Studies on the C22–C23 Aldol Coupling of Spirangien

Michael Lorenz, Nadine Bluhm, Markus Kalesse*

Leibniz Universität Hannover, Institut für Organische Chemie, Schneiderberg 1b, 30167 Hannover, Germany
Fax +49(511)7623011; E-mail: Markus.Kalesse@oci.uni-hannover.de

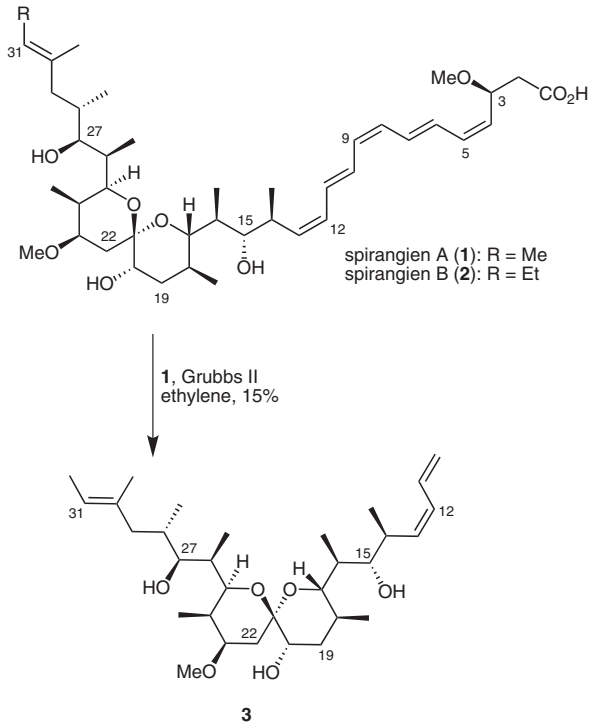
Received 5 March 2009; revised 6 May 2009

Abstract: The aldol reaction is one of the most powerful and versatile methods in polyketide synthesis. Nevertheless, the subtle directing effects remain very often obscure and impede complex natural products syntheses. Here, we report studies on the pivotal aldol coupling employed in the spirangien synthesis. We identified conditions for the stereoselective formation of both stereoisomers in the C22–C23 aldol juncture of spirangien.

Key words: aldol reaction, methyl ketone, natural products, 1,4-induction, Felkin product, Cornforth model

Myxobacteria are a valuable source for the isolation of structurally diverse biologically active natural products. In 2005 Höfle et al. isolated two novel compounds from the fermentation broth of strain *So Ce90*, spirangien A (**1**) and B (**2**)[1] (Scheme 1).

The spirangiens attracted considerable attention due to their complex structure and remarkable biological profile. These unique natural products unfold remarkably high cytotoxic activity against L929 mouse fibroblast cell lines with an IC_{50} value of 0.7 ng/mL for **1**. Additionally, they exhibit antibiotic activity against yeast and fungi (diameters of inhibition zones: *Pichia membranaefaciens* 24 mm, *Rhodotorula glutins* 19 mm, *Botrytis cinerea* 11 mm). In particular their novel yet unidentified mode of action highlights them as promising tools in chemical biology and as potential drug candidates.



Scheme 1 Formation of truncated spirangien **3**

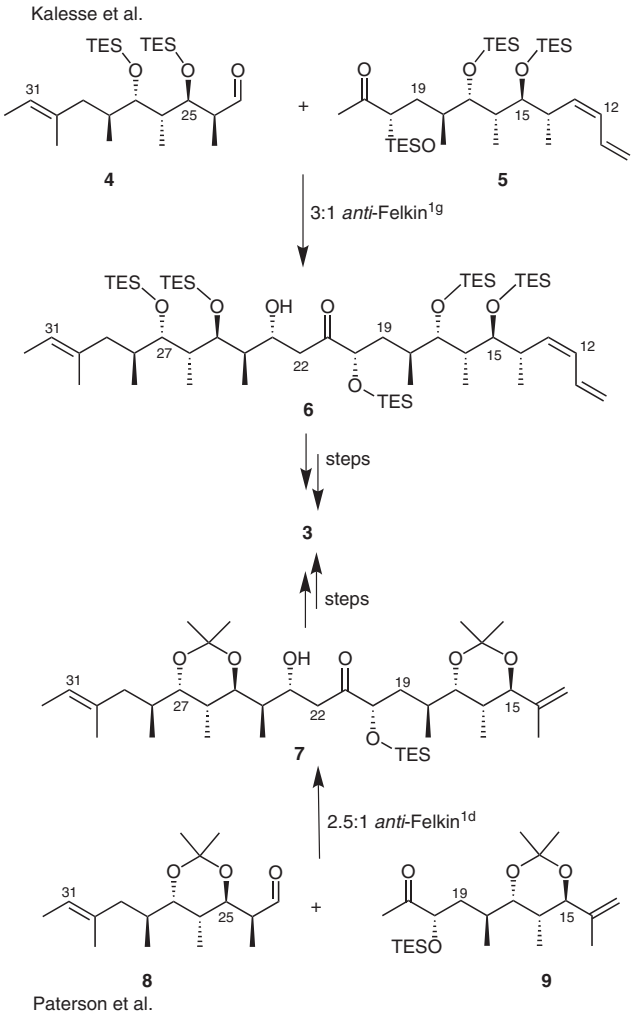
For structure elucidation, **1** was transferred into the truncated spirangien **3** via cross metathesis using ethylene and the Grubbs second generation catalyst. The relative configuration has been established by X-ray crystallography of **3** (Scheme 1) and the absolute configuration of the fourteen stereocenters was elucidated by total synthesis and gene cluster analysis.[1c,d]

Up to now, two synthetic approaches towards **3** and one synthesis of spirangien **A** (**1**) have been put forward.[1] In each approach, the pivotal disconnection was placed between C22 and C23 using an aldol reaction between a methyl ketone and the corresponding aldehyde (Scheme 2). The low selectivities obtained (ranging from 2.5:1 to 3:1) serve as a clear indication that opposing directing effects prevent an efficient aldol coupling.

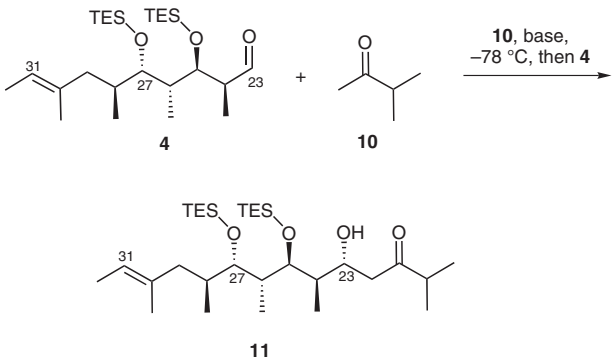
Even though a large body of data analyzing the different effects in aldol reactions is available, literature studies asserted a lack of mechanistic insights and explanation for this particular set-up, incorporating a protected α-hydroxy methyl ketone. Only few examples were reported in which the α-substituted methyl ketone was employed without any handicap resulting from an additional 1,5-induction.[2] One of the few examples was put forward in 2008 by Urpi and co-workers[2d] who published studies using titanium-based Lewis acids in combination with chelating protecting groups. In order to examine the directing effects of both coupling partners we initiated a program in which substrate-controlled aldol reactions were investigated using either the ketone or the aldehyde with their corresponding achiral substrates. Special focus was placed on investigating the effects of bases and counter ions such as LDA, KHMDS, and changing the reaction conditions from enolate activation to Lewis acid activation as employed in Mukaiyama aldol reactions. We had high expectations that changing the counter ions would significantly increase the selectivities since it led to improved results in the aldol coupling step during our tedanolide synthesis.[3]

First, we investigated the opposing directing effects inherent to aldehyde **4** with methyl ketone **10** as the achiral substitute for **5** (Scheme 3).[4] The *syn* configuration at the α

SYNTHESIS 2009, No. 18, pp 3061–3066
Advanced online publication: 23.07.2009
DOI: 10.1055/s-0029-1216918; Art ID: T05209SS



Scheme 2 Pivotal aldol reaction of the ketone and aldehyde fragments of **3**



Scheme 3 Model reaction with achiral methyl ketone **10**

and β position already led to opposing directing effects. The α-substituent favored the Felkin product whereas the β-substituent would be Felkin opposing.[5] When enolate activation was employed, as it was the case in our synthesis of **3**, 84–87% yield of the single desired diastereomer was observed (Table 1, entries 1 and 2). This result clearly shows that the aldehyde directs the aldol reaction to the desired *anti*-Felkin stereoisomer, controlled by the β-substituent, which can be explained by the polar Cornforth model.[2]

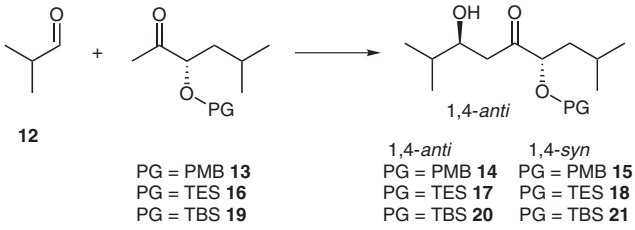
Table 1 Selectivities for Reactions Depicted in Scheme 3

	Solvent	Base	Yield, de[6]
1	THF	LiHMDS	87%, >95:5
2	CH_2Cl_2	LiHMDS	84%, >95:5
3	THF	KHMDS	61%, >95:5

In order to unravel the directing effects of the methyl ketone, we prepared the simplified methyl ketone analogues **13**, **16**, and **19**, which were obtained from L-leucine in three steps.[7]

The initial transformations using enolate activation (Table 2) resulted in low yields irrespective of the protecting groups and bases used. The least selective reactions were always those when sodium was used as the counter ion. As a general trend it became apparent that lithium bases provided the best selectivities, albeit for the undesired isomer in our case. The influence of the protecting group was also not fundamental, with the PMB group providing the best selectivities for the undesired isomer. The fact that in our synthesis of **3** LiHMDS provided acceptable yields and selectivities, parallels the trends observed for the separate coupling partners (Scheme 4, Table 2).

These results can be rationalized by transition state **A** (Figure 1) wherein chelation of the counter ion by the eno-



Scheme 4 Model reaction using simplified methyl ketones

Table 2 Reaction Conditions for Scheme 4

Entry	Ketone	PG	Base	dr *anti*/*syn* (yield)[a,6]
1	**13**	PMB	LiHMDS	87:13 (46%)
2	**13**	PMB	NaHMDS	68:32 (36%)
3	**13**	PMB	KHMDS	81:19 (38%)
4	**19**	TBS	LiHMDS	62:38 (37%)
5	**19**	TBS	NaHMDS	58:42 (36%)
6	**19**	TBS	KHMDS	59:41 (31%)
7	**16**	TES	LiHMDS	68:32 (43%)
8	**16**	TES	NaHMDS	50:50 (38%)
9	**16**	TES	KHMDS	53:47 (38%)

[a] No full conversion of the ketone could be obtained. The reaction stopped after 16 h, but unreacted ketone could be reisolated.

late and the oxygen protecting group shields one face of the enolate, whereas chelation is not so prominent with silicon protection groups and larger cations (R = TBS, TES; M = Na, K). In these cases an alternative transition state **B** (Figure 1) can be adopted.

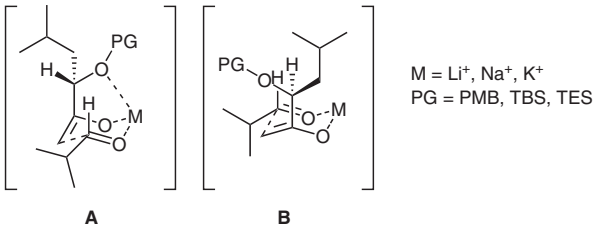


Figure 1 Transition states for reactions shown in Scheme 4

The outcome of our investigations corresponds to the results reported by Kobayashi, Carter, and Zhao in their synthetic approaches towards amphidinolide B1 and H1, respectively.[8] They refer to chelation of the α-protecting group on the methyl ketone employing MOM or PMB ether.

Next, we focused on boron enolates, which have been reported to change the selectivity for similar aldol reaction.[9] Nevertheless, changing sterically demanding groups at boron did not alter the selectivity and consequently we were not able to utilize these examples to perform the 1,4-*syn*-selective aldol reaction.

The boron-mediated aldol reactions gave good to excellent 1,4-*anti*-selectivities. Again, the reaction stopped after 16 hours and we were able to reisolate the unreacted ketone. An optimum of yield and diastereoselectivity (Table 3, entry 2) could be achieved with $(c\text{-Hex})_2BCl$ as Lewis acid at –20 °C with a TES protecting group. Unfortunately, optimization studies of the PMB protected model ketone **13** (Table 3, entry 5) at different reaction temperatures did not produce improved yields.

The observed selectivity can be explained with the aid of the Zimmerman–Traxler transition state **C** and **D** wherein attack on the *si*-face in **C** is favored as opposed to transition state **D**. In transition state **C** a minimum of steric hindrance occurs in contrast to transition state **D** where a minimum of electronic effects appears (Figure 2).

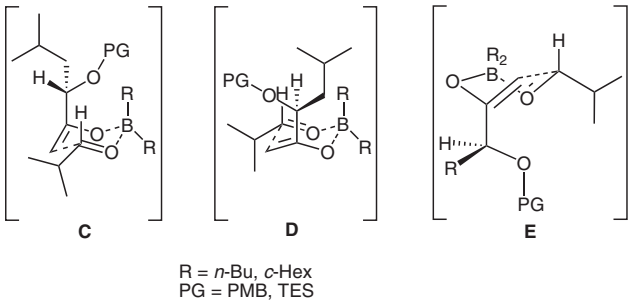


Figure 2 Transition states of the boron-mediated aldol reactions

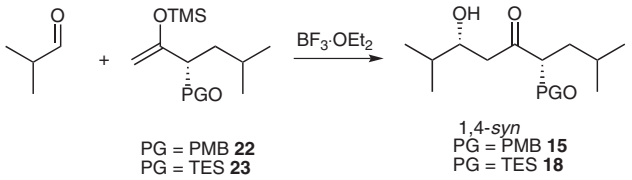
For aldol reactions with methyl ketones both boat and chair transition states are reasonable.[5g,h,i] This possible boat transition state combines a minimum of both steric and electronic effects as shown in **E** (Figure 2).

The Mukaiyama aldol reaction (Scheme 5) on the other hand led to a complete change in stereochemistry and provided the 1,4-*syn* product in excellent selectivity (Table 3, entries 8–10).[5f,10] Both transition states shown in Figure 3 lead to the obtained 1,4-*syn* product. The stereochemical outcome can be rationalized by an *anti*-periplanar transition state **F** with minimized steric hindrance compared to transition state **G** (Figure 3).

Table 3 Conditions for Boron-Mediated Aldol Reactions and Mukaiyama Aldol Reactions

Entry	Ketone	Lewis acid	Base/solvent	dr *anti*/*syn* (yield)[a,6]
1	**13**	$(c\text{-Hex})_2BCl$	Et_3N/Et_2O	77:23 (39%)
2	**16**	$(c\text{-Hex})_2BCl$	Et_3N/Et_2O	84:16 (63%)
3	**16**	$(c\text{-Hex})_2BCl$	Et_3N/Et_2O	85:15 (51%)[b]
4	**16**	$(c\text{-Hex})_2BCl$	Et_3N/Et_2O	72:28 (68%)[c]
5	**13**	$(n\text{-Bu})_2BOTf$	$DIPEA/CH_2Cl_2$	93:7 (35%)
6	**13**	$(n\text{-Bu})_2BOTf$	DIPEA/toluene	80:20 (84%)[d,e]
8	**13**[f]	$BF_3{\cdot}OEt_2$ (0.3 equiv)	toluene	4:96 (35%)
9	**13**[f]	$BF_3{\cdot}OEt_2$ (1 equiv)	toluene	6:94 (38%)
10	**16**[f]	$BF_3{\cdot}OEt_2$ (0.3 equiv)	toluene	2:98 (36%)

[a] No full conversion of the ketone could be obtained.
[b] Reaction run at –85 °C.
[c] Reaction run at 0 °C.
[d] Yield based on recovered starting material.
[e] Reaction run at –78 °C.
[f] Mukaiyama aldol.



Scheme 5 Mukaiyama aldol reactions

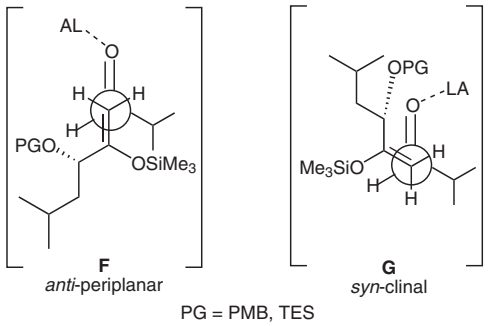


Figure 3 Transition states of the Mukaiyama aldol reactions

In conclusion, we have presented a detailed analysis of the subtle stereoselective contributions in the pivotal aldol reaction of spirangien. The use of the Mukaiyama aldol reaction will now enable us to install the new stereogenic center in using a 1,4-*syn*-selective induction. We have also provided the possibility of assembling either a 1,4-*anti* or a 1,4-*syn* motif selectively depending on the protecting group at the α-stereocenter of oxygenated ketones. Together with established procedures, this adds to the general applicability and prediction of aldol reactions in complex natural products total synthesis.

All manipulations and reactions were carried out under Schlenk technique in a N_2 atmosphere. Glassware were oven-dried for several hours, baked out with a heat gun under vacuum, and cooled in a stream of dry N_2 before reaction. THF was distilled over sodium and benzophenone ketyl and stored under N_2. CH_2Cl_2 was distilled over CaH_2 and stored under N_2. All other chemicals were purchased from Aldrich or Acros and used as delivered.

Column chromatography was performed on Macherey-Nagel silica gel (40–63 mm, 60 Å pores), using the same solvent system as specified for the *Rf* values. Experiments were monitored by thin layer chromatography (TLC) performed on Merck 60 F-254 (0.2 mm thick) silica gel aluminum-supported plates. Spots were visualized by exposure to ultraviolet light (254 nm) or by staining with bromine-cresol green or cerium reagent.

NMR spectra were recorded on Bruker AVS-400 or AVS-200 spectrometers. For ^{1}H NMR spectra in $CDCl_3$, the singlet of $CHCl_3$ at δ = 7.26 ppm served as an internal reference. For ^{13}C NMR spectra in $CDCl_3$, the triplet at δ = 77.2 ppm served as an internal reference. Values of the coupling constants are given in hertz (Hz). High-resolution electrospray mass spectra (HRMS-ESI) were recorded on a Waters Micromass LCT spectrometer with a Lock-Spray unit.

Ketone 11 by LiHMDS-Mediated Aldol Reaction of Ketone 10 with Aldehyde 4

To a solution of ketone **10** (11 μL, 100 μmol) in THF (1 mL) was added LiHMDS (1.3 M in THF, 175 μmol) dropwise at –78 °C and the mixture stirred for 2 h. Aldehyde **4** (4 mg, 8.5 μmol) was added slowly and the mixture was stirred at this temperature for 20 h. The reaction was stopped by the addition of sat. aq NH_4Cl (2 mL), the layers were separated, and the aqueous layer was extracted with MTBE (3 × 2 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Column chromatography of the residue provided the aldol product **11** (4.1 mg, 7.4 μmol, 87%); R_f = 0.45 (EtOAc–*n*-hexane, 1:50); $[\alpha]_D^{20}$ –6.7 (*c* 0.31, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.19 (q, *J* = 5.7 Hz, 1 H), 4.13 (d, *J* = 6.5 Hz, 1 H), 3.54 (dd, *J* = 4.8, 3.4 Hz, 1 H), 3.22 (d, *J* = 3.8 Hz, 1 H), 2.75 (dd, *J* = 17.6, 2.2 Hz, 1 H), 2.59–2.63 (m, 1 H), 2.47 (dd, *J* = 17.6, 9.4 Hz, 1 H), 2.11 (d, *J* = 13.7 Hz, 1 H), 1.80–1.84 (m, 2 H), 1.65–1.72 (m, 2 H), 1.58 (s, 6 H), 1.11 (d, *J* = 6.8 Hz, 6 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 0.94–0.99 (m, 18 H), 0.80 (d, *J* = 6.8 Hz, 3 H), 0.77 (d, *J* = 6.5 Hz, 3 H), 0.60–0.68 (m, 12 H).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{65}O_4Si_2$ [M + H$^+$]: 557.4416; found: 557.4418.

Ketone 13

Camphorsulfonic acid (0.5 g, 2.2 mmol) and *p*-methoxybenzyl trichloroacetimidate (4.6 g, 16.4 mmol) were dissolved in CH_2Cl_2 (10 mL). To this solution was added (*S*)-3-hydroxy-5-methylhexan-2-one (1.4 g, 10.9 mmol) and the mixture stirred for 16 h at r.t. The reaction was stopped by the addition of sat. aq $NaHCO_3$ (5 mL), the layers were separated, and the aqueous layer was extracted three times with MTBE (3 × 5 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Column chromatography of the residue afforded the ketone **13** (334.0 mg, 1.3 mmol, 12%) ; R_f = 0.38 (EtOAc–*n*-hexane, 1:15); $[\alpha]_D^{20}$ –37.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.50 (d, *J* = 11.3 Hz, 1 H), 4.32 (d, *J* = 11.3 Hz, 1 H), 3.81 (s, 3 H), 3.79–3.76 (m, 1 H), 2.16 (s, 3 H), 1.86–1.75 (m, 1 H), 1.65–1.58 (m, 1 H), 1.36–1.28 (m, 1 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.3, 159.6, 129.8, 129.6, 114.0, 83.7, 72.4, 55.4, 41.2, 25.1, 24.6, 23.4, 21.8.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{25}NO_3$ + Na [M + C_2H_3N + Na$^+$]: 314.1732; found: 314.1732.

Ketone 16

(*S*)-3-Hydroxy-5-methylhexan-2-one (1.3 g, 10.0 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. To this solution were added 2,6-lutidine (2.6 mL, 11.0 mmol) and TESOTf (2.5 mL, 22.0 mmol), and the mixture was stirred for 30 min at 0 °C and an additional 1 h at r.t. The reaction was stopped by the addition of sat. aq $NaHCO_3$ (10 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with aq 1 M $NaHSO_4$ (30 mL), sat. aq $NaHCO_3$ (30 mL), and brine (30 mL). After drying ($MgSO_4$) and filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography to give ketone **16** (1.2 g, 4.9 mmol, 48%); R_f = 0.75 (EtOAc–*n*-hexane, 1:20); $[\alpha]_D^{20}$ –19.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04 (dd, *J* = 8.2, 5.5 Hz, 1 H), 2.15 (s, 3 H), 1.77–1.66 (m, 1 H), 1.54–1.47 (m, 1 H), 1.46–1.33 (m, 1 H), 0.99–0.89 (m, 6 H + 6 H), 0.65–0.57 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.5, 74.9, 43.9, 24.7, 24.2, 23.3, 22.3, 6.9, 4.9.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{28}NO_2Si$ + Na [M + Na$^+$]: 267.1756; found: 267.1758.

Ketone 19

(*S*)-3-Hydroxy-5-methylhexan-2-one (1.9 g, 14.6 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. To this solution were added 2,6-lutidine (3.7 mL, 16.1 mmol) and TBSOTf (3.7 mL, 32.1 mmol), and the mixture was stirred for 15 min at 0 °C and for an additional 2 h at r.t. The reaction was stopped by the addition of sat. aq $NaHCO_3$ (10 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with aq 1 M $NaHSO_4$ (30 mL), sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give ketone **19** (2.2 g, 9.2 mmol, 64%); R_f = 0.63 (EtOAc–*n*-hexane, 1:20); $[\alpha]_D^{20}$ –20.8 (*c* 1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02 (dd, *J* = 8.5, 4.8 Hz, 1 H), 2.25 (s, 3 H), 1.77–1.68 (m, 1 H), 1.54–1.48 (m, 1 H), 1.38–1.31 (m, 1 H), 0.92–0.91 (m, 9 H + 6 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.6, 75.2, 43.9, 25.9, 24.1, 23.5, 22.2, 18.2, –4.7, –4.9.

MS: Mass was not detectable in EI-HRMS and ESI-HRMS.

LiHMDS-Mediated Aldol Reactions To Give Compounds 14, 17, and 20; General Procedure

The appropriate ketone **13**, **16**, **19** (50 mg, 1 equiv) was dissolved in THF (5 mL), the mixture was cooled to –78 °C, the base (2 equiv, Table 2) was added, and the mixture was stirred for 2 h. Isobutyraldehyde (**12**; 3 equiv) in THF (0.5 mL) was added dropwise and the mixture was stirred for 16 h. The reaction was stopped by the addition of sat. aq NH_4Cl (5 mL), the layers were separated, and the aqueous layer was extracted with MTBE (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Column chromatography of the residue afforded the *anti*-aldol product as the major compound (Table 2).

Major Diastereomer 14

R_f = 0.5 (EtOAc–*n*-hexane, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 2 H), 6.89 (d, *J* = 8.9 Hz, 2 H), 4.52 (d, *J* = 10.9 Hz, 1 H), 4.34 (d, *J* = 10.9 Hz, 1 H), 3.85–3.83 (m, 1 H), 3.82 (s, 3 H), 3.80–3.78 (m, 1 H), 2.89 (d, *J* = 3.4 Hz, 1 H), 2.69 (dd, *J* = 17.8, 2.4 Hz, 1 H), 2.57 (dd, *J* = 17.8, 9.6 Hz, 1 H), 1.86–1.76 (m, 1 H), 1.74–1.65 (m, 1 H), 1.64–1.57 (m, 1 H), 1.37–1.29 (m, 1 H), 0.96–0.89 (m, 9 H), 0.86–0.82 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.7, 159.7, 129.9, 129.5, 114.1, 83.4, 72.5, 72.3, 55.5, 41.3, 41.1, 33.3, 24.7, 23.4, 21.8, 18.5, 17.9.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{30}O_4$ + Na [M + Na$^+$]: 345.2042; found: 345.2047.

Major Diastereomer 17

R_f = 0.33 (EtOAc–*n*-hexane, 1:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11–4.04 (m, 1 H), 3.81–3.73 (m, 1 H), 3.10 (d, *J* = 3.1 Hz, 1 H), 2.76 (dd, *J* = 18.1, 2.1 Hz, 1 H), 2.58 (dd, *J* = 18.0, 9.9 Hz, 1 H), 1.76–1.66 (m, 2 H), 1.53–1.48 (m, 1 H), 1.42–1.37 (m, 1 H), 0.96–0.91 (m, 6 H + 12 H), 0.65–0.57 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.9, 77.8, 72.3, 44.0, 40.3, 33.3, 24.2, 23.3, 22.3, 18.5, 18.1, 6.9, 4.9.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{36}O_3Si$ + Na [M + Na$^+$]: 339.2331; found: 339.2334.

Major Diastereomer 20

R_f = 0.35 (EtOAc–*n*-hexane, 1:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09–4.06 (m, 1 H), 3.81–3.77 (m, 1 H), 3.08 (d, *J* = 3.1 Hz, 1 H), 2.74 (dd, *J* = 18.1, 2.1 Hz, 1 H), 2.59 (dd, *J* = 18.1, 9.9 Hz, 1 H), 1.74–1.69 (m, 2 H), 1.52–1.49 (m, 1 H), 1.39–1.36 (m, 1 H), 0.93–0.91 (m, 9 H + 12 H), 0.07–0.06 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.3, 77.9, 72.3, 44.0, 40.8, 33.2, 25.9, 24.1, 23.4, 22.2, 18.5, 18.2, 17.8, –4.6, –4.8.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{36}O_3Si$ + Na [M + Na$^+$]: 339.2331; found: 339.2332.

Boron-Mediated Aldol Reaction; Compound 14; Typical Procedure

In a 2-necked flask, ketone **13** (1 equiv) was dissolved in CH_2Cl_2 (4 mL) and cooled to –78 °C. To this solution were added (*n*-Bu)$_2$BOTf (1 M in CH_2Cl_2, 1.2 equiv) and DIPEA (1.4 equiv) and the mixture was warmed to 0 °C, stirred for 3 h and cooled to –78 °C. Isobutyraldehyde (**12**; 2 equiv) was added dropwise and stirred for 30 min. The reaction mixture was stirred for additional 16 h at –20 °C and quenched by the addition of aqueous pH 7 buffer (5 mL). After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were concentrated under reduced pressure, and the residue was dissolved in a mixture of MeOH (6 mL/mmol of ketone), aqueous pH 7 phosphate buffer (6 mL/mmol of ketone), and aq 30% H_2O_2 (30%, 3 mL/mmol of ketone). The solution was stirred for 2 h, and after separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc–*n*-hexane, 1:10) to give the product **14** (Table 3).

Mukaiyama Aldol Reaction; Compounds 15, 18; General Procedure

Freshly prepared LDA (1.05 equiv) in THF (1.5 mL) was added to a solution of the respective ketone **13**, **16** (1 equiv) in THF (2 mL) at –78 °C and stirred for 90 min at 78 °C. TMSCl (1.1 equiv) was added, the solution was warmed to r.t. and stirred for 16 h. The reaction was stopped by the addition of aqueous pH 7 buffer (5 mL), the layers were separated, the aqueous layer was extracted with MTBE (3 × 5 mL) and the combined organic phases were washed with aqueous pH 7 buffer (10 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was filtered through a plug of silica gel and the crude product was directly used for the Mukaiyama aldol reaction. The freshly prepared silyl enol ether **22**, **23** (1 equiv), respectively, was dissolved in toluene (1.5 mL), isobutyraldehyde (**12**; 2 equiv) and $BF_3{\cdot}OEt_2$ were added at –78 °C. The mixture was stirred for 1 h at –78 °C and the reaction was stopped by the addition of methanolic $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. After column chromatography, the *syn*-aldol product was obtained as the major compound (Table 3).

Major Diastereomer 15

R_f = 0.5 (EtOAc–*n*-hexane, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.9 Hz, 2 H), 4.47 (d, *J* = 11.3 Hz, 1 H), 4.37 (d, *J* = 11.6 Hz, 1 H), 3.85–3.82 (m, 1 H), 3.81 (s, 3 H), 3.79–3.73 (m, 1 H), 2.86 (d, *J* = 3.1 Hz, 1 H), 2.86 (dd, *J* = 17.6, 2.2 Hz, 1 H), 2.54 (dd, *J* = 17.6, 9.7 Hz, 1 H), 1.86–1.75 (m, 1 H), 1.71–1.58 (m, 2 H), 1.37–1.29 (m, 1 H), 0.96–0.88 (m, 9 H), 0.87–0.83 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.7, 159.7, 129.9, 129.6, 114.1, 83.9, 72.7, 72.4, 55.5, 41.2, 41.1, 33.3, 24.7, 23.3, 21.9, 18.5, 17.9.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{30}O_4$ + Na [M + Na$^+$]: 345.2042; found: 345.2045.

Major Diastereomer 18

R_f = 0.36 (EtOAc–*n*-hexane, 1:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09–4.05 (m, 1 H), 3.81–3.76 (m, 1 H), 3.00 (br s, 1 H), 2.83 (dd, *J* = 18.1, 2.1 Hz, 1 H), 2.54 (dd, *J* = 18.1, 9.9 Hz, 1 H), 1.73–1.68 (m, 2 H), 1.52–1.51 (m, 1 H), 1.50–1.48 (m, 1 H), 0.94–0.91 (m, 6 H + 12 H), 0.65–0.57 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.1, 77.8, 72.3, 44.1, 40.7, 33.2, 24.2, 23.3, 22.3, 18.5, 17.8, 6.9, 4.9.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{36}O_3Si$ + Na [M + Na^+]: 339.233; found: 339.2335.

References

(1) (a) Höfle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. German Patent DE 4211056, **1993**; *Chem. Abs*. **1993**, *119*, 180598. (b) Niggemann, J.; Bedorf, N.; Flörke, U.; Steinmetz, H.; Gerth, K.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2005**, 5013. (c) Frank, B.; Knauber, J.; Steinmetz, H.; Sharfe, M.; Blocker, H.; Beyer, S.; Müller, R. *Chem. Biol.* **2007**, *14*, 221. (d) Paterson, I.; Findlay, A. D.; Anderson, E. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 6699; *Angew. Chem.* **2007**, *119*, 6819. (e) Lorenz, M.; Kalesse, M. *Tetrahedron Lett.* **2007**, *48*, 2905. (f) Lorenz, M.; Kalesse, M. *Org. Lett.* **2008**, *10*, 4371. (g) Paterson, I.; Findlay, A. D.; Noti, C. *Chem. Commun.* **2008**, 6408. (h) Brodmann, T.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174. (i) Paterson, I.; Findlay, A. D.; Noti, C. *Chem. Asian J.* **2009**, *4*, 594.

(2) (a) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982. (b) Trost, B. M.; Rodriguez, M. S. *Tetrahedron Lett.* **1992**, *33*, 4675. (c) Denmark, S. E.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 9524. (d) Pellicena, M.; Solsona, J. G.; Romea, P.; Urpi, F. *Tetrahedron Lett.* **2008**, *49*, 5265. (e) For 1,4-stereoinduction in aldol additions of α-alkoxy boron enolates of ethyl ketones, see: Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083.

(3) (a) Kalesse, M.; Hassfeld, J.; Eggert, U. *Synthesis* **2005**, 1183. (b) Kalesse, M.; Ehrlich, G.; Hassfeld, J.; Eggert, U. *J. Am. Chem. Soc.* **2006**, *128*, 14038. (c) Kalesse, M.; Ehrlich, G.; Hassfeld, J.; Eggert, U. *Chem. Eur. J.* **2008**, *14*, 2232.

(4) (a) McCubbin, J. A.; Maddess, M. L.; Lautens, M. *Org. Lett.* **2006**, *8*, 2993. (b) Zhang, W. Y.; Jakiela, D. J.; Maul, A.; Knors, C.; Lauher, J. W.; Helquist, P.; Enders, D. *J. Am. Chem. Soc.* **1988**, *14*, 4652. (c) The analytical data were in accord with literature values.

(5) (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (c) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *89*, 2199. (d) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (e) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290. (f) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129. (g) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. (h) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443. (i) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322. (j) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(6) (a) Isolated yields. Configuration of the new stereogenic center was revised each by the Mosher-ester method. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (d) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (e) Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.

(7) Zhang, W. Y.; Jakiela, D. J.; Maul, A.; Knors, C.; Lauher, J. W.; Helquist, P.; Enders, D. *J. Am. Chem. Soc.* **1988**, *14*, 4652.

(8) (a) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1163. (b) Zhang, W.; Carter, R. G. *Org. Lett.* **2005**, *7*, 4209. (c) Deng, L.; Ma, Z.; Zhang, Y.; Zhao, G. *Synlett* **2007**, 87.

(9) Fürstner, A.; Kattrig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194.

(10) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *9*, 1011. (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381. (c) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Am. Chem. Soc.* **1986**, *51*, 3027. (d) Mori, I.; Ishihara, K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 1114. (e) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837.