CHEMISTRY
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Title: Polyoxygenated Tertiary Alcohols - A Kiyooka Approach

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201902589

Link to VoR: http://dx.doi.org/10.1002/chem.201902589

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Polyoxygenated Tertiary Alcohols - A Kiyooka Approach

Daniel Lücke, Markus Kalesse*

Dedicated to Prof. Hans-Ulrich Reißig on the occasion of his 70th birthday

Abstract: A Kiyooka aldol approach for the stereoselective synthesis of tertiary alcohols is presented. This approach allows for the incorporation of different substituents at all three remaining positions at the chiral center bearing the tertiary alcohol. To demonstrate the validity of this approach different chiral alcohols were depicted and the relationship of double bond geometry of the ketene acetal and the diastereoselectivity was established.

In the course of our program to provide synthetic access to biologically active natural products[1] we chose the tedanolides[2] as promising targets. Within this family of secondary metabolites tedanolide C (**1**)[3] (Figure 1) attracted our attention due to its unusual polyoxygenated structure exhibiting a tertiary alcohol. Additionally, the ongoing discussion about its configuration prompted us to focus on the Kiyooka aldol reaction with ketene acetal **7**. In general, tertiary alcohols are important structural motifs in the synthesis of natural products as well as challenging synthetic targets.[4] In 2011 our group reported a Kiyooka aldol[5] protocol for the stereoselective synthesis of tertiary alcohols flanked by three additional oxygenated carbon atoms (Figure 2).[3c] This was recently applied by Trauner and co-workers to their total synthesis of kweichowenol A (**3**).[6] In our initial studies only achiral aldehydes or such with distal stereocenters were used.

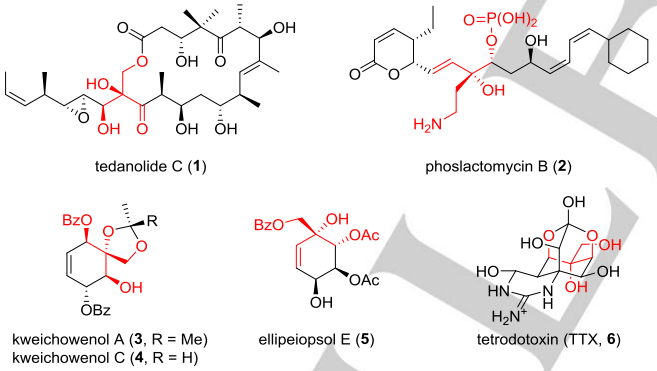

Figure 1. Natural products featuring polyoxygenated tertiary alcohols.

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As several natural products feature tertiary alcohols flanked by three oxygenated carbon atoms or functional groups derived from them and further stereogenic centers in close proximity (Figure 1), we planned on expanding the scope of our methodology to such motifs. Here, we describe the general applicability of this transformation using different α– and/or β–chiral aldehydes as such motifs are often found in a variety of other natural products[7] and not only in tedanolide C (**1**).

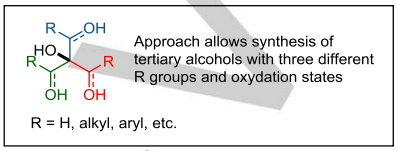
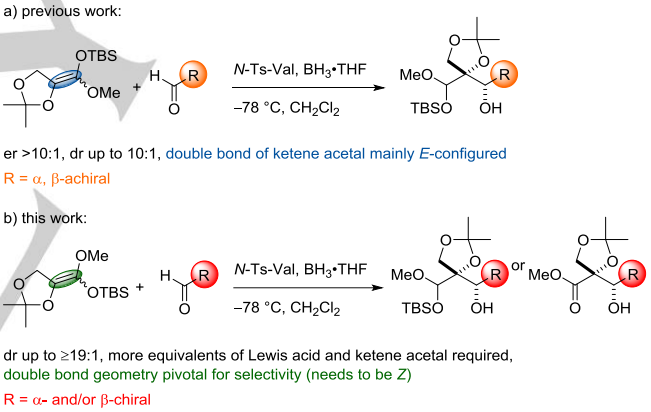


Figure 2. Structural motifs accessible via Kiyooka aldol reaction.



Scheme 1. Kiyooka aldol reaction for the synthesis of tertiary alcohols flanked by three oxygenated carbon atoms. TBS = *tert*-butyldimethylsilyl, Ts = tosyl, Val = valine.

We started our investigations with the Kiyooka aldol reaction of the (*R*)-Roche ester derived aldehyde **8**[3c], [8] (Table 1). Utilization of our previously established conditions[3c] provided TBS protected hemiacetal **9** in low yield due to major amounts of non-reacted aldehyde (entry 1). Conversion and yield were improved by increasing the amounts of ketene acetal **7** and the Lewis acid added to the reaction (entries 2 to 4). We rationalized the latter by coordination of the oxazaborolidinone to the PMB-ether. However, we were unable to push the reaction to full conversion as at some point massive formation of unknown by-products were observed (entry 5).

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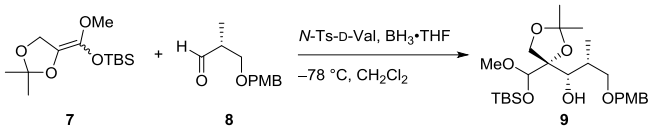
Table 1. Selected optimization results for the Kiyooka aldol reaction of aldehyde **8**.[a]



7 **8** **9**

entry	**8** (eq.)	*N*-Ts-D-Val (eq.)	BH_3·THF (eq.)	Yield[b]
1[c]	1.30	1.20	1.00	18%
2[c]	1.30	2.20	2.00	50%
3[c]	2.00	2.20	2.00	61%
4[c]	**2.50**	**2.70**	**2.50**	**67%**
5	3.00	3.20	3.00	nd[d]

[a] Reaction conditions **8** (1.00 eq., 0.31 – 0.37 mmol), *c* = 0.1 M. [b] Isolated yield after column chromatography. [c] Reaction did not go to full conversion. [d] Product could not be separated from unknown byproducts. PMB = *p*-methoxybenzyl.

When using different batches of ketene acetal **7** we were faced with problems of strongly varying diastereoselectivities for the newly formed tertiary and secondary alcohol. This we rationalized by different ratios of double bond isomers of ketene acetal **7**. To confirm this hypothesis we enriched both double bond isomers by fractionated distillation and applied the so-separated isomers to the Kiyooka aldol reaction. The obtained products were analyzed by ^{1}H-NMR focusing on the proton at the hemiacetal (Figure 3, highlighted in red). By doing so we observed a strong dependency between the formation of the desired diastereomer and the double bond geometry of the applied ketene acetal. (Figure 3, a to d). The required double bond geometry could be identified as *Z* using NOE correlations between the methoxy and methylene group (see Supporting Information). To further optimize this transformation we investigated different conditions to increase the amount of *Z*-configured ketene acetal. In accordance with the literature,[9] the use of potassium hexamethyldisilazide instead of its lithium analogue provided a massive increase of the *Z*-isomer (*E*:*Z* = 1:6 after distillation). Usage thereof not only provided the best diastereoselectivities (Figure 3, e), but also gave full conversion of aldehyde **8**. Even though it is known that ketene acetal double bond geometry can affect the diastereoselectivity of Mukaiyama aldol reactions,[10] we consider this observation noteworthy as there are no systematic investigations on this dependency. In this context it should also be mentioned that we obtained good selectivities in our previous Kiyooka study on achiral substrates using an excess of *E*-configured ketene acetal.[3c]

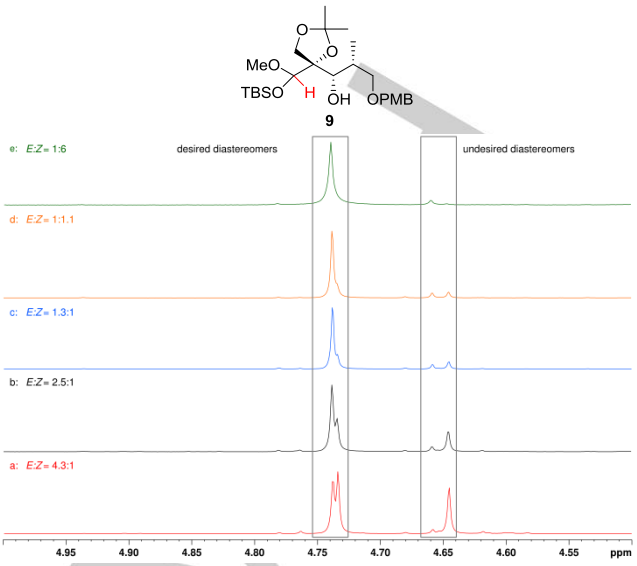


Figure 3. Dependency between stereoselcetivity and double bond geometry determined by ^{1}H-NMR of TBS protected hemiacetal **9**.

With the optimized conditions in hand, we examined the scope of the reaction. We started with α- or β-chiral aldehydes respectively, investigating both enantiomers of *N*-tosyl-valine for potential matched and mismatched cases (Scheme 2).[11], [12] For simplification, the diastereomeric ratio was determined after base initiated silyl migration and liberation of the masked aldehyde of the obtained TBS protected hemiacetals. For the products derived from aldehyde **8** (aldehydes **10** and **14**) comparable yields were achieved with both enantiomers of valine, whereas the selectivity dropped in the mismatched case. Better yields and comparable selectivities were obtained, when the stereocenter of the starting material was in the β-position (aldehydes **11** and **15**). For aldehydes bearing the PMB-ether in α-position in the matched case similar results as for aldehyde **8** were obtained (aldehyde **12**). In contrast, the mismatched case provided an unexpected result, as ester **16** was the main product isolated from the Kiyooka aldol reaction, meaning that no reduction occurred. A protecting group swap from PMB to TBDPS led to a slight increase in selectivity (aldehyde **13**), showing that the reaction conditions are applicable to silyl-ethers as well.

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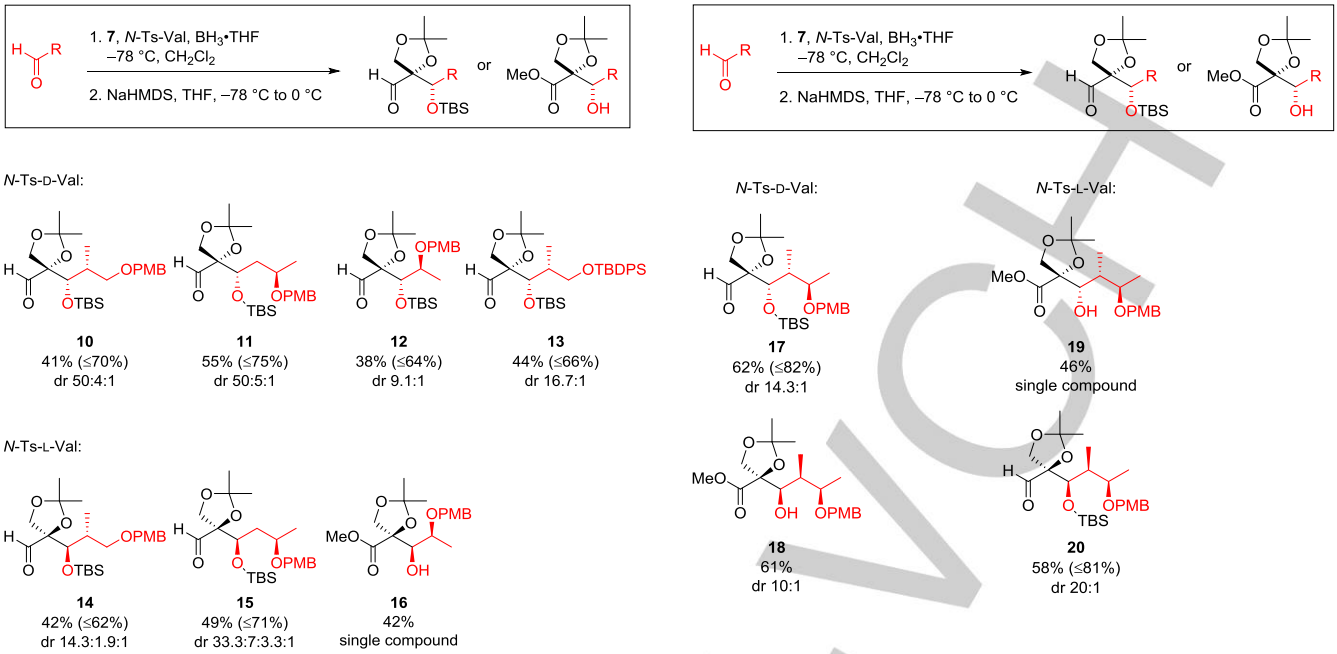
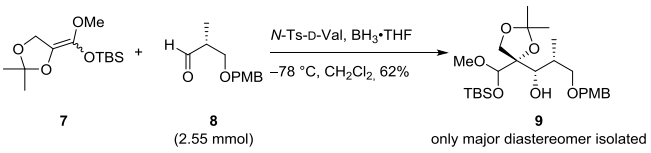


Scheme 2. Scope of Kiyooka aldol reaction with α- or β-chiral aldehydes. [a] all reactions were run on a 0.40 mmol scale, employing the conditions of table 1, entry 4. [b] Yield refers to isolated yield over two steps after column chromatography. Isolated yield of Kiyooka aldol reaction is given in parentheses. [c] dr was determined via ^{1}H-NMR after column chromatography. [d] Ester was obtained after Kiyooka aldol reaction. [e] Stereochemistry was determined via NMR experiments (acetonide method,[13] Karplus relation,[14] NOE correlations) or X-ray analysis. HMDS = hexamethyldisilazide. TBDPS = *tert*-butyldiphenylsilyl.

Having shown the general applicability for α- or β-chiral aldehydes we put our focus on α-, β-chiral aldehydes bearing a methyl group in α- and a PMB-ether in β-position. Thereby a 1,2-*anti* as well as a 1,2-*syn* substitution pattern for the aldehydes was investigated (Scheme 3). For the 1,2-*anti* substituted aldehyde the best yield of all substrates was achieved for the matched case, along with a very good selectivity (aldehyde **17**). For the mismatched case again no reduction took place, leading to ester **19** as the main product. Interestingly, aldehyde **17** and ester **19** showed the same stereochemistry, implying that the oxazaborolidinone only acted as a Lewis acid without any asymmetric induction. Similar results were observed when using the 1,2-*syn* substituted aldehyde, were it is noteworthy that the stereocenter in α-position did overrule the one in β-position entirely in terms of stereochemical induction favoring formation of the Felkin-product[11a] (products **18** and **20**).

Scheme 3. Scope of Kiyooka aldol reaction with α- and β-chiral aldehydes. [a] all reactions were run on a 0.40 mmol scale, employing the conditions of table 1, entry 4. [b] Yield refers to isolated yield over two steps after column chromatography. Isolated yield of Kiyooka aldol reaction is given in parentheses. [c] dr was determined via ^{1}H-NMR after column chromatography. [d] Esters were obtained after Kiyooka aldol reaction. [e] Stereochemistry was determined via NMR experiments (Karplus relation,[14] NOE correlations).

Having evaluated the scope of the reaction we were also interested in its scalability, running a Kiyooka aldol reaction of aldehyde **8** on a 2.55 mmol scale (Scheme 4). For simplification we did only isolate the major diastereomer of this reaction, as it is formed in large excess compared to all other diastereomers (Figure 3). The yield of 62% is comparable to the previously run reactions (Scheme 2), showing stability on up-scale.



Scheme 4. Up-scaling of Kiyooka aldol reaction of aldehyde **7**.

Furthermore, potential synthetic applications of the Kiyooka aldol products were investigated by the modification of aldehyde **10**. Horner-Wadsworth-Emmons olefination[15] with triethyl phosphonoacetate led to ester **21** in very good yield, allowing for different further functionalization. Addition of a synthetically useful vinyl handle gave allylic alcohol **22** with the expected stereochemistry.[6] Hydrogenation followed by Ley-Griffith oxidation[16] delivered highly substituted tetrahydropyrone **23** in very good yield.

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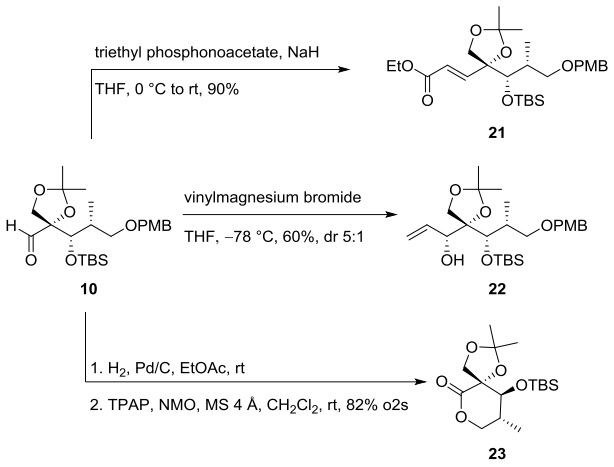

Scheme 5. Downstream functionalization of aldehyde **10**. TPAP = tetrapropylammonium perruthenate, NMO = *N*-Methylmorpholine *N*-oxide, MS = molecular sieves.

In summary, we have expanded our Kiyooka protocol for the stereoselective synthesis of tertiary alcohols to α- and/or β-chiral aldehydes. For this, the reaction conditions had to be re-developed and a strong dependency between the double bond geometry of the ketene acetal and the diastereoselectivity of the reaction was observed. However, in all cases good to excellent selectivities and synthetically useful yields were observed. Furthermore, a detailed substrate scope investigation showed possible synthetic applications and constrains. Finally, we were able to show that this transformation is also applicable to larger scales.

Acknowledgements

We thank Dagmar Körtje and Monika Rettstadt for NOE measurements as well as Dr. Jörg Fohrer for helpful discussion regarding the NOE correlations. We thank Dr. Gerald Dräger for X-ray analysis. Pascal Lienig is acknowledged for predominant studies about the Kiyooka aldol reaction with lactic acid derived aldehydes.

Keywords: aldol reaction • chiral aldehydes • double bond geometry • ketene acetal • structure elucidation

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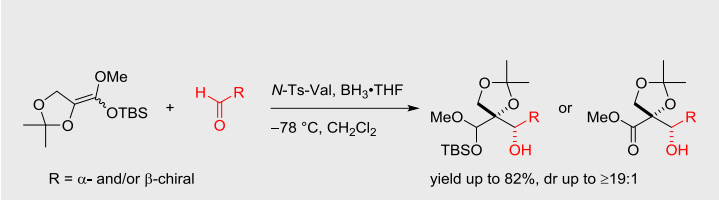

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Polyoxygenated Tertiary Alcohols – A Kiyooka Approach

A Kiyooka protocol for the stereoselective synthesis of tertiary alcohols is presented. The obtained highly complex building blocks feature up to four contiguous stereogenic centers and feature motifs of several natural products. Furthermore, a strong dependency between diastereoselectivity and double bond geometry of the ketene acetal was observed.