Tetrahedron Letters 50 (2009) 3485–3488

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantioselective synthesis of polyketide segments through vinylogous Mukaiyama aldol reactions

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ARTICLE INFO

Article history:
Received 15 January 2009
Revised 28 February 2009
Accepted 3 March 2009
Available online 9 March 2009

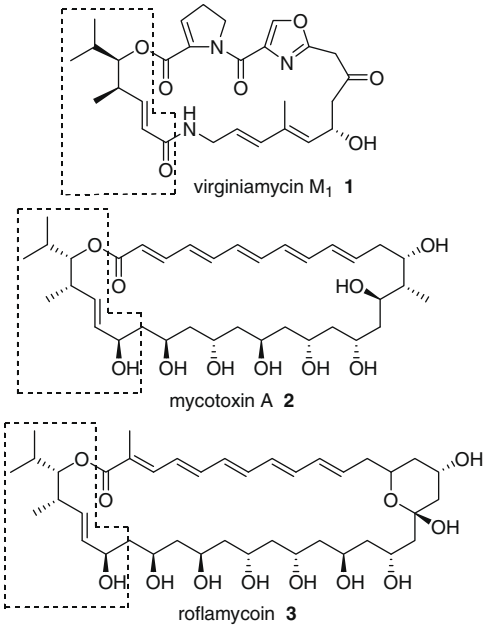
This work is dedicated to Professor Hans-Ulrich Reißig on the occasion of his 60th birthday

Keywords:
Vinylogous Mukaiyama aldol
Polyketides
Oxazaborolidines
Natural products
Enantioselective

ABSTRACT

The synthesis of polyketide segments through the vinylogous Mukaiyama aldol reaction is reported. The use of chiral oxazaborolidines allows using terminal substituted ketene acetals and provides access to extended segments and two new chiral centers.

The rapid and efficient assembly of polyketide segments is one of the pivotal requirements for the construction of biologically active compounds. In this context, the vinylogous extension of the Mukaiyama aldol reaction is a strategic concept by which not only larger segments can be constructed rapidly but also it avoids extensive functional group manipulations or protecting group shuffling. This set the background for groundbreaking contributions of various research groups.[1] In order to meet the stereochemical requirements of modern organic chemistry different approaches to provide enantioselective vinylogous aldol reaction have been put forward and in particular enolates or ketene acetals were successfully transformed. Despite the enormous success of such reaction the lack of substitution at the terminal position prevented the general applicability of this concept. The seminal contributions by Denmark[2] and co-workers allowed using terminal substituted ketene acetals in Mukaiyama aldol reactions with aromatic and unsaturated aldehydes leaving aliphatic aldehydes as an unmet challenge. On the other hand a methyl-substituted ketene acetal would allow for the rapid and efficient construction of polyketide segments found in natural products such as virginiamycin (**1**),[3] mycotoxin (**2**)[4] or roflamycoin (**3**)[5] (Scheme 1). In connection with our ongoing program dealing with the synthesis of complex natural products[6] we focused on different Lewis acids for the activation of aldehydes.[7] In this context chiral oxazaborolidinones proved to be superior to other boron centered catalysts and



Scheme 1. Antibiotics virginiamycin, mycotoxin A, roflamycoin.

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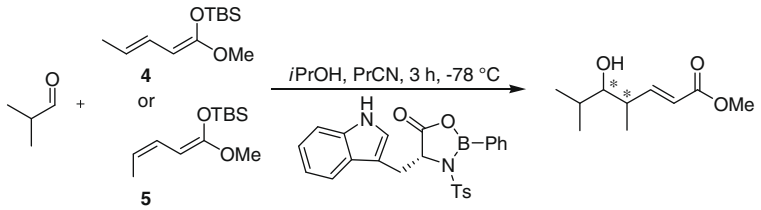
doi:10.1016/j.tetlet.2009.03.013



Scheme 2. Vinylogous Mukaiyama aldol reaction using terminal substituted ketene acetals and *N*-Ts-tryptophan-based oxazaborolidinone.

provided access to highly enantioselective vinylogous Mukaiyama aldol reactions.[8]

In our search for Lewis acids that would allow for the enantioselective addition of substituted ketene acetals, the above-mentioned oxazaborolidinones failed to provide satisfactory selectivities for both the 3,4-*E* (**4**) and the 3,4-*Z* (**5**) configured ketene acetals (Scheme 2, Table 1).

In order to extend the diversity of the catalysts employed we examined Lewis acids that proved to be successful in other vinylogous aldol reactions. Among these catalysts are the titanium-based complexes **6** and **7** developed by Carreira,[9] Evan's copper pybox complex **8**,[10] Yamamoto's[11] acyloxyboranes **9**–**11** for which Sato et al.[12] could show that they provide significantly higher selectivities compared to oxazaborolidinones as well as the Keck catalyst **12**[13] which was successfully employed in vinylogous Mukaiyama aldol reaction of terminally unsubstituted ketene acetals by Paterson et al. (Fig. 1).[14] Despite their structural diversity, none of these catalysts exceeded 76% enantiomeric excess in reactions with 4-methylated silyl ketene acetals.

We therefore changed our focus to the phenylalanine and valine derived oxazaborolidines that were employed either with no additive or with additional Lewis acid ($SnCl_4$) or Brønsted acid (TfOH), respectively.[15] Even though all catalysts provided acceptable yields in the order of 50% and with diastereomeric excess greater than 95%, the ee values never exceeded 80% (Fig. 2).

Finally, the contributions of Boeckman et al.[16] prompted us to examine proline-derived oxazaborolidines. In the first attempt

Table 1
Vinylogous Mukaiyama aldol reaction using *N*-Ts-tryptophan-based oxazaborolidinone

Entry	Ketene acetal	Yield (%)	de (%)	ee (%)
1	**4**	24	58	24
2	**5**	31	77	52

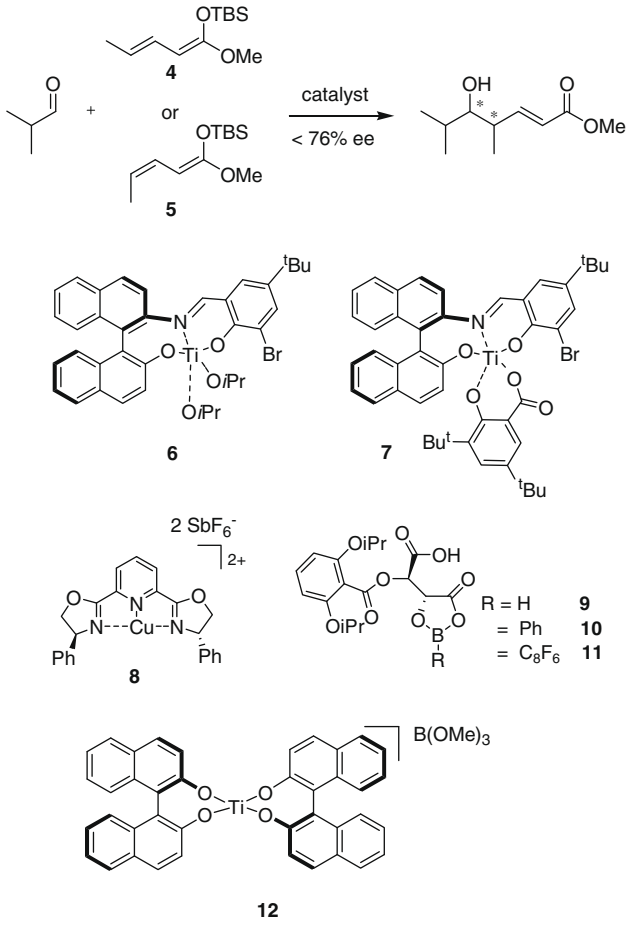


Figure 1. Lewis acids used in vinylogous Mukaiyama aldol reactions with terminal substituted silyl ketene acetals.

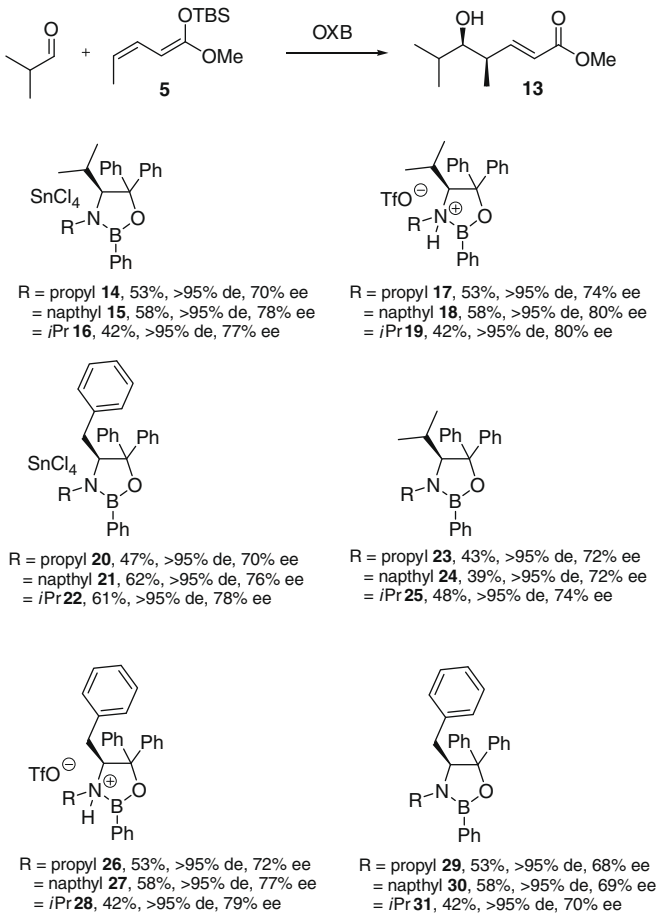


Figure 2. Oxazaborolidines (OXBs) used in vinylogous Mukaiyama aldol reactions.