78 °C	THF	1:2.0	25
7	**4**	PMB	NaHMDS, –40 °C	THF	1:1.3	33
8	**4**	TBS	(+)-Ipc$_2$BCl, Et$_3$N, –78 to –20 °C	Et$_2$O	1:2.6	5
9	**4**	PMB	TMS-OTf, Et$_3$N, BF$_3$, –78 °C	CH$_2$Cl$_2$	1:1	23
10	**4**	PMB	TBS-OTf, Et$_3$N, BF$_3$, –78 °C	CH$_2$Cl$_2$	1:1	6

Table 2 Aldol Couplings of Ketones **8a**/**8b** with Aldehyde **6**



Entry	PG	Conditions	Solvent	dr **18**/**19**	Yield (%)
1	PMB	LiHMDS, –78 °C	THF	1:2.4	83
2	PMB	NaHMDS, –78 °C	THF	1:2.4	58
3	PMB	KHMDS, –78 °C	THF	1:2.6	43
4	PMB	(+)-Ipc$_2$BCl, Et$_3$N, –78 to –20 °C	Et$_2$O	1:5.8	81
5	PMB	(–)-Ipc$_2$BCl, Et$_3$N, –78 to –20 °C	Et$_2$O	1:2.4	59
6	PMB	TMS-OTf, Et$_3$N, BF$_3$, –78 °C	CH$_2$Cl$_2$	2.2:1	5
7	TBS	LiHMDS, –78 °C	THF	1:1	45

a voluminous non-coordinating β-alkoxy substituent (Table 2, entry 7), which may favor an alternative, more open transition state of type **22** and then give the desired 1,4-*anti* product **18**, based on minimization of allylic strain. The β-alkoxy substituent of the aldehyde was, in turn, expected to exert a 1,3-*anti* induction, which may be explained by either the polar Evans model (**23**)[19] or the Reetz–Cram model (**24**),[20] leading to the desired epimer **18** (Figure 2). Based on the results shown in Table 2, this influence appeared to be overturned by the strong stereochemical influence exerted by the ketone.

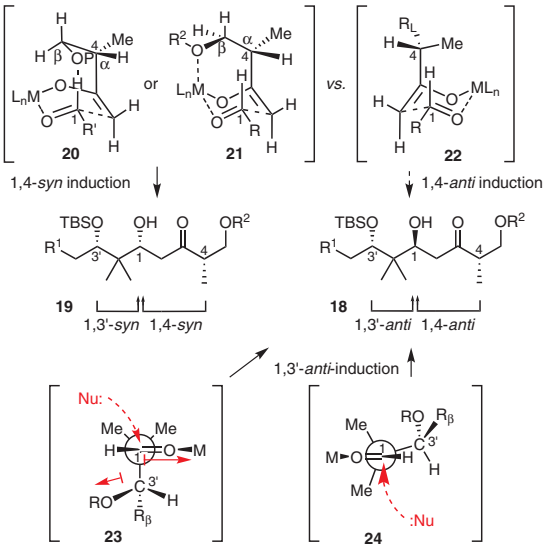


Figure 2 Possible transitions states for aldol couplings given in Table 2

To further analyze the respective contributions induced by the α-stereogenic center of the methyl ketone as well as the geminal dimethyl groups of the chiral aldehyde on the stereochemical outcome of this reaction, the coupling of methyl ketones **8a**/**8b** with simplified aldehydes **25** and **28** was studied (Scheme 3, Table 3). Comparison of the respective couplings presented in Table 2, entries 4 and 5 with the corresponding results in Scheme 3 suggest that the geminal dimethyl center decreases the inherent 1,3′-*anti* induction of the aldehyde. Furthermore, inversion of the stereochemistry at the β-center of the aldehyde led to increased diastereoselectivity towards **30** (Table 3, entry 1) based on a matched stereoinduction of the methyl ketone and the aldehyde, in agreement with our stereochemical model (Figure 2). The 1,3′-*anti* induction was confirmed in an analogous addition of a methyl ketone lacking the α-stereogenic center (entries 5 and 6).

In summary, these results suggest that the stereochemical outcome of the aldol coupling of type 2 is mainly governed by a 1,4-*syn* induction exerted by the ketone, and overrides an opposing stereochemical influence of the aldehyde from the β-substituent. Notably, the observed 1,4-*syn* selectivity could not be overcome by suitable choice of protective groups on either the aldehyde or ketone or by suitable enolization conditions. We therefore decided to

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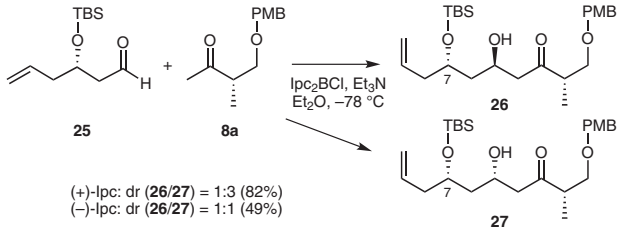
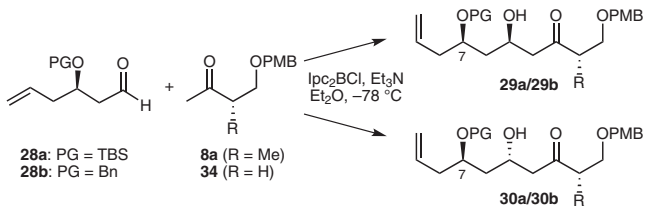


Scheme 3 Coupling of ketone **8a** with simplified aldehyde **25**

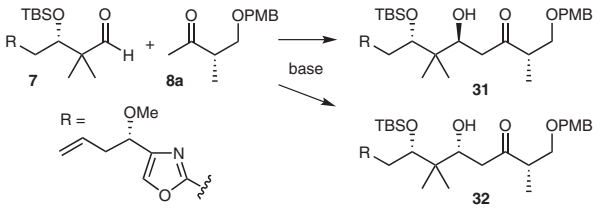
Table 3 Aldol Couplings of Ketones **8a**/**34** with Simplified Aldehydes **28a**/**28b**



Entry	PG	R	Ipc	dr **29**/**30**	Yield (%)[a]
1	TBS	Me	(+)-Ipc	1:10	85
2	TBS	Me	(–)-Ipc	1:2.5	43
3	Bn	Me	(+)-Ipc	1:19	95
4	Bn	Me	(–)-Ipc	1:6	95
5	TBS	H	(+)-Ipc	1:3	68
6	TBS	H	(–)-Ipc	1:2	66

[a] Yields estimated from the corresponding domino aldol/reduction process. See also Dieckmann and Menche.[8h]

Table 4 Aldol Couplings of Ketones **8a** with Aldehyde **7**



Entry	**8a** (equiv)	Conditions	Solvent	*dr* **31**/**32**	Yield (%)
1	1.3	(+)Ipc_2BCl, Et_3N, –78 to –20 °C, 20 h	Et_2O	1:4.0	17
2	1.3	(+)Ipc_2BCl, Et_3N, –78 to 25 °C, 20 h	Et_2O	1:4.8	95[a]
3	1.7	LiHMDS, –78 °C, 30 min	THF	1:2.5	60
4	1.7	LiHMDS, –40 °C, 30 min	THF	1:1.7	66
5	2.5	LiHMDS, –30 °C, 30 min	THF	1:2.1	50
6	1.3	LiHMDS, –40 °C, 40 min	THF	1:1.7	95
7	1.7	LiHMDS, –40 °C, 30 min	DMF	1:1.1	16
8	1.7	LiHMDS, –78 °C, 40 min	DMF–THF (3:1)	1:1.1	19

[a] The intermediate aldol product **32** was converted into the corresponding 1,3-*anti* diol under these conditions. See also Dieckmann and Menche.[8h]

optimize the chemical yield of aldol coupling of type 2 and correct the stereochemistry of the undesired epimer at a subsequent stage of the synthesis (see below). Notably, the resulting aldol products could be readily separated by HPLC.

Based on previous results, boron and lithium mediated aldol couplings were studied in more detail, as shown in Table 4. As shown, longer reaction times in the evaluated lithium-aldol reactions led to increased yields (entry 3) and only very low degrees of retro-aldol or elimination processes were observed. In detail, methyl ketone **8a** was treated at –78 °C in THF with equimolar amounts of LiHMDS and, after two hours, aldehyde **7** was added. It was shown that the ratio of the two resulting epimers could be influenced by the type of solvent and the reaction temperature. Improved selectivities were obtained in *N*,*N*-dimethylformamide (DMF; entries 7 and 8), resulting in a 1:1.1 diastereomeric ratio, albeit in only low yields which could not be further increased by using an excess of methyl ketone (entry 5). In a similar fashion, modified selectivities were also observed in THF by increasing the reaction temperature to –40 °C (entries 3 and 4), whereas higher reaction temperatures as well as the use of an excess of base lead to decreased yields. Very good yields could only be reproducibly obtained with a slight excess of methyl ketone and base (1.3 equivalents each) and a prolonged reaction time of 40 minutes (entry 6).

Due to the excellent yields and the relatively facile separation of the two diastereomers, this aldol coupling was selected for the synthesis of the desired C8–C22 fragment **2**. The reaction proved to be easily scalable and several grams of both isomers **31** and **32** were readily available after separation. For conversion of aldol product **31** into building block **2a**, the β-hydroxy-ketone was stereoselectively reduced in a 1,3-*anti* fashion with $NMe_4HB(OAc)_3$ in acetonitrile/THF/acetic acid according to the Evans–Carreira protocol (dr > 19:1),[21] whereas a similar alternative using the Evans–Tishchenko protocol[22] proved to be less reliable. The resulting diol could then be regioselectively methylated with sodium hydride and methyl iodide.[23] Minor amounts of the regioisomeric C18–OMe ether could be readily removed by chromatography. Selectivity could be controlled by the reaction temperature and time, and optimum results were obtained at 10 °C (80%, selectivity 8:1).[24]

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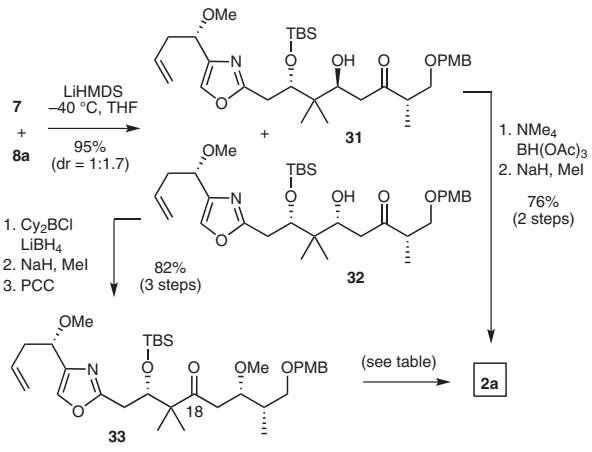

'H-'	yield (dr **2a**:18-*epi*-**2a**)
$NaBH_4$, r.t.	n.c.
DIBAl-H, –78 °C	n.c.
R-Me-CBS, BH_3, 0 °C to r.t.	n.c.
LAH, –20 °C	50% (1.3:1)
LAH, –90 °C	80% (8.0:1)
Red-Al, –78 °C	10% (1:2.5)

n.c.: no conversion

Scheme 4

Conversion of the epimeric aldol product **32** into **2a** was, in turn, effected by an oxidation/reduction sequence.[25] The conversion was initiated by a 1,3-*syn* reduction of sterically hindered β-hydroxy-ketone, which was efficiently effected by initial chelation with dicyclohexylboron chloride/Et_3N and subsequent treatment with $LiBH_4$ at –78 °C, resulting in high selectivities (dr > 19:1). To obtain high yields (95%) it was crucial to treat the crude product with 3 M $NaOH/H_2O_2$ for prolonged times (1.5 h) to secure complete cleavage of the intermediate boronate. Selective methylation was again effected by treatment with NaH/MeI under slightly modified conditions. Considerable efforts were then necessary to enable efficient conversion into ketone **33**. After several low-yielding attempts with various oxidizing agents (e.g., 2-iodoxybenzoic acid, Swern), it was found that high conversion could be achieved with PCC in dichloromethane heated to reflux. To obtain high yields (97%) it proved beneficial to directly purify the reaction mixture after absorption on Celite by silica gel chromatography. As shown in Scheme 4, strong reducing agents (LAH, Red-Al) were then required to effect the required stereoselective reduction of sterically hindered ketone **33** to **2a**. High selectivities and yields were obtained with LAH at –90 °C (dr = 8:1, 80%). This sequence allowed the conversion of **32** into **2a** in 62% yield over these four steps. Together with the conversion of **31**, the aldol products could be converted into the desired fragment **2a** in 68% overall yield. In combination with the high yield in the aldol coupling, these results demonstrate the usefulness of this approach.

In summary, we have presented a detailed analysis of the subtle stereoselective contributions in sterically hindered C18–C20 aldol reactions of rhizopodin. Based on this fundamental study, a high-yielding aldol coupling along the C18–C19 bond could be effected by use of a lithium-mediated reaction. Both epimeric aldol products could be effectively transformed into the desired C8–C22 building block of rhizopodin in a diastereoconvergent fashion. These results add to a more general understanding of the subtle stereoselective effects in complex aldol reactions and will be beneficial for the applicability and predictability of such couplings in elaborate target synthesis.

NMR spectra were recorded in $CDCl_3$ with a Bruker AM 300, AM 400 or DMX-600 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) with the residual non-deuterated solvent as internal standard. Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} (Merck) analytical plates and visualized by fluorescence quenching under UV light. Mass spectra were obtained with a Finnigan MAT 95 spectrometer, high-resolution data were acquired using peak matching (M/DM = 10000).

(*S*)-*tert*-Butyl[1-(4-methoxybenzyloxy)-2,2-dimethylhex-5-en-3-yloxy]dimethylsilane (10)

Allylmagnesium bromide (1.0 M in Et_2O, 10.7 g, 74.4 mL, 74.4 mmol, 1.9 equiv) was added dropwise to a stirred solution of (–)-$(ipc)_2$BOMe (24.8 g, 78.0 mmol, 2.0 equiv) in Et_2O (72 mL) at 0 °C and stirred for 10 min at this temperature. The mixture was then stirred for 1 h at r.t., the suspension was centrifuged under argon and the solution was separated from the settled magnesium salts. The residue was washed with pentane. The combined organic phase was concentrated, dissolved in Et_2O (10 mL) and cooled to –98 °C (liq. N_2/MeOH). To this cooled solution of the allylborane, a solution of the corresponding aldehyde **9** (8.70 g, 39.0 mmol) in Et_2O (10 mL) was added dropwise and the mixture was stirred for 3 h at –98 °C. The reaction mixture was warmed to r.t., treated with 3 M NaOH (24 mL) and 30% H_2O_2 (48 mL) then stirred at r.t. for 90 min, then sat. aq $NaHCO_3$ (50 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 150 mL), *tert*-butyl methyl ether (2 × 100 mL), and EtOAc (2 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexanes–EtOAc, 9:1) to give the desired homoallylic alcohol as a colorless oil (7.33 g, 32.8 mmol, 71%).

R_f = 0.25 (hexanes–EtOAc, 9:1); ee = 92% (Mosher ester analysis); $[\alpha]_D^{20}$ –14.4 (*c* = 0.42, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 3.96, 6 H), 2.02–2.05 (m, 1 H), 2.24–2.26 (m, 1 H), 3.25 (d, *J* = 8.9 Hz, 1 H), 3.35 (d, *J* = 8.9 Hz, 1 H), 3.50 (dd, *J* = 10.3, 2.5 Hz, 1 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 5.02–5.07 (m, *J* = 10.2, 1.5 Hz, 1 H), 5.10 (dq, *J* = 10.2, 1.5 Hz, 1 H), 5.91 (ddt, *J* = 18.0, 9.0, 6.2 Hz, 1 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 7.2 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 22.7, 36.6, 38.4, 55.3, 73.27, 79.4, 113.85, 116.56, 129.19, 130.1, 136.87, 159.26.

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{24}O_3Na$: 287.1623; found: 287.1621.

A solution of homoallylic alcohol obtained as described above (1.30 g, 4.92 mmol, 1.0 equiv) in CH_2Cl_2 (13 mL) under an argon atmosphere was cooled to 0 °C and 2,6-lutidine (1.16 g, 1.26 mL, 10.8 mmol, 2.2 equiv) was added. After stirring for 5 min, TBSOTf (1.93 g, 1.69 mL, 7.30 mmol, 1.5 equiv) was added dropwise. The mixture was stirred for 30 min at this temperature and at r.t. for 1 h, then sat. aq $NaHCO_3$ (10 mL) was added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL) and the combined organic phase was dried over $MgSO_4$, filtrated and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (hexanes–EtOAc, 19:1) to give TBS-ether **10** as a colorless oil (1.67 g, 4.40 mmol, 90%).

R_f = 0.61 (hexanes–EtOAc, 19:1); $[\alpha]_D^{20}$ –0.4 (*c* = 0.79, $CHCl_3$).

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^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00–0.04 (m, 6 H), 0.86–0.90 (m, 15 H), 2.13–2.15 (m, 1 H), 2.33–2.36 (m, 1 H), 3.10 (d, *J* = 8.7 Hz, 1 H), 3.22 (d, *J* = 8.7 Hz, 1 H), 3.66–3–38 (m, 1 H), 3.80 (s, 3 H), 4.31–4.33 (m, 1 H), 4.41–4.43 (m, 1 H), 4.94–4.96 (m, 1 H), 4.99–5.03 (m, 1 H), 5.85–5.89 (m, 1 H), 6.86 (d, *J* = 9.2 Hz, 2 H), 7.23–7.25 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –2.91, –3.31, 21.17, 21.66, 25.73, 26.13, 38.04, 40.35, 55.29, 72.77, 75.86, 113.67, 115.56, 129.00, 131.10, 137.62, 159.00.

HRMS (ESI+): *m*/*z* calcd for $C_{22}H_{39}O_3Si$: 379.2668; found: 379.2663.

(*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2,2-dimethylhex-5-en-1-ol (11)

PMB-ether **10** (200 mg, 0.53 mmol, 1.0 equiv) was dissolved in a mixture of CH_2Cl_2 and pH 7 phosphate buffer (10:1, 22.0 mL). DDQ (0.26 g, 1.16 mmol, 2.2 equiv) was added and the reaction mixture was stirred for 40 min at 0 °C. After stirring for an additional 1 h at r.t., the reaction mixture became dark-red. The reaction was quenched by adding sat. aq $NaHCO_3$ (20 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The recombined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel; hexanes–EtOAc, 10:1) to give alcohol **11** (132 mg, 0.51 mmol, 98% yield) as a yellowish oil.

R_f = 0.58 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ –9.2 (*c* = 9.90, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.81 (s, 3 H), 0.90 (s, 9 H), 1.03 (s, 3 H), 2.26–2.33 (m, 1 H), 2.43–2.53 (m, 1 H), 2.71 (s, 1 H), 3.18 (d, *J* = 10.8 Hz, 1 H), 3.65 (d, *J* = 10.8 Hz, 1 H), 3.60–3.63 (m, 1 H), 5.00–5.05 (m, 1 H), 5.09–5.10 (m, 1 H), 5.90 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.5, –3.6, 18.1, 21.7, 23.7, 26.0, 38.2, 39.7, 70.2, 79.9, 116.4, 136.5.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{30}NaO_2Si$: 281.1913; found: 281.1907.

(*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2,2-dimethylhex-5-en-1-al (6)

Alcohol **11** (570 mg, 2.19 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (25 mL) and DMP (3.64 g, 8.58 mmol, 3.9 equiv) was added at r.t. After stirring for 3 h, the solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (hexane–EtOAc, 10:1). The desired aldehyde **6** (490 mg, 1.93 mmol, 88%) was obtained as a yellowish liquid.

R_f = 0.70 (hexanes–EtOAc, 10:1); $[\alpha]_D^{20}$ +12.1 (*c* = 1.1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 1.04 (s, 3 H), 1.07 (s, 3 H), 2.29–2.31 (m, 2 H), 3.85–3.87 (m, 1 H), 5.06–5.10 (m, 2 H), 5.74–5.79 (m, 1 H), 9.60 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.0, –4.0, 17.7, 18.9, 25.5, 38.0, 51.0, 75.7, 117.2, 134.8, 205.9.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{28}O_2Si$: 256.1756; found: 256.1759.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,3-dimethylhept-6-en-2-one (3)

A solution of aldehyde **6** (360 mg, 1.40 mmol, 1.0 equiv) was dissolved in Et_2O (20 mL) under an argon atmosphere and cooled to –78 °C before a solution of methylmagnesiumbromide (3 M in Et_2O, 335 mg, 0.9 mL, 2.81 mmol, 2 equiv) was slowly dropped into the solution. The mixture was stirred for 30 min at this temperature, then the reaction was quenched by addition of sat. aq ammonium chloride (12 mL). After warming to r.t., the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained alcohol (380 mg, 1.40 mmol) was directly used for the next step.

The alcohol (380 mg, 1.40 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (18 mL), and DMP (1.37 g, 3.22 mmol, 2.3 equiv) was added at 0 °C. After stirring for 2 h, the solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (hexane–EtOAc, 40:1). The desired methylketone **3** (300 mg, 1.10 mmol, 78%) was obtained as a colorless oil.

R_f = 0.51 (hexane–EtOAc, 10:1); $[\alpha]_D^{20}$ +14.6 (*c* = 0.9, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 1.10 (s, 3 H), 1.11 (s, 3 H), 2.15 (s, 3 H), 2.18–2.20 (m, 2 H), 3.95 (dd, *J* = 6.2, 4.9 Hz, 1 H), 5.01–5.05 (m, 2 H), 5.79 (dddd, *J* = 17.1, 10.1, 7.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.4, –3.6, 18.2, 20.3, 22.2, 26.0, 39.0, 53.2, 76.7, 116.8, 136.1, 213.7.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{30}O_2Si$: 256.1756; found: 256.1759.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-4,4-dimethylpentanoic Acid (12)

The corresponding terminal alkene **10** (221 mg, 0.58 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4.0 mL) and cooled to –78 °C. A stream of ozone was transmitted through this solution for ca. 2 min, then oxygen was transmitted through this solution for a few minutes, before Ph_3P (280 mg, 1.06 mmol, 1.8 equiv) was added. The resulting mixture was stirred for 2 h at r.t., before the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (hexanes–EtOAc, 9:1) to give the desired aldehyde (173 mg, 0.458 mmol, 78%) as a light-yellow oil.

R_f = 0.37 (hexanes–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.06 (s, 3 H), 0.84 (s, 3 H), 0.86 (s, 9 H), 0.90 (s, 3 H), 2.45 (ddd, *J* = 16.7, 5.2, 2.8 Hz, 1 H), 2.66 (ddd, *J* = 16.7, 5.5, 1.9 Hz, 1 H), 3.11 (d, *J* = 8.9 Hz, 1 H), 3.20 (d, *J* = 8.9 Hz, 1 H), 3.22 (s, 3 H), 4.20 (t, *J* = 5.3 Hz, 1 H), 4.30 (d, *J* = 11.7 Hz, 1 H), 4.38 (d, *J* = 11.7 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 9.76 (t, *J* = 1.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, –3.9, 18.2, 21.1, 21.6, 26.0, 39.9, 48.2, 55.3, 71.5, 72.7, 76.3, 113.7, 129.1, 130.7, 159.1, 202.3.

The aldehyde derived from ozonolysis (620 mg, 1.63 mmol, 1.0 equiv) was dissolved in *tert*-butanol (120 mL) and H_2O (30 mL). 2-Methyl-2-butene (13 mL, 130 mmol, 80 equiv), sodium dihydrogen phosphate (586 mg, 4.89 mmol, 6 equiv) and sodium chlorite (884 mg, 9.77 mmol, 3 equiv) were added and the mixture was stirred for 1.5 h at r.t. under an argon atmosphere. The solvent was removed in vacuo and the residue was dissolved in EtOAc (200 mL) and washed with brine (100 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL), dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (hexanes–EtOAc, 4:1) to give the desired acid **12** (635 mg, 1.60 mmol, 98%).

R_f = 0.3 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ –8.1 (*c* = 1.11, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (m, 6 H), 0.87 (m, 9 H), 0.9 (s, 6 H), 2.41 (m, 1 H), 2.67 (dd, *J* = 4.7, 16.4 Hz, 1 H), 3.17 (m, 2 H), 3.79 (s, 3 H), 4.11 (m, 1 H), 4.38 (m, 2 H), 6.59 (d, *J* = 8.7, 2 H), 7.23 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.2, –4.9, 18.2, 21.1, 21.4, 26.0, 38.3, 40.0, 55.3, 72.8, 73.6, 76.3, 113.7, 128.6, 129.1, 130.7, 159.1, 176.0.

HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{35}O_5Si$: 395.2254; found: 395.2245.

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(*S*)-Methyl 2-[2-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-3,3-dimethylbutyl]oxazole-4-carboxylate (13)

A solution of carboxylic acid **12** (40.4 mg, 0.10 mmol, 1.0 equiv) in THF (25 mL) under an argon atmosphere was cooled to –30 °C, and treated with NMM (24.6 mg, 24 μL, 0.21 mol, 2.1 equiv) and IBC (15.0 mg, 15 μL, 0.11 mmol, 1.1 equiv). The resulting mixture was stirred at this temperature for 30 min, before L-serine methyl ester hydrochloride (17.4 mg, 0.11 mmol, 1.1 equiv) was added as a solid. The reaction mixture was warmed to r.t. and stirred overnight, then the solvent was removed in vacuo, the residue was dissolved in EtOAc (50 mL), filtered and washed exhaustively with EtOAc, before the solution was dried ($MgSO_4$), filtered and the solvent was evaporated. The obtained crude product (50.6 mg, 0.10 mmol, 99%) was used without further purification for the next step.

The obtained amide (50.6 mg, 0.10 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.5 mL) under an argon atmosphere. The resulting solution was cooled to –78 °C before DAST (24.2 mg, 20 μL, 0.15 mmol, 1.5 equiv) was added slowly over 15 min. This mixture was stirred at –78 °C for 1.5 h, before being slowly poured into sat. aq $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). After drying the combined organic layer with $MgSO_4$ and filtering, the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 2:1) to give the oxazoline (36.0 mg, 73.0 μmol, 73%) as a light-yellow oil.

R_f = 0.41 (hexanes–EtOAc, 2:1); $[\alpha]_D^{20}$ +24.4 (*c* = 0.18, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 0.86 (s, 3 H), 0.90 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 1 H), 2.34 (ddd, *J* = 15.5, 6.1, 0.9 Hz, 1 H), 2.72 (ddd, *J* = 15.6, 5.1, 1.3 Hz, 1 H), 3.16 (d, *J* = 8.9 Hz, 1 H), 3.20 (d, *J* = 8.9 Hz, 1 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.37–4.39 (m, 4 H), 4.67 (dd, *J* = 10.7, 8.1 Hz, 1 H), 6.85 (d, *J* = 8.9 Hz, 2 H), 7.22 (d, *J* = 8.7 Hz, 2 H).

^{13}C (100 MHz, $CDCl_3$): δ = –4.7, –4.3, 1.1, 18.2, 21.2, 26.0, 33.1, 40.3, 52.6, 55.3, 68.2, 69.0, 72.7, 73.8, 76.5, 113.7, 128.9, 131.0, 159.0, 169.7, 171.7.

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{41}NO_6SiNa$: 502.2601; found: 502.2604.

The obtained oxazoline (31.0 mg, 65.0 μmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) under an argon atmosphere. This solution was cooled to 0 °C, then DBU (19.8 mg, 20 μL, 130 μmol, 2 equiv) and $BrCCl_3$ (14.1 mg, 7 μL, 71.0 μmol, 1.1 equiv) were added successively. The resulting mixture was stirred without further cooling for 20 h. The resulting dark-brown solution was quenched with sat. aq NH_4Cl (2 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The obtained crude product was purified by column chromatography on silica gel (hexanes–EtOAc, 4:1) to give the desired oxazole (22.1 mg, 46.0 μmol, 71%) as a colorless oil.

R_f = 0.37 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ –11.6 (*c* = 0.57, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.38 (s, 3 H), 0.00 (s, 3 H), 0.82 (s, 9 H), 0.86 (s, 3 H), 0.90 (s, 3 H), 2.88 (dd, *J* = 15.3, 7.4 Hz, 1 H), 3.10 (dd, *J* = 15.3, 4.1 Hz, 1 H), 3.16 (d, *J* = 8.9 Hz, 1 H), 3.21 (d, *J* = 8.9 Hz, 1 H), 3.79 (s, 3 H), 3.89 (s, 3 H), 4.20 (dd, *J* = 7.4, 4.1 Hz, 1 H), 4.29 (d, *J* = 11.9 Hz, 1 H), 4.39 (d, *J* = 11.9 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.25 (s, 1 H).

^{13}C (100 MHz, $CDCl_3$): δ = –4.9, –4.6, 18.2, 21.0, 21.3, 26.0, 32.8, 40.1, 52.1, 55.3, 72.8, 74.6, 76.3, 113.7, 129.0, 130.8, 133.3, 143.6, 159.0, 161.8, 164.8.

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{39}NO_6SiNa$: 500.2444; found: 500.2468.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-{4-[(*S*)-1-methoxybut-3-enyl]oxazol-2-yl}-2,2-dimethylbutanal (7)

Methyl ester **13** (180 mg, 0.38 mmol, 1.0 equiv) was diluted in CH_2Cl_2 (5 mL) under an argon atmosphere and cooled to –78 °C. DIBAL-H (133 mg, 0.94 mL, 0.94 mmol, 2.5 equiv) was added and the resulting reaction mixture was stirred for 2 h at –78 °C. The reaction was quenched by successive addition of MeOH (1 mL), EtOAc (10 mL), and sat. aq NH_4Cl (5 mL). The biphasic mixture was warmed to r.t., then 1 M aqueous tartaric acid (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtrated, and the solvent was evaporated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes–EtOAc, 4:1) to give the desired aldehyde (169 mg, 0.38 mmol, quantitative).

R_f = 0.53 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ –12.5 (*c* = 0.61, CH_3Cl_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.29 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 9 H), 0.90 (s, 3 H), 0.95 (s, 3 H), 2.91 (dd, *J* = 15.3, 7.1 Hz, 1 H), 3.15 (dd, *J* = 15.5, 4.3 Hz, 1 H), 3.20 (d, *J* = 8.7 Hz, 1 H), 3.25 (d, *J* = 8.7 Hz, 1 H), 3.83 (s, 3 H), 4.29–4.31 (m, 1 H), 4.32 (d, *J* = 11.7 Hz, 1 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 8.15 (s, 1 H), 9.91 (s, 1 H).

^{13}C (100 MHz, $CDCl_3$): δ = –4.8, –4.6, 18.2, 21.1, 21.3, 26.0, 32.9, 40.2, 55.3, 72.8, 74.7, 76.3, 113.7, 129.0, 130.8, 141.1, 144.1, 159.1, 165.5, 189.1.

HRMS (ESI+): *m*/*z* calcd for $C_{24}H_{37}NO_5SiNa$: 470.2339; found: 470.2326.

A solution of (–)-$(Ipc)_2BOMe$ (229 mg, 0.72 mmol, 2 equiv) in Et_2O (1.0 mL) under argon was cooled to –78 °C and treated slowly with allylmagnesiumbromide (1 M in Et_2O, 100 mg, 0.68 mL, 0.69 mmol, 1.9 equiv). After stirring for 15 min at this temperature, the solution was warmed to r.t. and stirred for 1 h, then the precipitate was forced to settle by centrifugation. The solution was decanted into another flask under argon and the residue was washed twice with pentane. The combined solution was then concentrated and the residue was dissolved in Et_2O (1.0 mL) before the resulting solution was cooled to –100 °C (MeOH/liq. N_2). A solution the corresponding aldehyde (162 mg, 0.36 mmol, 1 equiv) in Et_2O (1.0 mL) was then added and the reaction mixture was stirred at –100 °C for 2 h. The reaction was warmed to r.t. and treated with 3 M aqueous NaOH (0.8 mL) and H_2O_2 (30% solution, 0.4 mL). The biphasic mixture was stirred for 1 h at r.t., then the organic layer was separated, the aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic layer was washed with H_2O (15 mL) and brine (15 mL). After drying ($MgSO_4$), filtering and evaporating, the crude product was purified by column chromatography on silica gel (hexanes–EtOAc, 4:1) to give the corresponding homoallylic alcohol (116 mg, 0.24 mmol, 67%) as a colorless oil.

R_f = 0.28 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ –16.4 (*c* = 0.33, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.30 (s, 3 H), 0.00 (s, 3 H), 0.83 (s, 9 H), 0.87 (s, 3 H), 0.91 (s, 3 H), 2.20 (br s, 1 H), 2.57–2.61 (m, 2 H), 2.80 (dd, *J* = 15.4, 7.6 Hz, 1 H), 3.02 (dd, *J* = 15.3, 4.0 Hz, 1 H), 3.15 (d, *J* = 8.9 Hz, 1 H), 3.23 (d, *J* = 8.9 Hz, 1 H), 3.79 (s, 3 H), 4.19 (dd, *J* = 7.5, 3.8 Hz, 1 H), 4.32 (d, *J* = 11.9 Hz, 1 H), 4.42 (d, *J* = 11.9 Hz, 1 H), 4.67 (dd, *J* = 7.3, 5.2 Hz, 1 H), 5.11–5.16 (m, 1 H), 5.17–5.22 (m, 1 H), 5.83 (ddd, *J* = 17.2, 10.2, 7.1 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 8.7 Hz, 2 H), 7.42 (s, 1 H).

^{13}C (75 MHz, $CDCl_3$): δ = –4.9, –4.7, 18.2, 20.8, 21.5, 26.1, 32.9, 40.1, 41.0, 55.3, 66.6, 72.8, 74.8, 76.5, 113.7, 118.7, 129.0, 131.0, 133.7, 134.0, 143.1, 159.0, 163.9.

HRMS (ESI+): *m*/*z* calcd for $C_{27}H_{43}NO_5SiNa$: 512.2808; found: 512.2817.

To a solution of the homoallylic alcohol obtained as described above (0.27 g, 0.55 mmol, 1 equiv) in Et_2O (20 mL), was added 4 Å molecular sieves, methyliodide (7.82 g, 3.4 mL, 55.1 mmol,

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100 equiv) and silver(I) oxide (1.28 g, 5.51 mmol, 10 equiv). The suspension was stirred for 18 h at r.t. without light, then the mixture was filtered through cotton/silica gel and washed with Et_2O. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (hexane–EtOAc, 7:1) to give the methyl ether (0.25 g, 0.50 mmol, 92%) as a colorless oil.

R_f = 0.72 (hexanes–EtOAc, 2:1); $[\alpha]_D^{20}$ –31.7 (c = 0.90, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.32 (s, 3 H), 0.00 (s, 3 H), 0.83 (s, 9 H), 0.86 (s, 3 H), 0.90 (s, 3 H), 2.56 (app t, J = 6.4 Hz, 2 H), 2.82 (dd, J = 15.3, 7.6 Hz, 1 H), 3.03 (dd, J = 15.5, 3.8 Hz, 1 H), 3.15 (d, J = 8.7 Hz, 1 H), 3.24 (d, J = 8.7 Hz, 1 H), 3.31 (s, 3 H), 3.79 (s, 3 H), 4.18–4.20 (m, 1 H), 4.32 (d, J = 11.7 Hz, 1 H), 4.42 (d, J = 11.7 Hz, 1 H), 5.02–5.06 (m, 1 H), 5.07–5.12 (m, 1 H), 5.80 (ddd, J = 17.2, 10.2, 7.0 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 2 H), 7.23 (d, J = 8.7 Hz, 2 H), 7.44 (s, 1 H).

^{13}C (75 MHz, $CDCl_3$): δ = –4.40, –4.41, 18.6, 21.1, 21.9, 26.4, 33.4, 39.6, 40.5, 55.7, 57.3, 73.2, 75.1, 76.7, 76.9, 113.7, 117.2, 129.0, 131.0, 134.4, 135.0, 140.8, 159.0, 164.0.

HRMS: m/z calcd for $C_{28}H_{45}NO_5SiNa$: 526.2965; found: 526.2998.

The PMB-ether obtained from above (30.0 mg, 59.4 μmol, 1.0 equiv) was dissolved in CH_2Cl_2–H_2O (10:1, 1.8 mL/0.18 mL) under an argon atmosphere, then DDQ (30.0 mg, 131 μmol, 2.2 equiv) was added at r.t. and the resulting suspension was stirred for 25 min. The reaction was quenched by addition of sat. aq $NaHCO_3$ (3 mL), then the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure, before the crude product was purified by flash chromatography on silica gel (hexane–EtOAc, 7:1 → 2:1) to give the desired alcohol (14 mg, 37.5 μmol, 63%) as a colorless liquid.

R_f = 0.45 (hexanes–EtOAc, 1:2); $[\alpha]_D^{20}$ –41.7 (c = 0.75, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.18 (s, 3 H), –0.06 (s, 3 H), 0.86 (s, 9 H), 0.87 (s, 3 H), 0.94 (s, 3 H), 2.56 (app. t, J = 6.6 Hz, 2 H), 2.87 (dd, J = 16.0, 5.7 Hz, 1 H), 3.04 (br s, 1 H), 3.12 (dd, J = 16.6, 5.5 Hz, 1 H), 3.31 (d, J = 11.3 Hz, 1 H), 3.31 (s, 3 H), 3.56 (d, J = 11.3 Hz, 1 H), 4.16–4.18 (m, 1 H), 5.05–5.10 (m, 2 H), 5.77 (ddd, J = 17.1, 10.2, 7.0 Hz, 1 H), 7.45 (s, 1 H).

^{13}C (75 MHz, $CDCl_3$): δ = –4.82, 18.0, 21.6, 25.9, 33.0, 39.0, 40.1, 56.9, 69.4, 76.1, 77.3, 117.4, 134.1, 135.2, 140.8, 163.6.

HRMS (ESI+): m/z calcd for $C_{20}H_{37}NO_4Na$: 406.2390; found: 406.2382.

The obtained primary alcohol (15.0 mg, 0.04 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) under an argon atmosphere, then a solution of DMP (23.2 mg, 0.06 mmol, 1.4 equiv) in CH_2Cl_2 (1.5 mL) was added and the resulting mixture was stirred at r.t. for 1 h. Sat. aq $NaHCO_3$ (2 mL) was added, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The resulting crude product was purified by column chromatography on silica gel (hexanes–EtOAc, 1:2) to give aldehyde **7** (14.0 mg, 94%) as a colorless oil.

R_f = 0.64 (hexanes–EtOAc, 1:2); $[\alpha]_D^{20}$ –18.0 (c = 0.1, CH_3Cl_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.24 (s, 3 H), –0.02 (s, 3 H), 0.81 (s, 9 H), 1.00 (s, 3 H), 1.09 (s, 3 H), 2.53–2.57 (m, 2 H), 2.86 (dd, J = 15.3, 7.1 Hz, 1 H), 2.95 (dd, J = 15.2, 7.1 Hz, 1 H), 3.30 (s, 3 H), 4.17 (t, J = 6.5 Hz, 1 H), 4.45 (dd, J = 7.1, 4.8 Hz, 1 H), 5.04–5.08 (m, 2 H), 5.76–5.80 (m, 1 H), 7.45 (s, 1 H), 9.49 (s, 1 H).

^{13}C (100 MHz, $CDCl_3$): δ = –4.8, –4.7, 17.3, 18.6, 25.8, 33.0, 39.1, 51.3, 56.9, 74.2, 76.1, 117.3, 134.2, 135.3, 141.0, 162.2, 204.9.

HRMS: m/z [M + Na]$^+$ calcd for $C_{20}H_{35}NO_4SiNa^+$: 404.2228; found: 404.2226.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-{4-[(*S*)-1-methoxybut-3-enyl]oxazol-2-yl}-3,3-dimethylpentan-2-one (4)

A solution of the aldehyde **7** (83 mg, 0.22 mmol, 1.0 equiv) was dissolved in Et_2O (10 mL) under an argon atmosphere and cooled to –78 °C, then a solution of methylmagnesiumbromide (3 M in Et_2O, 52 mg, 150 μL, 0.44 mmol, 2 equiv) was added. The resulting mixture was stirred for a further 30 min at this temperature and quenched by addition of sat. aq NH_4Cl (2 mL). After warming to r.t., the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic layer was dried ($MgSO_4$), filtered and the solvent was removed in vacuo to give the secondary alcohol (82.0 mg, 0.21 mmol) as the crude product, which was directly used for the next step.

The secondary alcohol (82.0 mg, 0.21 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5 mL) under an argon atmosphere and treated with Dess–Martin periodinane (123 mg, 0.29 mmol, 1.4 equiv) at 0 °C. The reaction mixture was stirred for 30 min at this temperature, then warmed to r.t. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexanes–EtOAc, 1:1), to give the desired ketone **4** (78.0 mg, 0.20 mmol, 92% over two steps) as a colorless liquid.

R_f = 0.67 (hexanes–EtOAc, 2:1); $[\alpha]_D^{20}$ –42.9 (c = 0.6, CH_3Cl_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.25 (s, 3 H), 0.01 (s, 3 H), 0.82 (s, 9 H), 1.08 (s, 3 H), 1.14 (s, 3 H), 2.17 (s, 3 H), 2.53–2.57 (m, 2 H), 2.79 (dd, J = 15.8, 7.2 Hz, 1 H), 2.86 (dd, J = 15.3, 4.1 Hz, 1 H), 3.30 (s, 3 H), 4.17 (t, J = 6.4 Hz, 1 H), 4.53 (dd, J = 7.1, 4.6 Hz, 1 H), 5.03 (dd, J = 10.2, 1.5 Hz, 1 H), 5.08 (dd, J = 17.3, 1.5 Hz, 1 H), 5.79 (ddt, J = 17.2, 10.3, 6.9 Hz, 1 H), 7.45 (s, 1 H).

^{13}C (100 MHz, $CDCl_3$): δ = –4.8, –4.8, 18.1, 20.2, 21.3, 25.9, 26.9, 33.5, 39.2, 53.0, 56.9, 74.9, 76.2, 117.3, 134.2, 135.3, 140.9, 162.7, 212.7.

HRMS (ESI+): m/z calcd for $C_{21}H_{37}NO_4SiNa$: 418.2390; found: 418.2549.

(2*S*,5*S*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-1-[(4-methoxybenzyl)oxy]-8-{4-[(*S*)-1-methoxybut-3-en-1-yl]oxazol-2-yl}-2,6,6-trimethyloctan-3-one (31) and (2*S*,5*R*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-1-[(4-methoxybenzyl)oxy]-8-{4-[(*S*)-1-methoxybut-3-en-1-yl]oxazol-2-yl}-2,6,6-trimethyloctan-3-one (32)

To a cooled (–78 °C) solution of methylketone **8a** (375 mg, 1.68 mmol, 1.3 equiv) in anhydrous THF (3.0 mL) was added a solution of LiHMDS (1 M in THF, 281 mg, 1.68 mL, 1.68 mmol, 1.3 equiv). The mixture was stirred at –78 °C for 2 h, then warmed to –40 °C, then aldehyde **7** (495 mg, 1.30 mmol, 1.0 equiv) was added as a solution in THF (2.0 mL) and the mixture was stirred at this temperature for 40 min. Sat. aq NH_4Cl (6 mL) was added and the solution was allowed to warm to r.t., then Et_2O (30 mL) was added and the solution was washed with sat. aq NaCl (25 mL). The aqueous layer was extracted with Et_2O (4 × 25 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by silica column chromatography (40 g SiO_2; petroleum ether–EtOAc, 80:20 → 50:50) gave a mixture (1:1.7) of aldol products **31** and **32** (747 mg, 1.24 mmol, 95%) as a light-yellow oil. Both diastereoisomers could be separated by reverse-phase HPLC [Machery-Nagel; Nucleodur-C18; MeCN–H_2O, 95:5; 35 mL/min; t_R = 4.5 (**31**), 5.0 min (**32**)].

Aldol Product 31

R_f = 0.10 (petrol ether–EtOAc, 80:20); $[\alpha]_D^{20}$ –24.1 (c = 0.63 in $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.26 (s, 3 H), 0.09 (s, 3 H), 0.76 (s, 3 H), 0.85 (s, 9 H), 0.92 (s, 3 H), 1.10 (d, J = 7.0 Hz, 3 H), 2.51 (d, J = 16.2 Hz, 1 H), 2.57 (ddd, J = 13.9, 13.9, 7.2 Hz, 2 H), 2.63 (dd, J = 16.9, 9.9 Hz, 1 H), 2.91–2.95 (m, 1 H), 2.93–2.97 (m, 1 H), 3.11 (dd, J = 15.6, 3.6 Hz, 1 H), 3.33 (s, 3 H), 3.46 (dd, J = 9.2, 5.5 Hz, 1 H), 3.62 (dd, J = 8.8, 8.0 Hz, 1 H), 3.67 (s, 1 H),

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3.80 (s, 3 H), 4.20 (t, *J* = 6.3 Hz, 1 H), 4.20 (t, *J* = 6.3 Hz, 1 H), 4.26 (d, *J* = 9.9 Hz, 1 H), 4.33 (dd, *J* = 7.0, 3.4 Hz, 1 H), 4.40 (d, *J* = 11.6 Hz, 1 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 5.09 (dd, *J* = 29.2, 13.9 Hz, 2 H), 5.79–5.83 (m, *J* = 24.0, 17.2, 7.0 Hz, 1 H), 6.87 (d, *J* = 6.3 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 7.47 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.1, –4.8, 13.4, 18.1, 19.1, 20.6, 25.9, 32.8, 39.1, 41.3, 44.1, 47.0, 55.2, 56.8, 70.7, 71.8, 72.9, 77.6, 77.6, 113.7, 117.3, 129.3, 130.1, 134.2, 135.1, 140.8, 159.2, 163.4, 213.8.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{53}NO_7SiNa$: 626.3489; found: 626.3494.

Aldol Product 32

R_f = 0.13 (petrol ether–EtOAc, 80:20); $[\alpha]_D^{20}$ +0.4 (*c* = 0.61 in $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.23 (s, 3 H), 0.03 (s, 3 H), 0.79 (s, 3 H), 0.88 (s, 9 H), 0.94 (s, 3 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 2.56 (t, *J* = 6.6 Hz, 2 H), 2.61–2.64 (m, 2 H), 2.80 (dd, *J* = 21.9, 5.8 Hz, 1 H), 2.89–2.92 (m, 1 H), 3.17 (dd, *J* = 16.1, 4.7 Hz, 1 H), 3.33 (s, 3 H), 3.44 (dd, *J* = 8.9, 5.4 Hz, 1 H), 3.58 (t, *J* = 8.5 Hz, 1 H), 3.72 (d, *J* = 3.0 Hz, 1 H), 3.81 (s, 3 H), 4.01 (d, *J* = 9.7 Hz, 1 H), 4.21 (t, *J* = 6.5 Hz, 1 H), 4.25 (t, *J* = 5.2 Hz, 1 H), 4.40 (d, *J* = 11.6 Hz, 1 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 5.07 (dd, *J* = 28.1, 13.7 Hz, 2 H), 5.77–5.82 (m, 1 H), 6.87 (d, *J* = 7.9 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.47 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –4.8, 13.2, 15.3, 18.1, 18.5, 19.5, 26.0, 33.0, 39.1, 42.5, 44.5, 47.1, 55.2, 56.9, 70.6, 71.9, 72.9, 75.1, 76.1, 113.8, 117.3, 129.3, 130.0, 134.2, 135.1, 140.6, 159.2, 164.0, 214.3.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{53}NO_7SiNa^+$: 626.3489; found: 626.3494.

(2*S*,4*S*,6*S*,7*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-8-[(4-methoxybenzyl)oxy]-1-{4-[(*S*)-1-methoxybut-3-en-1-yl]oxazol-2-yl}-3,3,7-trimethyloctan-4-ol (2a from 31)

$NMe_4HB(OAc)_3$ (160 mg, 606 μmol, 4.7 equiv) was added to a mixture of MeCN–acetic acid (1:1, 1.0 mL) at r.t. and stirred for 30 min. This solution was added to a solution of β-hydroxy-ketone **31** (78.0 mg, 129 μmol, 1.0 equiv) in THF–MeCN (1:1, 1.5 mL) at –30 °C. The mixture was warmed to –20 °C, stirred for 3.5 h at this temperature and kept in a freezer overnight (–20 °C, 12 h). An aqueous solution of Na/K-tartrate (20%, 3.0 mL) was added at –20 °C and the mixture was allowed to warm to r.t., then CH_2Cl_2 (25 mL) was added and the solution was washed with Na/K-tartrate solution (20%, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Silica column chromatography (7 g SiO_2; pentane–EtOAc, 80:20 → 50:50) gave the corresponding 1,3-*anti*-diol product (74.0 mg, 123 μmol, 95%) as a colorless oil.

R_f = 0.11 (pentane–EtOAc, 2:1); $[\alpha]_D^{20}$ –29.3 (*c* = 1.50 in $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.27 (s, 3 H), 0.09 (s, 3 H), 0.78 (s, 3 H), 0.86 (s, 9 H), 0.99 (d, *J* = 7.0 Hz, 3 H), 1.02 (s, 3 H), 1.39 (dd, *J* = 12.9, 11.0 Hz, 1 H), 1.49 (dd, *J* = 12.7, 10.6 Hz, 1 H), 1.87 (br s, 1 H), 2.58 (m, 2 H), 3.01 (dd, *J* = 15.8, 7.4 Hz, 1 H), 3.17 (dd, *J* = 15.7, 2.2 Hz, 1 H), 3.32 (s, 3 H), 3.49 (dd, *J* = 8.9, 5.5 Hz, 1 H), 3.55 (dd, *J* = 9.0, 4.2 Hz, 1 H), 3.80 (s, 3 H), 4.07–4.09 (m, 1 H), 4.11–4.13 (m, 1 H), 4.16–4.18 (m, 1 H), 4.19–4.21 (m, 1 H), 4.41 (d, *J* = 11.6 Hz, 1 H), 4.46 (d, *J* = 11.3 Hz, 1 H), 4.46 (d, *J* = 11.3 Hz, 1 H), 5.06 (d, *J* = 10.2 Hz, 1 H), 5.12 (d, *J* = 17.3 Hz, 1 H), 5.78–5.83 (m, 1 H), 6.86 (d, *J* = 8.1 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.47 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.2, –4.7, 11.3, 18.0, 20.1, 22.9, 25.9, 32.6, 35.7, 38.5, 39.1, 40.8, 55.3, 56.7, 60.4, 70.6, 71.5, 73.1, 74.9, 76.1, 81.7, 113.8, 117.3, 129.2, 130.2, 134.2, 135.1, 140.9, 159.2, 163.3.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{56}NO_7Si^+$: 606.3826; found: 606.3818.

To a stirred solution of the 1,3-*anti* diol obtained above (49.0 mg, 80.9 μmol, 1.0 equiv) in anhydrous THF (1.0 mL) was added NaH (60% dispersion in oil, 32.2 mg, 809 μmol, 10.0 equiv) at 0 °C. The mixture was stirred for 10 min at 0 °C, then iodomethane (150 μL) was added and the solution was stirred at +10 °C for 65 min before the addition of sat. aq NH_4Cl (2 mL). The mixture was warmed to r.t., Et_2O (10 mL) was added and the mixture was washed with sat. aq NaCl (5 mL), the aqueous layer was extracted with Et_2O (4 × 10 mL), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (10 g SiO_2; pentane–EtOAc, 3:1) gave C20-monomethylated **2a** (40.1 mg, 64.7 μmol, 80%) in addition to C18-monomethylated sideproduct (3.1 mg, 5.1 μmol, 6%, both isomers could be separated by column chromatography) as a colorless oil.

R_f = 0.55 (pentane–EtOAc, 2:1); $[\alpha]_D^{20}$ –34.3 (*c* = 0.81 in $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.30 (s, 3 H), 0.06 (s, 3 H), 0.75 (s, 3 H), 0.83 (s, 9 H), 0.94 (d, *J* = 6.8 Hz, 1 H), 0.94 (s, 3 H), 1.38–1.40 (m, 2 H), 1.94–2.02 (m, 1 H), 1.99 (qddd, *J* = 7.2, 7.0, 4.7, 4.4 Hz, 1 H), 2.50–2.60 (m, 2 H), 2.97 (dd, *J* = 15.7, 7.6 Hz, 1 H), 3.14 (dd, *J* = 15.8, 3.4 Hz, 1 H), 3.27 (dd, *J* = 16.1, 5.8 Hz, 1 H), 3.30 (s, 3 H), 3.41 (s, 3 H), 3.46 (dd, *J* = 16.0, 4.7 Hz, 1 H), 3.54 (ddd, *J* = 7.7, 4.4, 4.4 Hz, 1 H), 3.78 (s, 3 H), 3.93 (dd, *J* = 5.6, 5.5 Hz, 1 H), 4.16–4.20 (m, 2 H), 4.39 (d, *J* = 11.5 Hz, 2 H), 4.43 (d, *J* = 11.5 Hz, 2 H), 5.03 (d, *J* = 10.1 Hz, 1 H), 5.08 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.78 (dddd, *J* = 17.1, 10.0, 6.9, 6.9 Hz, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.45 (s, 1 H).

^{13}C NMR (150.90 MHz, $CDCl_3$): δ = –5.2, –4.7, 12.7, 18.0, 19.8, 22.4, 25.9, 32.7, 34.0, 37.4, 39.1, 41.0, 55.3, 56.9, 59.2, 71.4, 72.4, 72.7, 76.1, 79.1, 80.6, 113.7, 117.3, 129.1, 129.2, 130.8, 134.2, 135.1, 140.9, 159.0, 163.3.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{57}NO_7SiNa^+$: 642.3802; found: 642.3810.

(2*S*,6*S*,7*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-8-[(4-methoxybenzyl)oxy]-1-{4-[(*S*)-1-methoxybut-3-en-1-yl]oxazol-2-yl}-3,3,7-trimethyloctan-4-one (33)

Aldol product **32** (930 mg, 1.54 mmol, 1.0 equiv) was dissolved in Et_2O (9.0 mL) and cooled to –30 °C, then anhydrous Et_3N (322 μL, 2.31 mmol, 1.5 equiv), and Cy_2BCl (1 M in THF, 2.31 mL, 2.31 mmol, 1.5 equiv) were added and the white mixture was stirred for 90 min. The solution was cooled to –78 °C and $LiBH_4$ (2 M in THF, 3.85 mL, 7.70 mmol, 5.0 equiv) was added and the mixture was stirred at this temperature for 90 min. Sat. aq NH_4Cl (10 mL) was added slowly and the mixture was allowed to warm to r.t., then Et_2O (20 mL) and sat. aq NH_4Cl (10 mL) were added. The solution was washed, the aqueous layer was extracted with Et_2O (4 × 20 mL) and the combined organic layers were concentrated in vacuo. The colorless residue was dissolved in MeOH (6.0 mL) and cooled to 0 °C. The solution was stirred and aq NaOH (3 M, 3.0 mL) and H_2O_2 (30%, 3.0 mL) were added and the mixture was stirred for 2 h at r.t. The solution was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and, after washing and separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (90 g SiO_2; petrol ether–EtOAc, 3:1 → 1:1) gave the corresponding 1,3-*syn*-diol (886 mg, 1.46 mmol, 95%) as a colorless oil.

R_f = 0.18 (pentane–EtOAc, 3:1); $[\alpha]_D^{20}$ –29.3 (*c* = 1.50 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.16 (s, 3 H), 0.07 (s, 3 H), 0.82 (s, 3 H), 0.92 (s, 9 H), 0.97 (d, *J* = 7.2 Hz, 3 H), 0.99 (s, 3 H), 1.51–1.73 (m, 2 H), 1.89 (qddd, *J* = 7.2, 6.9, 5.0, 1.5 Hz, 1 H), 2.60 (t, *J* = 6.7 Hz, 2 H), 2.84 (dd, *J* = 16.5, 5.0 Hz, 1 H), 3.22 (dd, *J* = 16.6, 5.4 Hz, 1 H), 3.36 (s, 3 H), 3.48 (dd, *J* = 9.0, 5.0 Hz, 1 H), 3.54 (dd, *J* = 8.8, 6.9 Hz, 1 H), 3.68–3.75 (m, 2 H), 3.85 (s, 3 H), 3.96 (dt, *J* = 9.2, 2.5 Hz, 1 H), 4.15 (d, *J* = 5.8 Hz, 1 H), 4.24 (t, *J* = 6.5 Hz, 1 H),

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4.29 (t, *J* = 5.1 Hz, 1 H), 4.47 (s, 2 H), 5.08 (d, *J* = 11.6 Hz, 1 H), 5.15 (d, *J* = 17.2 Hz, 1 H), 5.82 (dddd, *J* = 17.1, 10.0, 6.9, 6.9 Hz, 1 H), 6.92 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 7.51 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, –4.7, 11.3, 17.4, 18.0, 19.2, 25.9, 32.9, 33.9, 38.9, 39.0, 43.2, 55.3, 56.9, 73.0, 73.7, 74.8, 76.0, 76.6, 77.2, 113.8, 117.4, 129.3, 134.0, 135.2, 142.0, 158.9, 164.2.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{56}NO_7Si^+$: 606.3826; found: 606.3835.

To a stirred solution of the 1,3-*syn*-diol obtained above (15.0 mg, 24.8 μmol, 1.0 equiv) in anhydrous THF (0.5 mL) was added NaH (60% dispersion in oil, 5.0 mg, 124 μmol, 5.0 equiv) at 0 °C. The mixture was stirred for 10 min at 0 °C, then iodomethane (100 μL) was added and the solution was stirred at 0 °C for 40 min before the addition of sat. aq NH_4Cl (1 mL). The mixture was warmed to r.t., Et_2O (10 mL) was added, and the mixture was washed with sat. aq NaCl (5 mL), the aqueous layer was extracted with Et_2O (4 × 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by silica column chromatography (5 g SiO_2; pentane–EtOAc, 3:1→1:1) gave the corresponding C20-monomethylated product (10.0 mg, 16.1 μmol, 65%, 89% brsm) besides recovered starting material (4.0 mg, 6.60 μmol, 27%) as a colorless oil.

R_f = 0.27 (pentane–EtOAc, 3:1); $[\alpha]_D^{20}$ –27.5 (*c* = 1.59 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.27 (s, 3 H), 0.02 (s, 3 H), 0.78 (s, 3 H), 0.87 (s, 9 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.93 (s, 3 H), 1.39–1.63 (m, 2 H), 1.97–2.18 (m, 1 H), 2.56 (t, *J* = 6.6 Hz, 2 H), 2.83 (dd, *J* = 15.8, 6.6 Hz, 1 H), 3.18 (dd, *J* = 15.9, 4.1 Hz, 1 H), 3.28–3.35 (m, 1 H), 3.33 (s, 3 H), 3.37 (s, 3 H), 3.42–3.56 (m, 2 H), 3.62 (d, *J* = 9.4 Hz, 1 H), 3.81 (s, 3 H), 3.99 (d, *J* = 1.8 Hz, 1 H), 4.20 (t, *J* = 6.1 Hz, 1 H), 4.26 (dd, *J* = 6.4, 4.1 Hz, 1 H), 4.43 (s, 4 H), 5.05 (d, *J* = 10.7 Hz, 1 H), 5.15 (s, 1 H), 5.81 (ddd, *J* = 17.1, 10.0, 6.9, 6.9 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 7.46 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –4.7, –4.7, 12.6, 17.6, 18.1, 19.5, 26.0, 29.7, 32.1, 32.8, 36.0, 39.1, 42.9, 55.3, 56.9, 57.6, 71.9, 72.8, 75.1, 75.2, 76.2, 83.9, 113.7, 117.2, 129.2, 130.5, 134.2, 135.0, 140.6, 159.1, 164.1.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{57}NO_7SiNa^+$: 642.3802; found: 642.3829.

To a stirred solution of the alcohol prepared above (290 mg, 469 μmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) was added PCC (506 mg, 2.35 mmol, 5.0 equiv) at r.t. The mixture was heated at reflux for 90 min, cooled to r.t., filtered over Celite, which was rinsed with CH_2Cl_2 (50 mL), and concentrated in vacuo. Purification by silica column chromatography (20 g SiO_2; pentane–EtOAc, 3:1) gave the corresponding ketone **33** (281 mg, 455 μmol, 97%) as a colorless oil.

R_f = 0.38 (pentane–EtOAc, 3:1); $[\alpha]_D^{20}$ +40.0 (*c* = 1.13 in $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.31 (s, 3 H), 0.00 (s, 3 H), 0.80 (s, 9 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 1.10 (s, 3 H), 1.11 (s, 3 H), 1.92–1.98 (m, 1 H), 2.46 (dd, *J* = 18.0, 4.1 Hz, 1 H), 2.53 (t, *J* = 6.6 Hz, 2 H), 2.75 (dd, *J* = 15.5, 7.5 Hz, 1 H), 2.78–2.84 (m, 2 H), 3.27 (s, 3 H), 3.28–3.31 (m, 1 H), 3.29 (s, 3 H), 3.45 (dd, *J* = 9.0, 6.6 Hz, 1 H), 3.78 (s, 3 H), 3.85 (ddd, *J* = 7.8, 3.9, 3.8 Hz, 1 H), 4.16 (t, *J* = 6.5 Hz, 1 H), 4.40 (d, *J* = 11.7 Hz, 1 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.51 (dd, *J* = 7.4, 3.4 Hz, 1 H), 5.05–5.11 (m, 2 H), 5.78 (dddd, *J* = 17.1, 10.0, 6.9, 6.9 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 7.44 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9, –4.7, 12.0, 18.1, 19.6, 21.8, 25.9, 33.6, 37.0, 39.1, 41.2, 53.1, 55.3, 56.9, 58.6, 72.2, 72.6, 74.8, 76.2, 77.2, 113.7, 117.2, 129.2, 130.7, 134.3, 135.2, 140.9, 159.1, 162.8, 212.7.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{55}NO_7SiNa^+$: 640.3645; found: 640.3642.

(2*S*,4*S*,6*S*,7*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-8-[(4-methoxybenzyl)oxy]-1-{4-[(*S*)-1-methoxybut-3-en-1-yl]oxazol-2-yl}-3,3,7-trimethyloctan-4-ol (2a from 32)

To a stirred solution of the ketone **33** (264 mg, 427 μmol, 1.0 equiv) in THF (10.0 mL) under argon at –90 °C was added a precooled solution of $LiAlH_4$ (2 M in THF, 65.0 mg, 855 μL, 1.71 mmol, 4.0 equiv). The mixture was stirred at –90 °C for 45 min, and H_2O (0.6 mL) and a solution of NaOH (3 M, 1.8 mL) were added. The mixture was warmed to r.t., Et_2O (20 mL) and H_2O (15 mL) were added and the aqueous phase was separated and extracted with Et_2O (4 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (25 g SiO_2; pentane–EtOAc, 3:1 → 1:1) gave alcohol **2a** (211 mg, 341 μmol, 80%, dr = 8.0:1) as a colorless oil.

R_f = 0.55 (pentane–EtOAc, 2:1); $[\alpha]_D^{20}$ –34.3 (*c* = 0.81 in $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.30 (s, 3 H), 0.06 (s, 3 H), 0.75 (s, 3 H), 0.83 (s, 9 H), 0.94 (d, *J* = 6.8 Hz, 1 H), 0.94 (s, 3 H), 1.38–1.40 (m, 2 H), 1.94–2.02 (m, 1 H), 1.99 (qddd, *J* = 7.2, 7.0, 4.7, 4.4 Hz, 1 H), 2.50–2.60 (m, 2 H), 2.97 (dd, *J* = 15.7, 7.6 Hz, 1 H), 3.14 (dd, *J* = 15.8, 3.4 Hz, 1 H), 3.27 (dd, *J* = 16.1, 5.8 Hz, 1 H), 3.30 (s, 3 H), 3.41 (s, 3 H), 3.46 (dd, *J* = 16.0, 4.7 Hz, 1 H), 3.54 (ddd, *J* = 7.7, 4.4, 4.4 Hz, 1 H), 3.78 (s, 3 H), 3.93 (dd, *J* = 5.6, 5.5 Hz, 1 H), 4.16–4.20 (m, 2 H), 4.39 (d, *J* = 11.5 Hz, 2 H), 4.43 (d, *J* = 11.5 Hz, 2 H), 5.03 (d, *J* = 10.1 Hz, 1 H), 5.08 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.78 (dddd, *J* = 17.1, 10.0, 6.9, 6.9 Hz, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.45 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.2, –4.7, 12.7, 18.0, 19.8, 22.4, 25.9, 32.7, 34.0, 37.4, 39.1, 41.0, 55.3, 56.9, 59.2, 71.4, 72.4, 72.7, 76.1, 79.1, 80.6, 113.7, 117.3, 129.1, 129.2, 130.8, 134.2, 135.1, 140.9, 159.0, 163.3.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{57}NO_7SiNa^+$: 642.3802; found: 642.3810.

Acknowledgment

This work was generously supported by the Deutsche Forschungsgemeinschaft (Me 2756/4-1).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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