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Preparative-scale synthesis of both antipodes of *B*-γ,γ-dimethylallyldiisopinocampheylborane: application for the synthesis of C_1–C_6 subunit of epothilone

P. Veeraraghavan Ramachandran,* Bodhuri Prabhudas, J. Subash Chandra, M. Venkat Ram Reddy and Herbert C. Brown

Department of Chemistry, Herbert C. Brown Center for Borane Research, 560 Oval Drive, Purdue University, West Lafayette, IN 47907-82084, USA

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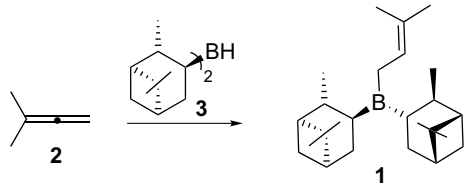
Abstract—A preparative-scale synthesis of *B*-γ,γ-dimethylallyldiisopinocampheylborane starting from prenyl alcohol has been described. This reagent, upon reaction with various aldehydes, provides the corresponding α,α-dimethylhomoallylic alcohols in high enantioselectivities. The application of this reagent has been demonstrated for the synthesis of C_1–C_6 subunit of epothilone.

Allylboration is one of the extremely important carbon–carbon bond forming reactions in organic synthesis.[1] For the past two decades, we have developed several highly functionalized 'allyl' boranes based on terpenes.[2] While some of these reagents have been well utilized by the synthetic organic community for the total synthesis of a variety of complex natural products,[3] others have been sparsely used. One of the main reasons for the lack of interest for such reagents could be due to the difficulty in their preparation or the cost of the starting materials. One of the rarely used allylborane reagents is *B*-γ,γ-dimethylallyldiisopinocampheylborane[4] **1** for the preparation of α,α-dimethylhomoallylic alcohols. Several natural products, such as artemesia alcohol,[5] bryostatin,[6] epothilone,[7] pederin,[8] and mycalamide[9] contain an α,α-dimethylhydroxy unit in them and one could envisage the use of **1** for the preparation of the dimethyl alcohol moiety. Since our initial report of the synthesis of artemesia alcohol,[4] only recently Schinzer described the application of **1** for the synthesis of epothilones.[10] The wide range of potential application of **1** persuaded us to develop a simple and inexpensive method for the preparative-scale synthesis of the reagent. Our original preparation of *B*-γ,γ-dimethylallyldiisopinocampheylborane **1** involves the hydroboration of relatively expensive (Aldrich $53/g) 1,1-dimethylallene **2** with diisopinocampheylborane **3**, thus making it impractical for large-scale applications (Scheme 1).

B-Allyldialkylboranes can be prepared by the reaction of the corresponding allyl Grignard reagent with *B*-halodialkylborane or *B*-methoxydialkylborane. Our approach was to use the dimethylallyl Grignard reagent, that can be readily prepared from the relatively inexpensive prenyl alcohol (Aldrich $94/500 g). Prenyl alcohol was converted to the corresponding bromide by treatment with PBr_3. However, the reaction of dimethylallylbromide with magnesium turnings was not satisfactory and resulted in the predominant formation of the homocoupling product. Treatment of this reagent with (+)-*B*-methoxydiisopinocampheylborane (**4**) resulted in very low yields of the 'allyl' borane reagent **1** (~10% based on ^{11}B NMR). We sought to change the halide from bromide to chloride **5** in an



Scheme 1.

Keywords: Dimethylallylboration; *B*-Methoxydiisopinocampheylborane; Prenyl alcohol; Epothilone.
* Corresponding author. Tel.: +1-765-494-5303; fax: +1-765-494-0239; e-mail: chandran@purdue.edu

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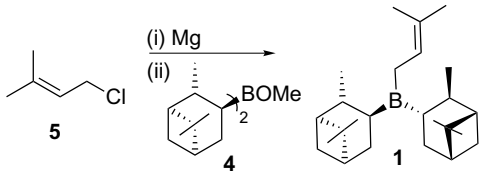


Scheme 2.

attempt to minimize the homocoupling. The chloride was prepared by the reaction of prenyl alcohol with thionyl chloride and subsequent addition of magnesium resulted in the successful formation of Grignard reagent. This, upon reaction with (+)-**4** at 0 °C, provided the required 'allyl' borane **1** in essentially quantitative yield. Methoxymagnesium chloride was filtered using a Kramer filter under nitrogen and the solvent was evaporated under vacuum to provide 90% yield of *B*-γ,γ-dimethylallyldiisopinocampheylborane **1** (^{11}B NMR peak at δ 79) (Scheme 2). Similarly starting from (−)-*B*-methoxydiisopinocampheylborane, the antipode of the reagent **1** was prepared. To demonstrate the potential for large-scale applications, we carried out the reaction on a 0.5 mol scale and obtained highly reproducible results.[11]

We then studied the allylboration of various aldehydes with **1**. The reaction of aliphatic aldehydes, such as propionaldehyde **6a**, isobutyraldehyde **6b**, pivalaldehyde **6c** (entries 1–3), took place smoothly, and the product homoallylic alcohols **7a**–**c** were obtained in very good yields (81%–88%) and in excellent ee (95%–97%) (Table 1). The ee was determined by derivatizing the homoallylic alcohols as their *p*-nitrobenzoate esters, and analyzed on an HPLC using a Chiralcel OD-H^{TM} column. Similarly benzaldehyde **6d** and cinnamaldehyde **6e** (entries 4–5) also provided alcohols **7d** and **7e** in excellent yield and ee. The reaction of an α-chiral aldehyde **6f** (entry 6) took place in a reagent-controlled manner and the homoallylic alcohol **7f** was obtained in 92% de.

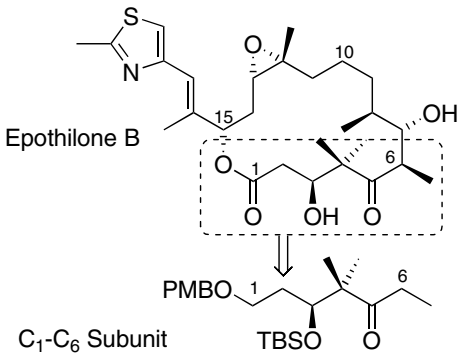


Figure 1.

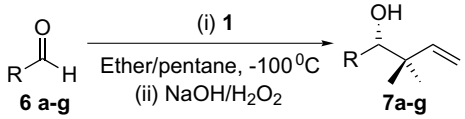
Similarly, β-chiral aldehyde **6g** (entry 7) also provided the homoallylic alcohol **7g** in 93% yield and 95% de (Table 1).

To demonstrate the application of the above reagent for organic synthesis, we synthesized the C_1–C_6 subunit **8** of the potent anti-cancer molecule epothilone B[7] (Fig. 1).

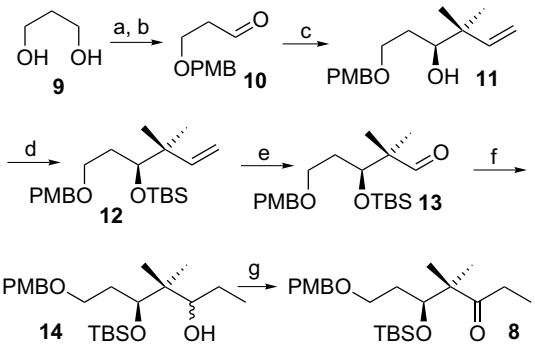
Monoprotection of 1,3-propanediol **9** as the *p*-methoxybenzyl ether followed by Swern oxidation provided 3-(*p*-methoxybenzyloxy)propionaldehyde **10**. Dimethylallylboration of **10** with **1** at −100 °C furnished the homoallylic alcohol **11** in 95% ee. Protection of **11** as the silyl ether **12**, followed by ozonolysis afforded the aldehyde **13**. Reaction of **13** with ethylmagnesium bromide yielded the alcohol **14**. Dess–Martin periodinane oxidation of **14** resulted in the formation of the required C_1–C_6 subunit **8** of epothilone (Scheme 3).

In conclusion, we have developed a simple and inexpensive procedure for the preparative-scale synthesis of both antipodes of *B*-γ,γ-dimethylallyldiisopinocampheylborane and have examined the reactivity of the reagent with a wide variety of aldehydes providing

Table 1



Entry	Aldehyde		Homoallylic alcohol		
	#	R	#	Yield (%)	ee/de (%)
1	**6a**	CH_3CH_2–	**7a**	81	97
2	**6b**	$(CH_3)_2CH$–	**7b**	85	95
3	**6c**	$(CH_3)_3C$–	**7c**	88	95
4	**6d**	C_6H_5–	**7d**	92	95
5	**6e**	$C_6H_5CH{=}CH$–	**7e**	90	87
6	**6f**	PMBO	**7f**	90	92
7	**6g**	OMe, MeO	**7g**	93	95



Scheme 3. Reagents and conditions: (a) NaH, *p*-$CH_3OC_6H_4CH_2Cl$, $N^+Bu_4I^-$, 80%; (b) $(COCl)_2$, DMSO, Et_3N, 85%; (c) **1**, 82%; (d) TBSOTf, 2,6-lutidine, 90%; (e) O_3, 78%; (f) EtMgBr; (g) DMP, 88% (overall for the two steps).

homoallylic alcohols in high diastereo- and enantioselectivities. We have also demonstrated the applicability of this reagent for the synthesis of C_1–C_6 subunit of the potent anti-cancer agent epothilone B. With an economical procedure now available, we believe that this reagent will find further applications in organic synthesis.

Acknowledgements

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11. Preparation of *B*-γ,γ-dimethylallyldiisopinocampheylborane (1): 1-Chloro-3-methyl-2-butene (90.2 mL, 1.0 mol) was added dropwise to a stirred suspension of Mg (120 g, 2.5 mol) in 200 mL ether cooled to 0–10 °C and was stirred for 1 h. Meanwhile, a solution of **4** (158.2 g, 0.5 mol) in 500 mL ether was cooled to 0 °C. The previously made Grignard reagent was added to **4**. After the completion of the reaction (3 h) as monitored by ^{11}B NMR (δ 79), the reaction mixture was filtered under nitrogen and concentrated under vacuum. *n*-Pentane (200 mL) was added to it using a canula, stirred for 5 min and allowed to settle down. The supernatant liquid was then transferred via a canula into another round bottom flask under nitrogen and the solvent was evaporated off under vacuum. After repeated washing with pentane (4×200 mL), the concentrate (90%, 159.4 g, 450 mmol) was dissolved in 450 mL pentane to prepare a 1 M stock solution. ^{11}B NMR analysis of the stock solution showed a clean formation of the product allylborane (singlet: δ 79).
12. Contribution # 30 from Herbert C. Brown Center for Borane Research.