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PAPER

Substrate-controlled stereoselectivity in the Yamamoto aldol reaction†

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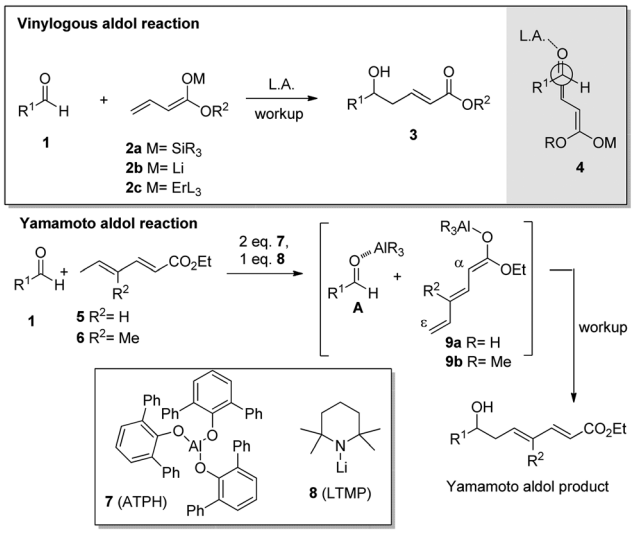
The Yamamoto aldol reaction is a vinylogous aldol reaction that relies on bulky aluminium-based Lewis acids. These activate both the aldehyde as well as become part of the enolate moiety. The report discloses the first detailed study on the substrate-controlled Yamamoto aldol reaction in which 2,3-*syn* and 2,3-*anti* disubstituted aldehydes serve as the stereodirecting elements. The "size" of the substituent in the β-position strongly determines the facial selectivity of enolate addition to the aldehyde. Large substituents favour formation of 1,3-*syn* diols while slim alkynyl groups preferentially lead to 1,3-*anti* products.

Introduction

Aldol reactions play an integral part in total synthesis programs of polyketide-based natural products.[1] Many methods have been developed for the enantioselective construction of α-alkyl/α-hydroxy and β-hydroxy carboxylic acid derivatives. Vinylogous reactions are especially powerful as they open up opportunities to build up extended polyketide-type fragments in a single step (Scheme 1).[2] A key method among the many vinylogous aldol reactions is based on Mukaiyama's use of silylenol ethers **2a** (VMAR). In fact, a large number of asymmetric conditions have been reported to date that include chiral auxiliaries (R^2) as well as chiral Lewis acids (L.A.) depending on the requirements regarding starting materials and products.[2,3] Classically, silylenol ethers are preferred for the VAR but also lithium enolates **2b** or in one case the enolate generated in the presence of a preformed chiral erbium (Er) Lewis acid **2c** have been employed. In contrast, Yamamoto's aldol reaction is less well established in natural product synthesis.[4] Previously, the method was employed by Paterson[5] *et al.* in the total synthesis of the callipeltoside aglycone and by Sammakia and Abramite[6] who used the Yamamoto protocol for macrolactonisation with preformed esters. The Yamamoto aldol reaction relies on the use of bulky Lewis acids such as the C_3-symmetric aluminium-tris-2,6-diphenylphenoxide **7** (ATPH) and lithium tetramethylpiperidine **8** (LTMP) as the base, the latter being responsible for generating the lithium enolate *e.g.* from unsaturated esters **5** or **6**, respectively.



Scheme 1 Methods of vinylogous aldol reactions.

Commonly, 2 equiv. of the aluminium-based Lewis acid **7** are being added in order to achieve metal exchange at the enolate moiety **9** as well as activation of the aldehyde (**A**) (Scheme 1).

This scenario guarantees that enolate **9** will be sterically masked at the α-position and instead will couple to the activated aldehyde **A** at the remote terminus of the vinylogous enolate moiety.

As part of our total synthesis program towards elansolid A (**10**), a polyketide-based antibiotic from *Chitinophaga sancti*,[7] we envisaged a Yamamoto aldol reaction for preparing the fragment C1–C11 **11** (Scheme 2). We planned to use the chirality present in aldehyde **12** (representing C7–C11 of the eastern fragment **11**) to control the absolute configuration of the newly formed stereogenic centre at C7 in the reaction with the enolate derived from (2*E*,4*E*)-ethyl-4-methylhexa-2,4-dienoate (**6**). Importantly, facile access to diene ester **6** is achieved by Wittig

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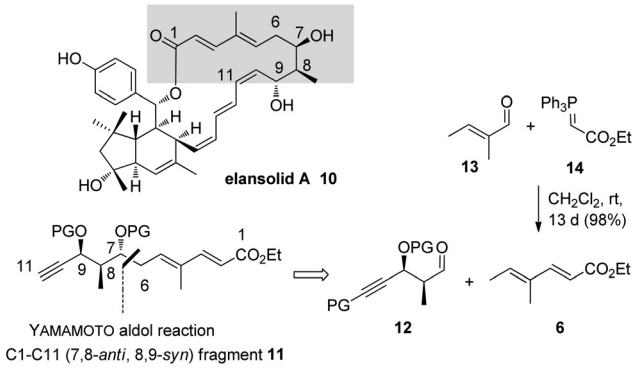


Scheme 2 Structure of elansolid A (**10**), retrosynthesis of the C1–C11 fragment **11** and synthesis of dienyl ester **6**.[7]

olefination of 2-methyl-but-2-enal **13** with ylide **14**.[8] So far, no studies on the substrate controlled Yamamoto aldol reaction have been conducted. Only recently, this issue was independently addressed for the VMAR by List[9] and Denmark.[10]

Here, we provide a report on the substrate-controlled, diastereoselective Yamamoto aldol reaction which eventually leads to the synthesis of protected C1–C11 fragment **11** of elansolid A **10**.

Results and discussion

One of the first reported examples of the Yamamoto aldol reaction was the selective 1,4-alkylation of α,β-unsaturated carbonyl compounds with Grignard reagents.[11] The bulky, most likely monomeric Lewis acid **7** does not provide space for chelating two carbonyl groups at the same time, as is commonly the case for smaller aluminium-based Lewis acids.[12] The monomeric character of **7** compensates for the fact that the electron donating phenol substituents cause reduced Lewis acid activity.[3,11]

The first asymmetric examples were disclosed by Yamamoto *et al.* using chiral esters while the use of chiral aldehydes is unexplored.[13] In view of the fact that our studies are part of the total synthesis program towards the elansolids we particularly focussed our efforts on aldehydes of the general type **B** and **C**, respectively. We studied the influence on the stereochemical outcome of the vinylogous aldol reaction with respect to three structural parameters: (a) the side chain R^1, (b) the protecting group of the hydroxyl group R^2 and (c) the relative stereochemistry of the α- as well as β-substituents (Fig. 1).

All α,β-*syn*-configured aldehydes **B** were prepared according to Evans's protocol[14] while α,β-*anti*-configured aldehydes **C** were accessed by the Masamune[15] aldol reaction. In both synthetic sequences we first blocked the newly formed hydroxyl group which was followed by reductive cleavage of the chiral

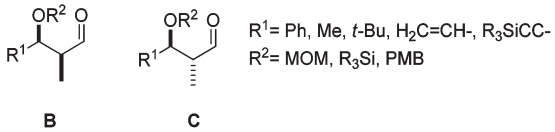


Fig. 1 General presentation of 2,3-*syn* **B** and 2,3-*anti* aldehydes **C**.

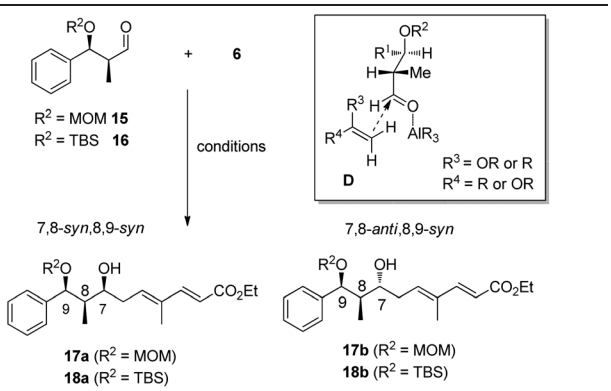
auxiliary and oxidation of the intermediate alcohol to yield the corresponding aldehydes. Experimental details and relevant analytical data of all aldehydes are given in the accompanying ESI.† In comparison to Yamamoto's original protocol we slightly modified his procedure[4] by coordinating the aldehyde with ATPH and separately forming the ester enolate in a second flask. Then, the activated aldehyde **A** was added to the ATPH enolate like **9b**. This modified procedure avoids the risk of enolisation and hence in the present cases epimerisation of the aldehyde.

Aldol reactions with 2,3-*syn* aldehydes

We initiated our studies with the 2,3-*syn*-aldehydes **15** and **16** in which R^1 is a phenyl substituent and R^2 either represents the MOM protecting group that in principle is able to exert chelation control or the sterically demanding TBS group (Table 1). In all cases, the Yamamoto aldol reaction using the enolate derived from **6** preferentially gave the 7,8-*syn*,8,9-*syn* diastereomers **17a** and **18a**, respectively. The outcome of these reactions can be rationalised if one takes Evan's transition state model into account. Here, the nucleophile attacks the aldehyde *via* an antiperiplanar transition state **D**, thereby minimizing all steric and dipole–dipole interactions to yield the Felkin–Anh product.[16]

The stereochemical outcome of the aldol reaction was elucidated by utilising Rychnovsky's acetonide method.[17] For that purpose, the protecting groups were removed (MOM: HCl–EtOH; TBS: TBAF·$3H_2O$–THF) and the resulting diols were transformed into the cyclic acetonides **19a** and **19b** (2,2-dimethoxypropane–PPTS–CH_2Cl_2), respectively. Relevant and

Table 1 Yamamoto aldol reaction with 2,3-*syn* aldehydes **15** and **16** and antiperiplanar transition state **D** for the formation of *all-syn* products (MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl)



Entry[a]	Aldehyde	Temp.	Isolated yield (%)	Diastereomeric ratio 7,8-*syn*/7,8-*anti*
1	**15**	−78 °C	88	5 : 1
2	**15**	0 °C	89	2 : 1
3	**16**	−78 °C	49	2 : 1
4	**16**	0 °C	90	1.5 : 1

[a] Conditions: (i) **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) aldehyde **15**/**16** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C, added to solution (i), 30 min; (iv) solution of (ii) added to solution (iii), −78 °C or 0 °C, 16 h.

diagnostic ^{1}H- and ^{13}C-NMR data for both diastereoisomers are listed in Fig. 2.

This method of assignment was also used to unravel the stereochemical preference of all other Yamamoto aldol reactions described below. Details are found in the ESI.†

This study was extended to aldehydes **20–25** that differ in the substituent R^1 (methyl, vinyl, *t*-butyl) and the protecting group R^2 (MOM, TBS). When R^1 equals methyl or vinyl the stereocontrol was only low to moderate again with preference for the 7,8-*syn* diastereomers **26b–29b**, irrespective of the protecting group chosen (Table 2, entries 1–4). However, facial selectivity considerably improved when the bulky *t*-butyl group was chosen for R^1. Aldehydes **24** and **25** preferentially afforded the 7,8-*syn*, 8,9-*syn* Yamamoto aldol products **30a** and **31a** when reacted with enolate **9b** (Table 2, entries 5–7). In the case of the TBS-protection the *syn*-selectivity turned out to be excellent at −78 °C (Table 2, entry 7). Steric hindrance exerted by the *t*-butyl group probably hampered the facile approach of the enolate **9b** so that we also conducted the reaction at 0 °C (Table 2, entry 7). The yield improved for the TBS-protected aldehyde **25** but the facial selectivity dropped. It can be assumed that particularly the bulky substituent R^1 strongly favours transition state **D** (Scheme 1).

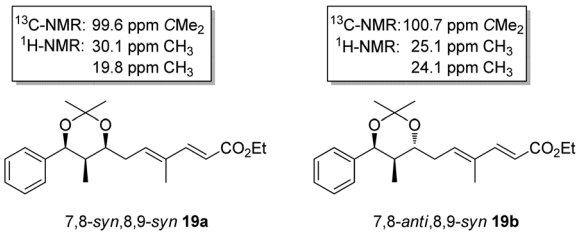
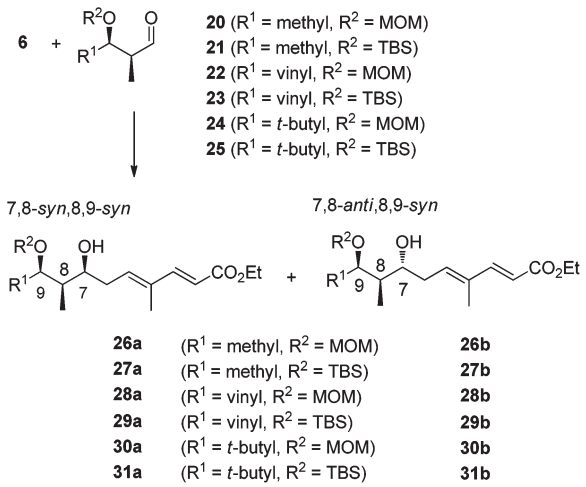


Fig. 2 Diagnostic ^{1}H- and ^{13}C-NMR data of acetonides 7,8-*syn*,8,9-*syn* **19a** and 7,8-*anti*,8,9-*syn* **19b** according to Rychnovsky *et al.*[17]

Table 2 Yamamoto aldol reaction with 2,3-*syn* aldehydes **20–25** (stereochemical assignment in analogy to Fig. 2; see ESI†)



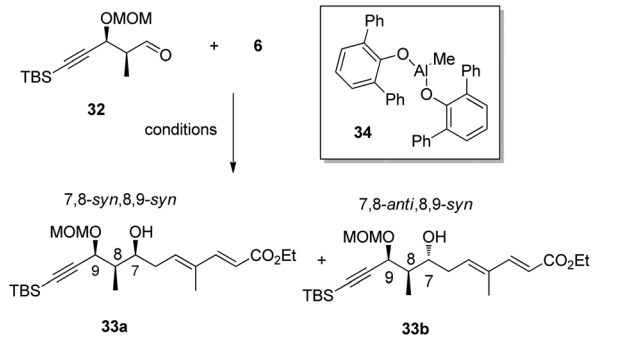
Entry[a]	Aldehyde	Isolated yield (%)	Diastereomeric ratio 7,8-*syn*/7,8-*anti*
1	**20**	72	**26a** : **26b** = 3 : 1
2	**21**	80	**27a** : **27b** = 2 : 1
3	**22**	91	**28a** : **28b** = 1 : 1
4	**23**	90	**29a** : **29b** = 2 : 1
5	**24**	69	**30a** : **30b** = 6 : 1
6	**25**	62	**31a** : **31b** > 10 : 1
7	**25**[b]	90	**31a** : **31b** = 6 : 1

[a] Standard conditions: (i) **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) aldehydes **20–25** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C added to solution (i), 30 min; (iv) solution (ii) added to solution (iii), −78 °C or 0 °C, 16 h. [b] Reaction temperature 0 °C.

However, these results suggest that the *anti*-selective Yamamoto aldol reaction would be difficult to achieve. Thus, use of this protocol for the preparation of the eastern fragment **11** of elansolid A **10** has to be regarded as a challenge.[18] Nevertheless, we first tested the TBS-substituted alkyne **32** in combination with a MOM protection (Table 3). Under the standard conditions at −78 °C the Yamamoto aldol reaction yielded the aldol products **33a,b**, this time however, with a small preference for the 7,8-*anti*,8,9-*syn* diastereomer **33b** (Table 3, entries 2 and 3). This promising trend became more pronounced when the reaction temperature was raised (Table 3, entries 4–6). However, higher temperatures were accompanied by formation of degradation products and at 50 °C selectivity was lost completely (Table 3, entry 7).

Interestingly, when we exchanged the Lewis acid for coordination to the aldehyde from ATPH **7** to the sterically less

Table 3 Yamamoto aldol reaction with alkynyl-substituted 2,3-*syn* aldehyde **32** (stereochemical assignment in analogy to Fig. 2; see ESI†)



Entry[a]	Conditions	Isolated yield (%)	Ratio **33a**/**33b**
1	**32** not precomplexed	18	2 : 1
2	Standard, −78 °C, 105 min	51	1 : 1.5
3	Standard, −78 °C, 16 h	80	1 : 1.5
4	Standard, −40 °C, 75 min	65	1 : 2.5
5	Standard, 0 °C, 16 h	61	1 : 3
6	Standard, rt, 16 h	58	1 : 3
7	Standard, 50 °C, 2 h	77	1 : 1
8	Standard except **32** was complexed with **34**, −78 °C, 16 h	84	2.5 : 1
9	One pot, −78 °C, 16 h ref. 4	93	1 : 1

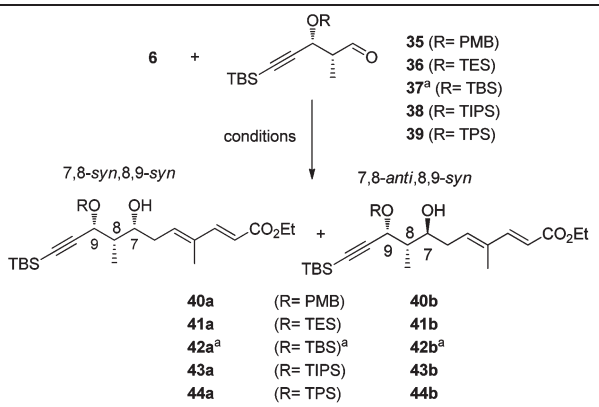
[a] Standard conditions: **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) **32** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C, added to solution (i), 30 min; (iv) solution (ii) added to solution (iii), −78 °C or 0 °C, 16 h.

demanding Lewis acid methyl-aluminium-bis-2,6-diphenylphenoxide (MAPH, **34**) the diastereoselectivity was reversed again favouring the *all-syn* product **33a** (Table 3, entry 8). We also probed the one pot procedure originally reported by Yamamoto *et al.*[4] but did not encounter improved yields or selectivities. Finally, precomplexation of the aldehyde and formation of intermediate **A** (Scheme 1) is crucial because otherwise the aldol reaction only proceeded in very low yield (Table 3, entry 1).

With these promising results in hand we next studied the influence of different protecting groups on the β-hydroxyl group of the aldehyde on the facial selectivity of the aldol reaction (Table 4). Besides the *p*-methoxybenzyl (PMB) group which in our hands turned out not to be suited for the Yamamoto aldol reaction, we chose four different silyl groups. Our results reveal that silyl protecting groups exhibit similar or even better 7,8-*anti* stereoselectivities compared to the MOM group. Best results were obtained for the TBS group at −78 °C (Table 4, entries 4, 8 and 9). In some cases, particularly when the reaction temperature was kept above 0 °C, by-products were detected which most likely are isomers that have Z-stereochemistry in the diene unit. These isomers showed almost identical ^{1}H NMR spectra except that H5 and neighbouring protons showed major chemical shift differences compared to the desired aldol products. Noteworthy, the use of the Lewis acid MAPH **34** yielded similar yields and selectivities with aldehyde **37** as did the standard Lewis acid ATPH **7**. The newly formed stereogenic center at C7 was also assigned using Rychnovsky's acetonide method.[17] However, slim substituents like the alkynyl group are problematic to impose a defined conformation on the dioxolane ring.[19] A few standard transformations yielded acetonides **46a** and **46b**, respectively (Scheme 3). While the NMR data collected for **46a** are clearly diagnostic for the expected chair conformation of 1,3-*syn* diols, the other diastereomer **46b** gave ambiguous results. In order to secure the stereochemistry, **46b** was hydrogenated to the corresponding alkene **47** and the NMR data were compared with the dioxolane generated from aldol products **29** (see ESI†) unequivocally confirming the 1,3-*anti* relationship of the two alkoxy-functionalities.

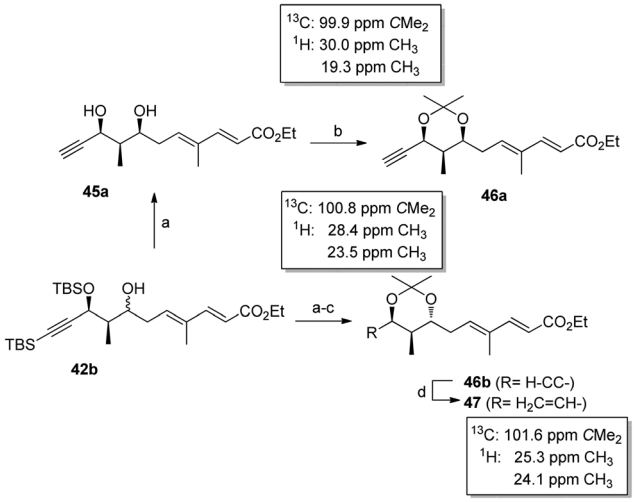
The preferred formation of the 7,8-*anti* diastereomers in the Yamamoto aldol reactions of aldehydes that bear a silyl-substituted alkynyl group in the β-position requires one to consider a transition state alternative to **D** that supposedly is responsible for the formation of the 7,8-*syn* products. We propose that the aldehyde preferentially adopts the conformation **E** in which all sterically demanding structural elements (a. Lewis acid ATPH opposite to the siloxy group and b. the alkynyl-bound TBS group opposite to the activated carbonyl group) are as far apart from each other as possible (Scheme 4). Thus, the alkynyl moiety directs the TBS group away from the reaction centre. In fact, this TBS group influences the preferred conformation in the transition state because we observed no stereoselectivity for

Table 4 Yamamoto aldol reaction with alkynyl-substituted 2,3-*syn* aldehydes **35**–**39** (TES = triethylsilyl, TIPS = triisopropylsilyl, TPS = triphenylsilyl) (stereochemical assignment in analogy to Fig. 2; see ESI†)

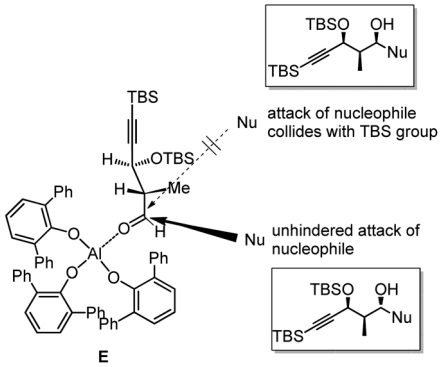


Entry[a]	Aldehyde	Conditions[b]	Isolated yield (%)	Diastereomeric ratio 7,8-*syn* : 7,8-*anti*
1	**35**	−78 °C, 16 h	—	—[c]
2	**36**	−78 °C, 16 h	55	**41a** : **41b** = 1 : 1
3	**36**	0 °C, 16 h	9	**41a** : **41b** = ~1 : 1.5[d]
4	**37**	−78 °C, 16 h	89	**42a** : **42b** = 1 : 3
5	**37**	0 °C, 16 h	62	**42a** : **42b** = 1 : 2[e]
6	**37**	rt, 16 h	41	**42a** : **42b** = 1 : 2[e]
7[f]	**37**	−78 °C, 16 h	n.r.	—
8[g]	**37**	−78 °C, 16 h	74	**42a** : **42b** = 1 : 3.5
9[h]	**37**	−78 °C, 16 h	70	**42a** : **42b** = 1 : 3.5
10	**38**	−78 °C, 16 h	61	**43a** : **43b** = 1 : 2.5
11	**38**	0 °C, 16 h	40	**43a** : **43b** = 1 : 2.5
12	**39**	−78 °C, 16 h	78	**44a** : **44b** = 1 : 2
13	**39**	0 °C, 2 h	50	**44a** : **44b** = 1 : 2.5

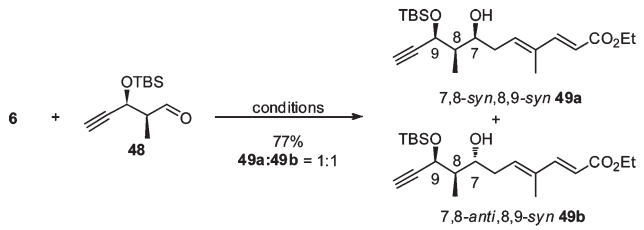
[a] The enantiomer with respect to the general structure was employed instead. [b] Standard conditions: **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) **35**–**39** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C, added to solution (i), 30 min; (iv) solution (ii) added to solution (iii), −78 °C or 0 °C, 16 h. [c] ~1 : 1 mixture and complex mixture of by-products along with decomposition products. [d] About 25% *Z*-isomers. [e] About 15% *Z*-isomers. [f] $AlMe_3$ as the Lewis acid. [g] MAPH **34** as the Lewis acid. [h] One pot procedure.[4]



Scheme 3 Syntheses of acetonides **46a**,**b** and **47** and diagnostic ^{1}H- and ^{13}C-NMR-data. Reagents and conditions: a. TBAF·3H_2O, THF, 0 °C, 25 min, 96% (69% for **46b** + 27% for diastereomers **45b**/separated afterwards by flash chromatography); b. 2,2-dimethoxypropane, PPTA, CH_2Cl_2, rt, 3 h, 85% for **46a** and 95% for **46b**; c. TBAF·3H_2O, THF, 0 °C, 25 min, 96%; d. Lindlar catalyst (3 mol% Pd), H_2, CH_2Cl_2, rt, 105 min, 75%.



Scheme 4 Postulated transition state for the formation of 7,8-*anti* aldol products from β-alkynyl substituted aldehydes.



Scheme 5 Aldol reaction of enolate derived from diene **6** and 2,3-*syn* aldehyde **48** (stereochemical assignment in analogy to Fig. 2; see ESI†). Conditions: (i) **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) **48** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C, added to solution (i), 30 min; (iv) solution (ii) added to solution (iii), −78 °C, 16 h.

Yamamoto aldol reactions of β-alkynyl-substituted aldehydes without an alkynyl-bound TBS group (Scheme 5; for the preparation of **48**: see ESI†). In essence, conformation **E** supports a different angle of approach for nucleophiles. Attack from the backside is hindered by the silyloxy group while the front face is less hindered for nucleophilic attack.

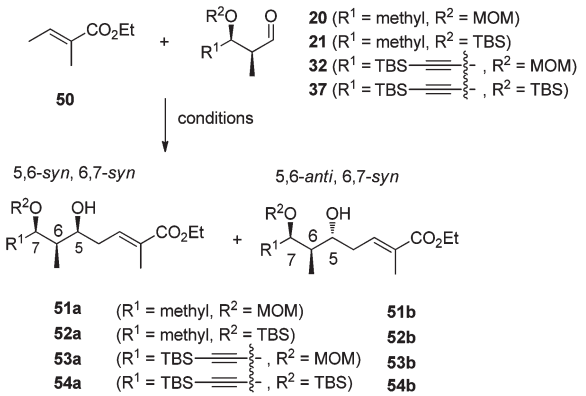
When a smaller coordinating Lewis acid such as MAPH **34** is chosen and the size of the hydroxyl protection is reduced, as is the case for the MOM group, transition state **D** prevails and the Yamamoto aldol reaction becomes *syn*-selective (see Table 3, entry 8).

Based on these results, we studied the Yamamoto aldol reaction employing two different enolates, the first one generated from ethyl tiglate (**50**). It is a simpler analogue of enolate **9b** that derives from ester **6**. For comparison reasons we chose four 2,3-*syn* aldehydes **20**, **21**, **32** and **37** (Table 5). The Yamamoto aldol reaction furnished aldol products **51**–**54** with good isolated yields and the expected stereoselectivities except with aldehyde **32** which are in the range of enolate **9b** (see Table 2, entries 1 and 2, and Table 4, entries 8 and 9). Only for aldehyde **32** selectivities changed towards **53a**, giving similar selectivities as with MAPH as the Lewis acid. This might be due to the fact that MOM is not stabilising transition state **E** as good as TBS and with the sterically less demanding enolate preferences are changing.

Likewise, we employed the extended enolate derived from triene **55**. Ester **55** was prepared in overall 64% yield by means of a three step procedure from ester **6** that included reduction and Wittig olefination (see ESI†). The Yamamoto aldol reaction with 2,3-*syn* aldehyde **37** furnished the desired product as a mixture of diastereomers **56** in excellent yield with the 9,10-*anti* product **56b** being the major isomer (Scheme 6).

These examples clearly demonstrate that the preferred conformation of the complexed aldehyde **A** (see Scheme 1) is responsible for the stereochemical outcome of the substrate-controlled Yamamoto aldol reaction.

Table 5 Yamamoto aldol reaction of enolate derived from ethyl tiglate (**47**) with 2,3-*syn* aldehydes (stereochemical assignment in analogy to Fig. 2; see ESI†)

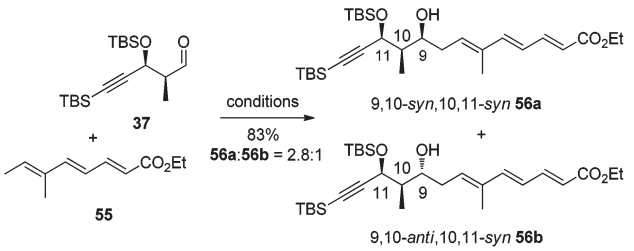


Entry[a]	Aldehyde	Isolated yield (%)	Diastereomeric ratio 5,6-*syn* : 5,6-*anti*
1	**20**	72	**51a** : **51b** = 2.5 : 1
2	**21**	80	**52a** : **52b** = 2.5 : 1
3	**32**	70	**53a** : **53b** = 4 : 1
4	**37**	87	**54a** : **54b** = 1 : 2.5

[a] Standard conditions: **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) **20**, **21**, **32** or **37** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C, added to solution (i), 30 min; (iv) solution (ii) added to solution (iii), −78 °C or 0 °C, 16 h.

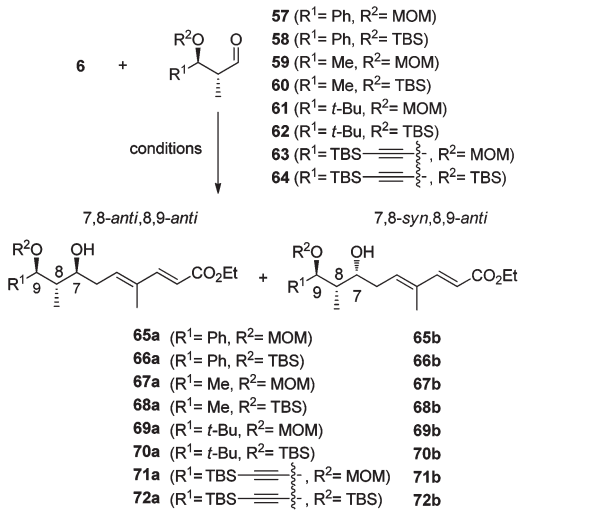
Aldol reactions with 2,3-*anti* aldehydes

In a second series of experiments we investigated the use of 2,3-*anti* aldehydes **57**–**64** in the Yamamoto aldol reaction with enolate **9b** (Table 6). Commonly, aldol products **65** to **72** were obtained in good to very good yields. Similar to the results obtained with 2,3-*syn* aldehydes **24** and **25** (Table 2, entries 5, 7 and 8) the bulky *t*-butyl group (R^1) provided best selectivities yielding 7,8-*syn*,8,9-*anti* aldol products **69b** and **70b**, respectively, as major isomers (Table 6, entries 5 and 6) which may be formed *via* transition state **F**. Here, reinforcing effects of Felkin–Anh control and preferred 1,3-*anti* diol formation are operative.[16] To a lesser extent the smaller methyl side chain follows the same trend (Table 6, entries 3 and 4). When R^1 equals phenyl or the TBS-substituted alkynyl group, diastereocontrol is lost or reversal of selectivity has to be encountered (Table 6, entries 1, 2, 7 and 8). Here, transition state **G** may play a more dominant role in which the substituents in the β-position are rotated to new positions, because not R^1 but the protected hydroxyl group become



Scheme 6 Aldol reaction of enolate derived from triene **52** and 2,3-*syn* aldehyde **37** (stereochemical assignment in analogy to Fig. 2; see ESI†). Conditions: (i) **55** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) **37** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C, added to solution (i), 30 min; (iv) solution (ii) added to solution (iii), −78 °C, 16 h.

Table 6 Yamamoto aldol reactions with 2,3-*anti* aldehydes **57–64** and proposed transition states **F** (leading to 7,8-*syn*,8,9-*anti* products) and **G** (leading to 7,8-*anti*,8,9-*anti* products)[16] (stereochemical assignment in analogy to Fig. 2; see ESI†)



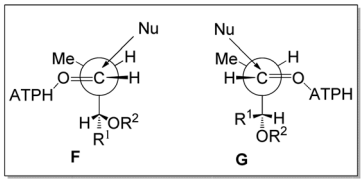
Entry[a]	Aldehyde	Isolated yield (%)	Diastereomeric ratio 7,9-*syn* : 7,9-*anti*
1	**57**	64	**65a** : **65b** = 1 : 1
2	**58**	79	**66a** : **66b** = 2 : 1
3	**59**	87	**67a** : **67b** = 1 : 2.5
4	**60**	79	**68a** : **68b** = 1 : 2
5	**61**	63	**69a** : **69b** > 1 : 10
6	**62**	77	**70a** : **70b** = 1 : 7
7	**63**	58	**71a** : **71b** = 2 : 1
8	**64**	88	**72a** : **72b** = 1 : 1

[a] Standard conditions: **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) **57–64** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C, added to solution (i), 30 min; (iv) solution (ii) added to solution (iii), −78 °C or 0 °C, 16 h.

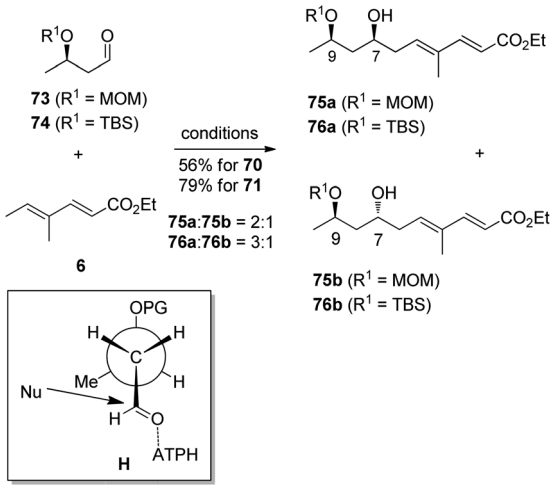
sterically more demanding. Now, the nucleophile **9b** accesses the carbonyl group from the other face.

Aldol reactions with β-alkoxy aldehydes

All discussion on the proposed transition states **D–G** did not centre on the role of the α-methyl group in the aldehyde moiety.



Therefore, also aldehydes **73** and **74**, both lacking α-branching, were employed in the Yamamoto aldol reaction (Scheme 7). In both cases, the 7,9-*syn* diastereomers were formed as major products. Due to the lack of the methyl group in the α-position, only the alkoxy group in the β-position exhibits stereochemical control. In the proposed transition state **H** the interaction between the side chain (here the small methyl group) and the bulky ATPH that is complexed to the carbonyl group is minimised. The OR group is proposed to be the sterically most demanding group and is therefore placed in the antiperiplanar position with respect to the carbonyl group.



Scheme 7 Aldol reactions with β-alkoxy aldehydes **73** and **74** and postulated transition state **H**[16] (stereochemical assignment in analogy to Fig. 2; see ESI†). Conditions: (i) **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) **73**/**74** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.), THF, −78 °C, added to solution (i), 30 min; (iv) solution (ii) added to solution (iii), −78 °C, 16 h.

Aldol reactions with ketone 78

Finally, we chose alcohol **77** that is available en route towards aldehyde **60** and initiated proton-induced silyl migration to form the corresponding secondary alcohol which then was oxidised to the ketone **78** using Dess–Martin periodinane (DMP) (Scheme 8). Stereocontrol was found to be minute in the following Yamamoto aldol reaction that yielded a diastereomeric mixture of (7*S*)-**79a** and (7*R*)-**79b** with minor preference for the Felkin–Anh product (7*S* : 7*R* = 1.5 : 1).

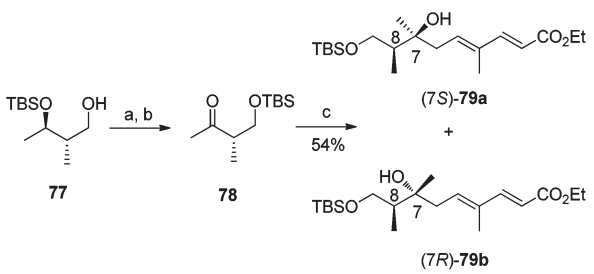
For structure elucidation the TBS group was removed at which point both diastereomers were separated chromatographically. The 7*R*-diol was transformed into the corresponding acetonide (7*R*)-**80** (Scheme 9). NMR data that included analysis of nOe-experiments proved the 7*R*-configuration. Particularly the

coupling constant $^3J_{8,9a}$ = 11.7 Hz supported the antiperiplanar orientation of H8 and H9a that can only be expected for the 7*R*-diastereomer (conformation **I**). It needs to be pointed out that conformation **II** is also feasible, yet H8 and H9 cannot adopt an axial–axial orientation responsible for a large $^3J_{8,9a}$ coupling constant. Furthermore, it should be unlikely for the sterically demanding R group to be in the axial orientation although both methyl groups have to be axial instead. In the case of the (7*S*)-diastereomer both protons are either oriented equatorially or adopt an equatorial–axial orientation with subsequent smaller coupling constants (*J*).[20] In fact, this is the first reported application of the Yamamoto aldol reaction with a ketone. Still, this preliminary result needs to be studied in more detail with respect to the scope and control of selectivity.

Conclusion

We found that the substrate-controlled asymmetric Yamamoto aldol reaction is feasible with respect to yields and selectivities under certain conditions. Clearly, the enolate although containing the large ATPH moiety does not influence the stereochemical outcome of the vinylogous aldol reaction with 2,3-disubstituted aldehydes. It is the preferred conformation of the aldehyde in the transition state which is activated by ATPH that determines the facial selectivity of the Yamamoto aldol reaction. The "size" of the substituent in the β-position strongly influences aldehyde conformation and determines the facial selectivity. Large substituents favour formation of 1,3-*syn* diols while slim alkynyl groups preferentially lead to 1,3-*anti* products. The current study led to the successful synthesis of the eastern fragment of elansolid A **10** by utilising the substrate-controlled Yamamoto aldol reaction.

Further studies will have to be directed towards the complexation of the aldehyde moiety with even larger Lewis acids than ATPH or with bulky chiral Lewis acids.

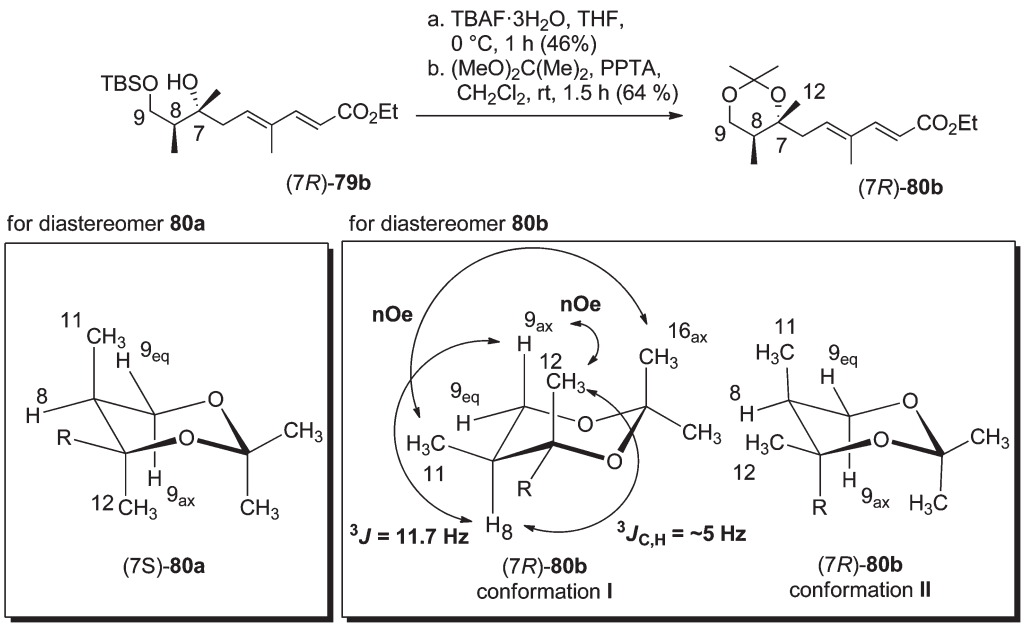


Scheme 8 Synthesis of ketone **78** and Yamamoto aldol reaction with enolate **9b** derived from ester **6**. Reagents and conditions: (a) silica gel; (b) DMP, $NaHCO_3$, CH_2Cl_2, rt, 1 h, 64%; (c) (i) **6** (2.0 equiv.), **7** (2.2 equiv.), toluene, −78 °C, 30 min; (ii) **78** (1.0 equiv.), **7** (2.0 equiv.), toluene, −78 °C, 30 min; (iii) **8** (2.3 equiv.) to (i), THF, −78 °C, 30 min; (iv) (ii) to (iii), −78 °C, 16 h.

Experimental

General remarks

Unless otherwise stated, all chemicals and solvents were purchased in per analysis quality and used as received. ^{1}H NMR spectra were recorded at 400 MHz or 500 MHz and ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz with a BRUKER Avance 400, a DPX 400 or a DRX 500. Chemical shift values of NMR data are reported as values in ppm relative to (residual undeuterated) the solvent signal as an internal standard. Multiplicities for ^{1}H NMR signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; where appropriate with the addition of b = broad. ^{13}C multiplicities refer to the resonances in the off-resonance decoupled spectra and were elucidated using the distortionless enhancement by the polarisation transfer (DEPT) spectral editing technique. Multiplicities for ^{13}C NMR signals are reported using the following abbreviations: q = quaternary (CR_4), t = tertiary



Scheme 9 Synthesis of acetonide **80b** and diagnostic NMR data for determining the configuration at C7 in (7*R*)-**79b**.

(R_3CH), s = secondary (R_2CH_2) and p = primary (RCH_3). Mass spectra were obtained with a type LCT (ESI) (Micromass) equipped with a lockspray dual ion source in combination with a Waters Alliance 2695 LC system, or with a type Q-TOF premier (Micromass) spectrometer (ESI mode) in combination with a Waters Acquity UPLC system equipped with a Waters BEH C18 1.7 μm (SN 01473711315545) column (solvent A: water + 0.1% (v/v) formic acid; solvent B: MeOH + 0.1% (v/v) formic acid; flow rate = 0.4 mL min^{-1}; gradient (t [min]/solvent B [%]): (0 : 5) (2.5 : 95) (6.5 : 95) (6.6 : 5) (8 : 5)). Ion mass signals (m/z) are reported as values in atomic mass units. Optical rotations were measured on a Perkin-Elmer polarimeter type 341 or 241 in a quartz glass cuvette at l = 589 nm (Na D-line). The optical rotation is given in [° ml g^{-1} dm^{-1}] with c = 1 corresponding to 10 mg ml^{-1}. Flash-chromatography was done with silica gel (Acros, particle size 35–70 μm) by applying moderate pressure. Preparative HPLC was operated at a MERCK HITACHI LaChrome HPLC (Pump L7150 or L7100, Interface D-7000, Diode Array Detector L-7450) respectively at a BECKMANN system Gold HPLC (Solvent Module 125, Detector 166). Solvents, columns, operating procedures and retention times are given with the corresponding experimental and analytical data.

General procedure for the Yamamoto-aldol reaction

Solution A: 2,6-Diphenylphenol (6.6 equiv.) was dissolved in toluene (c = 0.28 mol l^{-1}, with respect to $AlMe_3$) and $AlMe_3$ (c = 2 mol l^{-1} in toluene, 2.2 equiv.) was slowly added over 30 min after which time the yellow solution was stirred for 30 min at rt and then cooled to −78 °C. The ester (2.0 equiv.) was dissolved in toluene (c = 1 mol l^{-1}) and slowly added. The resulting solution was stirred for 30 min at −78 °C. **Solution B (LTMP-solution 8)**: 2,2,6,6-Tetramethyl-piperidine (2.3 equiv.) was dissolved in THF (c = 0.19 mol l^{-1}) and cooled to −78 °C. n-BuLi (c = 2.5 mol l^{-1} in hexane, 2.3 equiv.) was added dropwise. The resulting solution was stirred for 20 min at −78 °C and slowly added to solution A. The resulting mixture was stirred for 40 min at −78 °C. **Solution C**: 2,6-Diphenylphenol (6.0 equiv.) was dissolved in toluene (c = 0.28 mol l^{-1} with respect to $AlMe_3$) and $AlMe_3$ (c = 2 mol l^{-1} in toluene, 2.0 equiv.) was slowly added over 45 min. Afterwards the solution was stirred for 30 min at rt and then cooled to −78 °C. The aldehyde (1.0 equiv.) was dissolved in toluene (c = 1 mol l^{-1}) and added dropwise. The solution was stirred for 30 min at −78 °C. Solution C was added over 10 min to solution A and the resulting reaction mixture was stirred at −78 °C overnight. The reaction was terminated by addition of aq. NH_4Cl, warmed up to rt and stirred for 3 h after the addition of a solution of Na-K-tartrate. The layers were separated and the aqueous layer extracted with EE. The combined, organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography (petroleum ether : ethyl acetate; ratios are given).

Specifically for the Yamamoto aldol product **31**: Aldehyde **25** (48 mg, 0.18 mmol, 1.0 equiv.) was reacted with ester **6** (56 mg, 0.36 mmol, 2.0 equiv.) at −78 °C overnight using the general procedure. The crude product was purified by flash chromatography (petroleum ether : ethyl acetate = 30 : 1 → 10 : 1) and furnished alcohol 7,8-*syn*,8,9-*syn*-**31** (*dr*: >10 : 1, 46 mg, 0.11 μmol; 62%) as a yellow oil.

R_f = 0.23 (PE : EE = 10 : 1); $[\alpha]_D^{20}$ = −13.0 (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ 7.33 (d, 1H, J = 15.7 Hz, H-3), 5.96 (dd, 1H, J = 7.5, 7.2 Hz, H-5), 5.82 (d, 1H, J = 15.7 Hz, H-2), 4.20 (q, 2H, J = 7.3 Hz, H-14), 3.55 (ddd, 1H, J = 6.2, 6.2, 6.2 Hz, H-7), 3.33 (d, 1H, J = 2.4 Hz, H-9), 2.40–2.48 (m, 1H, H-6_a), 2.28–2.39 (m, 1H, H-6_b), 1.79–1.90 (m, 1H, H-8), 1.80 (s, 3H, H-12), 1.54 (brs, 1H, OH), 1.29 (t, 3H, J = 7.3 Hz, H-15), 0.88–0.96 (m, 12H, H-11 + H-13), 0.86 (s, 9H, TBS), 0.08 (s, 3H, TBS), 0.05 (s, 3H, TBS) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ 167.6 (q, C-1), 149.2 (t, C-3), 137.9 (t, H-5), 135.0 (q, C-4), 116.4 (t, C-2), 80.2 (t, C-9), 75.4 (t, C-7), 60.4 (s, C-14), 39.8 (t, C-8), 37.2 (q, C-10), 35.3 (s, C-6), 26.7 (p, C-11), 26.5 (p, TBS), 18.9 (q, TBS), 14.5 (p, C-15), 12.6 (p, C-12), 10.2 (p, C-13), −2.8 (p, TBS), −4.0 (p, TBS) ppm; **HRMS** (ESI): m/z: calculated for $C_{23}H_{45}O_4Si$: 413.3087 $[M + H]^+$, found: 413.3075 $[M + H]^+$.

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