Tetrahedron xxx (2016) 1–7

Contents lists available at ScienceDirect

Tetrahedron

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

Stereoselective construction of all-carbon quaternary stereocenters by allylboration of chiral aldehydes: synthesis of a fragment of (+)-vibsanin A

Akihiro Sakama, Yoshiyasu Nishimura, Yuko Motohashi, Keisuke Yoshida, Ken-ichi Takao *

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

ARTICLE INFO

Article history:
Received 7 June 2016
Received in revised form 6 July 2016
Accepted 8 July 2016
Available online xxx

Keywords:
Allylation
Boronates
Carbohydrates
Diastereoselectivity
Quaternary stereocenter

ABSTRACT

Stereoselective construction of all-carbon quaternary stereocenters by allylboration of chiral aldehydes is described. Sugar-derived aldehydes were allylated with geranylboronate or nerylboronate to provide γ-adducts possessing quaternary stereocenters with high diastereoselectivity. The reaction was applied to the synthesis of a fragment of (+)-vibsanin A.

1. Introduction

All-carbon quaternary stereocenters are found in many pharmaceuticals and bioactive natural products. For example, (+)-hyperforin (**1**),[1] (−)-hyphenrone A (**2**),[2] and (+)-vibsanin A (**3**)[3] have a common structural motif including an asymmetric quaternary stereogenic center (Fig. 1). To synthesize such complex compounds, it is essential to develop a practical method for constructing the quaternary stereocenter. However, this remains a challenge due to steric factors and the difficulty of asymmetric induction.[4] One approach uses 3,3′-disubstituted allylmetal reagents. Although much research has focused on developing stereoselective carbonyl allylation reactions,[5] the construction of an asymmetric quaternary stereocenter by these reactions is still challenging.[6] Denmark and co-workers have reported a solution to this problem using allylic trichlorosilanes.[7] We also reported a zinc-mediated Barbier-type allylation of sugar-derived aldehydes in aqueous media (Scheme 1a).[8]

Thus, the reaction of D-glyceraldehyde acetonide **4** (prepared from D-mannitol in two steps)[9] and geranyl chloride (**5**) in the presence of zinc powder preferentially provides γ-adduct **6-C**, which contains an all-carbon quaternary stereocenter with (*R*)-configuration, in accordance with the β-chelation/six-membered

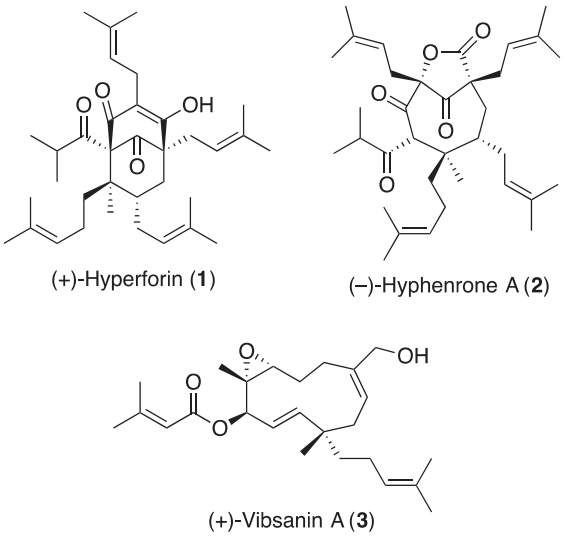
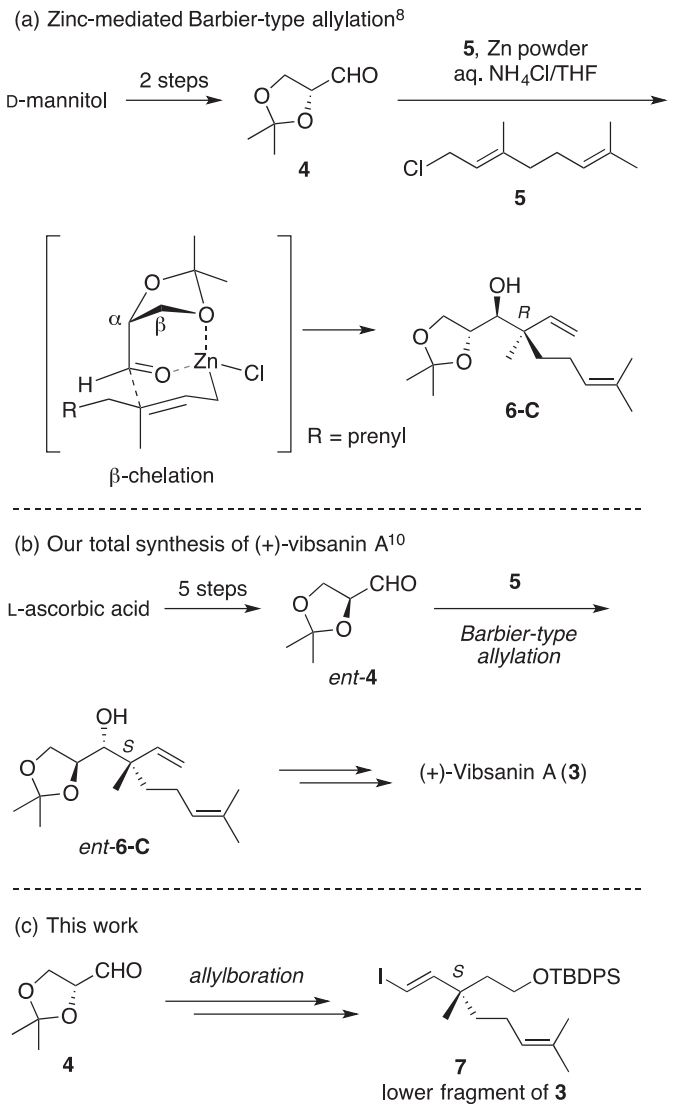


Fig. 1. Structures of (+)-hyperforin, (−)-hyphenrone A, and (+)-vibsanin A.

* Corresponding author. Fax: +81 45 566 1551; e-mail address: takao@applc.keio.ac.jp (K. Takao).

http://dx.doi.org/10.1016/j.tet.2016.07.030
0040-4020/



Scheme 1. (a) Zinc-mediated Barbier-type allylation, (b) our total synthesis of (+)-vibsanin A, and (c) this work.

model. Recently, we achieved the first total synthesis of (+)-vibsanin A (**3**) by using the Barbier-type allylation (Scheme 1b).[10] In our total synthesis, we needed to use *ent*-**4** as a substrate for the Barbier-type allylation because an (*S*)-configured quaternary stereocenter was required for the natural enantiomer of **3**. Compound *ent*-**4** was prepared from L-ascorbic acid in five steps,[11] taking more time and effort than preparation of **4**. To achieve the synthesis of **3** from **4**, we aimed to develop a stereochemically complementary method to the zinc-based Barbier-type allylation, this time using the allylboration reaction where chelation of the aldehyde would not be possible because of the limited coordination shell of boron.[12]

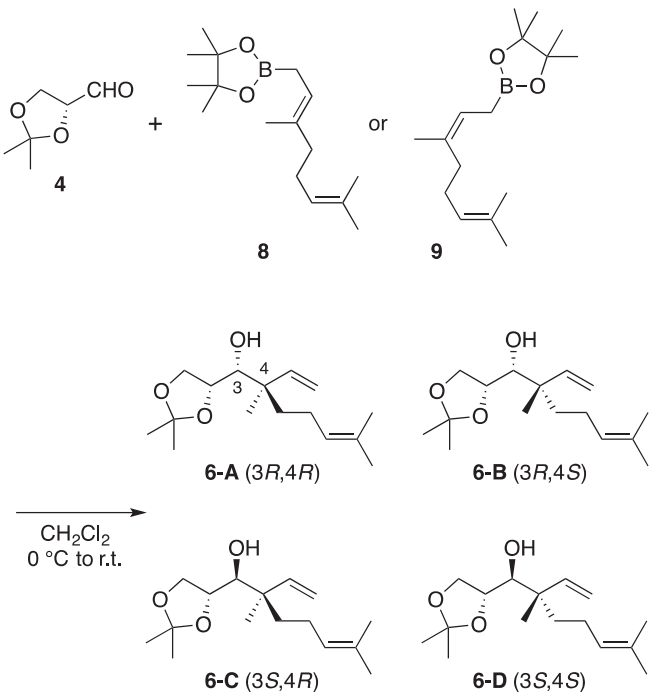
There are only limited examples of allylboration in the synthesis of optically active compounds bearing all-carbon quaternary stereocenters. Although Szabó and co-workers recently reported catalytic asymmetric allylboration in the synthesis of quaternary stereocenters,[13,14] most methods use chiral allylboron reagents as chiral sources.[15] Herein, we describe the construction of all-carbon quaternary stereocenters by allylboration of chiral aldehydes with achiral 3,3′-disubstituted allylboronic esters, thereby extending the approach to lower fragment **7** of (+)-vibsanin A (**3**) (Scheme 1c).

2. Results and discussion

The allylboration reaction was investigated with readily available sugar-derived aldehydes, also used in the Barbier-type allylation,[8] and with pinacol allylboronic ester **8** or **9** as substrates. Geranylboronate **8** was prepared from geraniol according to the convenient procedure developed by Szabó and Aggarwal.[16] Nerylboronate **9**[17] was also prepared from nerol by a similar method.[18] These 3,3′-disubstituted allylboronic esters were configurationally stable, and equilibrium between *E*- and *Z*-isomers was not observed at room temperature.

As shown in Table 1, the reaction of **4** with **8** in CH_2Cl_2 at 0 °C to room temperature provided γ-adducts **6-A**–**D** with high stereoselectivity and complete regioselectivity (entry 1). The γ-adducts were separated into (3*R*)-isomers **6-A**/**6-B** (4*R*/4*S*=9:1) and (3*S*)-isomers **6-C**/**6-D** (4*R*/4*S*=1:5) by column chromatography in yields of 5% and 71% from **8**, respectively. In this case, (3*S*,4*S*)-isomer **6-D** was obtained as the major product.[19] Thus, the synthesis of the chiral building block with (4*S*)-configuration was achieved in three steps from D-mannitol, which is a more concise route than Barbier-type allylation of *ent*-**4**. By using **9** instead of **8**, the reaction preferentially produced (3*S*,4*R*)-isomer **6-C**, which is the epimer of **6-D** at the quaternary stereocenter (entry 2). The stereoselectivity was slightly lower than in the reaction with **8**, but was still good. In both cases (entries 1 and 2), the stereochemical outcomes were the opposite of the Barbier-type allylation using the corresponding allyl chlorides (Scheme 1).[8] Products **6-D** and **6-C** possessing a quaternary carbon are inseparable, although the two diastereomers can be separated at a later stage.[10] Therefore, they are expected to be useful chiral building blocks for natural product synthesis.

Table 1
Allylboration of D-glyceraldehyde derivative **4**



Entry	Allylboronate	A+B		C+D	
		Yield[a]	A/B[b]	Yield[a]	C/D[b]
1	**8**	5%	9:1	71%	1:5
2	**9**	6%	1:8	66%	4:1

[a] Yield from **8** or **9**.
[b] Ratio was determined by ^{1}H NMR analysis.

Please cite this article in press as: Sakama, A.; et al., Tetrahedron (2016), http://dx.doi.org/10.1016/j.tet.2016.07.030