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Stereoisomer-differentiating esterification of diols with methylboronic acid. A simple method for the separation of *cis*- and *trans*-1,2-diols

Chandra D. Roy[a,b,*] and Herbert C. Brown[a,†]

[a]*Department of Chemistry, Herbert C. Brown Center for Borane Research, Purdue University, West Lafayette, IN 47907, USA*
[b]*EMD Biosciences, Inc., 10394 Pacific Center Court, San Diego, CA 92121, USA*

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Abstract—A simple procedure for the separation of cis–trans-stereoisomeric 1,2-diols by the selective esterification of cis-isomer with methylboronic acid is described.

1. Introduction

The need for the separation of nucleosides or saccharides[1] has led to the development of various affinity absorbent gels. These absorbents are also capable of binding specific diol from a mixture of diols which are highly useful in organic synthesis, especially for the protection of desired diol or seizure of diol of interest from a mixture of diols. Apart from absorbents, several bead polymers[2] have also been reported which were employed as temporary diol protecting groups in carbohydrates chemistry.

In 1962, we reported *n*-butylboronic acid as a convenient reagent for the separation of isomeric *cis*,*trans*-cycloalkanediols. Although *cis*-cycloalkanediols yielded volatile cyclic boronic esters, *trans*-cycloalkanediols formed nonvolatile polymeric materials.[3] Seymour and Frechet selectively functionalized some glycosides using polystyrylboronic acid resin.[4] Later, they successfully separated *cis*-diols from isomeric cis, trans-mixtures by selective coupling to a regenerable solid support (polystyrylboronic acid resin). Sillanpaa and co-workers reported the separation of *cis*- and *trans*-1,3-cyclohexanediol isomers by complexation with copper salt.[5] Recently, Tucker et al. chemoselectively removed the unwanted dimeric 1,3-diol impurities from crude tertiary alcohol by simple recrystallization in the presence of phenylboronic acid (due to the preferential formation of soluble cyclic boronic esters).[6] Springsteen and Wang have studied in great details the complexation of boronic acid with diols.[7] While studying the thermodynamic stability of 2-(phenyl)-1,3,2-dioxaborolane[8] in $CDCl_3$ using transesterification with stereoisomeric diols (*cis*, *trans*-cyclopentane and cyclohexane diols, we did not observe the formation of any polymeric materials under the reaction condition. As cyclic diols are useful building blocks in organic synthesis, their separation, characterization, and purity determination of individual stereoisomers become a challenging task. This prompted us to undertake the separation of constituent stereoisomeric diols from the cis,trans-mixture (Chart 1) by selective esterification with methylboronic acid.

First we studied the esterification of methylboronic acid (0.5 equiv) with an equimolar mixture of *cis*,*trans*-cyclohexanediols **1** and **2** (0.5 equiv each) by ^1H NMR spectroscopy, in an NMR tube in $CDCl_3$ solvent under

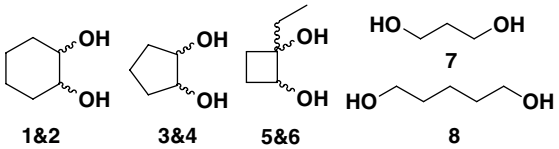

Chart 1. Various stereoisomeric and structural diol mixtures.

* Corresponding author. Tel.: +1 858 450 5618; fax: +1 858 453 3552; e-mail: chandra61804@yahoo.com
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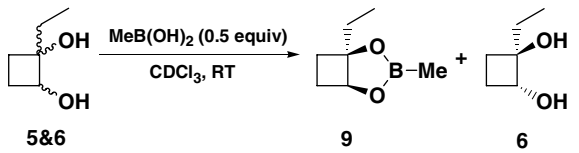
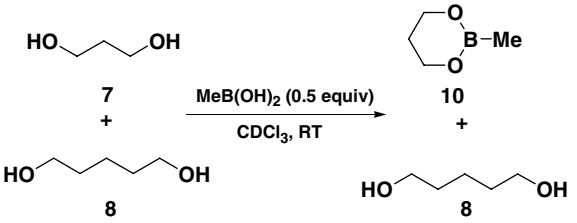
an inert atmosphere. The protons attached to the carbons bearing the hydroxyl groups were very distinct and well separated in an equimolar mixture of *cis*- and *trans*-1,2-cyclohexanediols. The –C*H*OH proton signal of *cis*-1,2-cyclohexanediol appeared at 3.75 ppm, whereas the *trans*-stereoisomer showed around 3.35 ppm. Upon treatment with methylboronic acid, the signal at 3.75 ppm disappeared and the new signal appeared downfield at 4.34 ppm, due to the selective formation of *cis*-1,2-cyclohexanediol boronic ester. Again, the proton signal at 3.35 ppm remained unaffected. The spectral characteristics matched with the authentic boronic ester prepared from pure *cis*-1,2-diol with methylboronic acid. The preferential formation of the cyclic boronic ester with *cis*-1,2-cyclohexanediol from a mixture of two stereoisomeric 1,2-cyclohexanediols can be rationalized based on conformational factors. The coplanar arrangement (for an intramolecular esterification) of the hydroxyl groups appears to be a prerequisite for cyclic boronate formation. The hydroxyl groups in *cis*-1,2-cyclohexanediol achieve coplanarity via a lower energy conformational change (possibly by the partial inversion of a chair form into a boat form). In the case of *trans*-1,2-cyclohexanediol, such coplanar arrangement of the hydroxyl groups is likely to increase the strain (higher energy pathway) in the cyclohexane, which, in turn, disfavors the formation of cyclic boronic ester. As expected, similar results were achieved with both *cis*,*trans*-cyclopentanediols **3** and **4** and *cis*,*trans*-1-ethyl-1,2-cyclobutanediols **5** and **6** (Scheme 1). The ^{11}B NMR spectrum (sharp peaks at 31 ppm for *cis*-1,2-cyclopentanediol methylboronic ester and 35 ppm for *cis*-1-ethyl-1,2-cyclobutanediol methylboronic ester **9**) of the individual reaction mixture clearly indicated that there were no oligomeric or polymeric boron species present in the reaction mixture (also supported by ^{1}H NMR spectroscopy, sharp signal for B–CH_3 group).

After successful selective esterification of three cyclic *cis*,*trans*-diols with methylboronic acid, we next considered to examine the selective esterification of acyclic 1,3-diol from a mixture of 1,3-propanediol and 1,5-pentanediol **7** and **8** with methylboronic acid. Understanding the relationship between the relative stability of boronic ester and the size of the heterocycle, it was hoped that methylboronic acid would selectively form cyclic boronic ester **10** with 1,3-propanediol. The ^{11}B (30 ppm) and ^{1}H NMR spectral data indeed (triplet at 3.85 ppm due to –CH_2OH of 1,3-propanediol shifted downfield around 4.00 ppm due to the formation of cyclic boronic ester, whereas the triplet at 3.66 ppm due to –CH_2OH of 1,5-pentanediol remained unchanged) revealed the exclusive formation of 2-methyl-[1,3,2]dioxaborinane (Scheme 2). In the case of 1,3-propanediol and 1,5-pentanediol mixture, the selective formation of 2-methyl-1,3,2-dioxaborinane **10** can be explained based on the thermodynamic stability of six-membered boronic ester over eight-membered boronic ester. Transesterification of boronic ester with other structural diols provides valuable information regarding the relative stability of boronic esters.[8]



Scheme 1. Selective esterification of 1-ethyl-*cis*-1,2-cyclobutanediol with MeB(OH)$_2$.



Scheme 2. Selective esterification of 1,3-propanediol with MeB(OH)$_2$.

The physical separation of the *cis*,*trans*-diol mixture of 1-ethyl-1,2-cyclobutanediols is achieved by selective esterification of $CH_3B(OH)_2$ with cis-stereoisomeric diol from a mixture of *cis*,*trans*-diols. The *cis*-diol boronic ester, being highly soluble in *n*-pentane is very easily separated from the insoluble *trans*-diol. The *cis*-diol can be retrieved by simple H_2O_2/NaOH oxidation of the boronic ester.

In conclusion, we have demonstrated the application of methylboronic acid to the efficient separation of stereoisomeric *cis*,*trans*-diols. The separation of acyclic diols (1,3-propanediol and 1,5-pentanediol) has also been achieved, due to the thermodynamic stability of the boronic ester derived from 1,3-propanediol. This methodology can be extended to 1,2-aminoalcohols.

2. A representative procedure for the separation of *cis*- and *trans*-1-ethyl-1,2-cyclobutanediols

A mixture of *cis*- and *trans*-1-ethyl-1,2-cyclobutanediols (stereoisomeric ratio = 1.2:0.8, 2.0 mmol, 233 mg) was stirred with methylboronic acid (1.2 mmol) in *n*-pentane (10 mL) under nitrogen atmosphere for 5 h. After 5 h of stirring, the pentane soluble part was transferred by cannula and the residue was washed with *n*-pentane (5 mL). The evaporation of *n*-pentane layer provided pure *cis*-1-ethyl-1,2-cyclobutanediol methylboronic ester **9** (150 mg, 89%) which was characterized by spectroscopic means. Although the boronic ester derived from *cis*-1-ethyl-1,2-cyclobutanediol was utilized as such, the *cis*-diol can very easily be retrieved by simple H_2O_2/NaOH oxidation of boronic ester. The *n*-pentane insoluble part was dissolved in $CHCl_3$, dried (anhyd Na_2SO_4), and concentrated to get *trans*-1-ethyl-1,2-cyclobutanediol which was spectroscopically pure (85 mg, 91%). Most of the diols are insoluble in *n*-pentane, whereas most of the boronic esters are highly soluble in *n*-pentane.

2.1. *cis*-1-Ethyl-1,2-cyclobutanediol methylboronic ester 9

89%. ^{11}B NMR ($CDCl_3$) δ 35. ^{1}H NMR ($CDCl_3$) δ 4.43 (m, 1H, –C*H*O), 2.30–1.50 (m, 6H, –CH_2), 0.90 (t, 3H,

–CH_3), 0.34 (s, 3H, –BCH_3). ^{13}C NMR ($CDCl_3$) δ 87.60, 78.91, 31.51, 29.26, 25.80, 7.20.

2.2. *trans*-1-Ethyl-1,2-cyclobutanediol 6

91%. ^{1}H NMR ($CDCl_3$) δ 4.15 (m, 1H, –C*H*OH), 2.20–1.10 (m, 8H, –CH_2 and –OH), 1.00 (t, 3H, –CH_3). ^{13}C NMR ($CDCl_3$) δ 79.81, 75.89, 25.82, 24.75, 22.67, 8.74.

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