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Application of 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol as the chiral director in Matteson's asymmetric homologation

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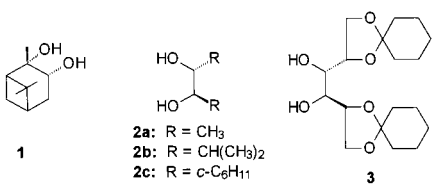
Abstract

1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol is the good chiral director in Matteson's asymmetric homologation as indicated by the high enantiomeric excesses (ee's) of the secondary alcohols produced by treatment of the homologation products with alkyllithium or Grignard reagents followed by oxidation.

Keywords: Boronates; 1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol; Homologation

1. Introduction

Asymmetric homologation via α-chloroboronic esters provides an extremely efficient method for constructing chiral centers [1]. The reaction has been extensively employed in syntheses of biologically important molecules including pheromones [2], homoallylic alcohols [3], sugars [4], amino acids [5] and aminoboronic acids [6]. Pinanediol is often used as the chiral director but the hydrolytic stability of pinanediol boronates is problematic in some syntheses. The lack of C_2 symmetry is another disadvantage associated with pinanediol and it accounts for the poor diastereoselectivities observed in the reactions of pinanediol dichloromethylboronate with organolithium or Grignard reagents. To circumvent these difficulties, C_2 symmetric 1,2-diols are being developed as chiral ligands. Diacetone mannitol and tartrates [7] are ineffective but (*R*,*R*)-2,3-butanediol gives satisfactory results when used as the chiral director [8]. 1,2-Di-isopropylethanediol [9] and 1,2-dicyclohexylethanediol [1c,d, 3c] are also effective chiral directors, providing diastereomeric purities in excess of 98%. However, these chiral diols (**1** and **2**) are either expensive or are not yet commercially available.



1 **2a:** R = CH_3; **2b:** R = $CH(CH_3)_2$; **2c:** R = *c*-C_6H_{11} **3**

In light of the fact that the enantioselectivity increases as the size of the substituent increases in **2a**–**c**, we felt that the C_2 symmetric 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol, **3**, which is sterically similar to **2b** and is commercially available at a modest price, might serve as an effective chiral director. We wish to report the results of an investigation in which **3** was used as the chiral director in asymmetric homologation reactions.

2. Results and discussion

The starting 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol boronic esters, easily prepared via the quantitative reactions of the corresponding boronic acids and **3**, are stable in air and can be purified by column chromatography on silica gel to give crystalline solid products in 90–95% isolated yields. In order to evaluate **3** as the chiral director in asymmetric homologations, a series of reactions (scheme) were carried out under conditions similar to those described by Matteson [2b]. Preformed

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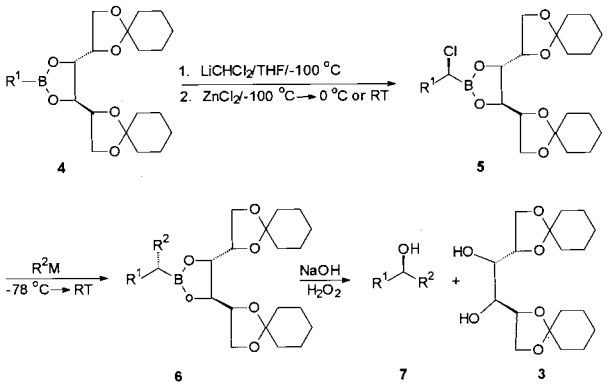
dichloromethyllithium, generated via the slow addition of BuLi to CH_2Cl_2 in THF at ca. −100°C, readily reacted with the boronates to form borate complexes. After the addition of anhydrous $ZnCl_2$, the reaction mixture was warmed to room temperature and stirred for 24 h except in the case of R^1 = Ph (0°C for 1 h).



The mixture was cooled to −78°C prior to the addition of R^2M. Warming to room temperature for 24 h converted the α-chloroboronates **5** to boronates **6**. The routine alkaline oxidation of **6** furnished the desired alcohol **7**, along with recovered chiral diol **3** which was readily separated by column chromatography. The percentage enantiomeric excess (% ee) of product alcohols **7** were determined by GC analysis of the (+)-menthyl chloroformate derivatives and the results are summarized in Table 1.

The reaction of phenylboronate was examined initially and (*S*)-1-phenyl-1-pentanol was obtained in 50% yield and in 91% ee (entry 1, the absolute configuration was confirmed by optical rotation). This was quite promising since pinanediol phenylboronate often provides lower ee's than other boronates due to the well-documented epimerization of the resulting benzylic α-chloroboronates in the presence of LiCl [10]. For example, an 88% ee was reported for (*S*)-1-phenyl-1-ethanol when pinanediol was used as the chiral director under otherwise identical conditions [11]. Our results indicated that the % ee of the final alcohol **7** is dependent upon R^1. For example, *n*-butylboronate gave (*R*)-1-phenyl-1-pentanol in 90% ee (entry 2) while the isopropylboronate produced the corresponding product in 96% ee (entry 4). *t*-Butylboronate generated the desired alcohol in 87% ee but the reaction required additional time (entry 6). In contrast to reports that the highest % ee is obtained when an extra equivalent of $ZnCl_2$ is added for each oxygenated substituent in the substrates [4][1], the addition of five equivalents of $ZnCl_2$ (4 additional equivalents for the four oxygen atoms in the mannitol derivative) resulted in a dramatic drop in % ee (entry 3). Apparently, excess $ZnCl_2$ significantly accelerated the epimerization of the intermediate **5** [10]. The results of reactions in which R^1 is cyclohexyl paralled those obtained with the isopropyl boronate, yielding the corresponding products in 95% ee (entry 7 and 8). It is noteworthy that the highest ee (99%) was obtained when the α-chloroboronate ($R^1 = c\text{-}C_6H_{11}$, entry 9) was reacted with vinylmagnesium bromide. In these reactions, a byproduct identified as a mixture of (*E*)- and (*Z*)-3-cyclohexyl-2-propen-1-ol (*E*/*Z* = 85/15) was isolated in 25% yield. The byproduct could have resulted from the slow 1,3-allylic rearrangement of the intermediate boronate **6** ($R^1 = c\text{-}C_6H_{11}$, $R^2 = CH_2{=}CH$). Such a rearrangement could explain the enhanced ee (99%) compared with 95% ee in other cases, assuming the minor diastereomer of **6** undergoes a faster allylic rearrangement leaving **6** diastereomerically enriched. Furthermore, the 1,3-rearrangement of propargylboronate (entry 10, $R^2 = n\text{-}C_3H_7C{\equiv}C$) was so rapid that the only isolated product was the corresponding α,β-unsaturated ketone, 1-cyclohexyl-1-hexene-3-one (in 54% yield), which was produced by oxidation of the allenylic boronate. It is important to note that the 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol recovered from the reaction in about 85% yield can be

Table 1
Homologation of 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol boronates using dichloromethyllithium

Entry	R^1	R^2M	Yield of **7** (%)[a]	ee of **7** (%)[b]
1	Ph	*n*-BuLi	50	91
2	*n*-Bu	PhLi	71	90
3	*n*-Bu	PhLi	72	36[c]
4	*i*-Pr	PhLi	65	96
5	*t*-Bu	PhLi	54	70
6	*t*-Bu	PhLi	68	87[d]
7	*c*-C_6H_{11}	$CH_2{=}CHCH_2MgBr$	77	95
8	*c*-C_6H_{11}	MeMgBr	71	95
9	*c*-C_6H_{11}	$CH_2{=}CHMgBr$	41[e]	99
10	*c*-C_6H_{11}	*n*-$C_3H_7C{\equiv}CLi$	–[f]	–

[a] Isolated yields based on **4**.

[b] Determined by capillary GC analysis of the corresponding (+)-menthyl chloroformate (99% ee) derivatives of **7**.

[c] Five equivalents of $ZnCl_2$ were used.

[d] The reaction mixture was stirred at r.t. for 90 h after addition of $ZnCl_2$.

[e] A mixture of (*E*)- and (*Z*)-3-cyclohexyl-2-propen-1-ol (*E*/*Z* = 85/15) was isolated in 25% yield.

[f] No propargylic alcohol was obtained; the major product was 1-cyclohexyl-1-hexene-3-one (54%).

[1] In the reactions of 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol boronates with dichloromethyllithium, little variation in the % ee was noted within the range of 0.6 to 1.2 equivalents of $ZnCl_2$. 1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol is very different from its analog diacetone mannitol. When diacetone mannitol was used as the chiral director, 0.6 equivalent of $ZnCl_2$ did not improve the diastereoselectivity while 2.7 equivalents raised the ee from 36% to 82–87% [4]. The authors thank Dr Matteson for disclosing his unpublished findings that diacetone mannitol undergoes ketal cleavage when large amounts of $ZnCl_2$ are used.

repeatedly used without any noticeable deterioration in asymmetric induction.

3. Conclusions

Preliminary results demonstrate that 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol is a useful chiral director in Matteson's asymmetric homologation due to its ready availability and the high enantiomeric purity of the homologation products.

4. Experimental section

4.1. General methods

All air- and moisture-sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen. Dry solvents were distilled under nitrogen prior to use from an appropriate drying agent: tetrahydrofuran and diethyl ether from the sodium benzophenone ketyl, dichloromethane from phosphorous pentoxide. Boronic acids were prepared according to literature methods (*n*-butyl-, isopropyl- and *t*-butylboronic acids were prepared from triisopropyl borate and the corresponding alkyllithium or Grignard reagents followed by acidic hydrolysis [12] while cyclohexylboronic acid was prepared by hydroboration of cyclohexene with dibromoborane methyl sulfide complex followed by hydrolysis [13]) and used immediately in the preparation of 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol boronates. Anhydrous zinc chloride was prepared by melting zinc chloride (reagent grade), and the molten zinc chloride was cooled and crushed in a dry box under nitrogen. All other reagents were purchased from Aldrich and used without further purification. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC 250 (250.13 and 62.89 MHz respectively) spectrometer. Chemical shifts for ^{1}H- and ^{13}C-NMR are reported in ppm on the δ scale with internal reference to $SiMe_4$ (δ 0.00) and $CDCl_3$ (δ 77.00), respectively. Coupling constants (J) are given in hertz (Hz). GC analysis was performed on a HP 5890 instrument equipped with a capillary column (Carbowax, 30 m × 0.25 mm ID × 0.25 mm). Rotations were determined using a Perkin–Elmer 241 Polarimeter at room temperature.

4.2. 1,2:5,6-Di-O-cyclohexylidene-D-mannitol-phenylboronate

The synthesis of 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol phenylboronate is representative. A mixture of phenylboronic acid (0.558 g, 4.58 mmol), 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol (1.57 g, 4.58 mmol), anhydrous $MgSO_4$ (2 g) in Et_2O was stirred at room temperature (r.t.) for 24 h. The filtrate was concentrated and the residue purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to afford a crystalline solid (1.72 g, 90%). ^{1}H-NMR ($CDCl_3$) δ 7.85–7.75 (m, 2H), 7.50–7.35 (m, 3H), 4.50–4.35 (m, 2H), 4.20–3.90 (m, 6H), 1.80–1.25 (m, 20H). ^{13}C-NMR ($CDCl_3$) δ 134.98, 131.62, 127.79, 110.48, 79.91, 76.36, 65.96, 36.24, 34.51, 25.15, 24.02, 23.75.

4.3. 1,2:5,6-Di-O-cyclohexylidene-D-mannitol-n-butylboronate

^{1}H-NMR ($CDCl_3$) δ 4.22–4.15 (m, 2H), 4.12–4.00 (m, 4H), 3.95–3.87 (m, 2H), 1.75–1.35 (m, 24H), 0.95–0.78 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ 110.35, 79.16, 76.31, 65.85, 36.17, 34.43, 26.12, 25.17, 23.99, 23.74, 13.84.

4.4. 1,2:5,6-Di-O-cyclohexylidene-D-mannitol-isopropylboronate

^{1}H-NMR ($CDCl_3$) δ 4.25–4.15 (m, 2H), 4.12–4.00 (m, 4H), 3.95–3.85 (m, 2H), 1.70–1.30 (m,20H), 1.15 (m, 1H), 0.98 (d, 6H, $J = 6.40$). ^{13}C-NMR ($CDCl_3$) δ 110.32, 79.16, 76.31, 65.80, 36.17, 34.46, 25.15, 24.00, 23.75, 18.00.

4.5. 1,2:5,6-Di-O-cyclohexylidene-D-mannitol t-butylboronate

^{1}H-NMR ($CDCl_3$) δ 4.25–4.15 (m, 2H), 4.12–4.00 (m, 4H), 3.96–3.86 (m, 2H), 1.70–1.32 (m, 20H), 0.95 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ 110.27, 79.19, 76.33, 65.75, 36.18, 34.49, 27.00, 25.17, 24.01, 23.77.

4.6. 1,2:5,6-Di-O-cyclohexylidene-D-mannitol cyclohexylboronate

^{1}H-NMR ($CDCl_3$) δ 4.23–4.15 (m, 2H), 4.12–3.97 (m, 4H), 3.95–3.85 (m, 2H), 1.72–1.28 (m, 31H). ^{13}C-NMR ($CDCl_3$) δ 110.32, 79.09, 76.33, 65.81, 36.18, 34.46, 27.95, 26.94, 26.70, 25.16, 23.99, 23.75.

4.7. (S)1-cyclohexyl-1-ethanol [14]

The synthesis is representative: *n*-BuLi (1.57 ml, 3.94 mmol) was slowly added to a solution of CH_2Cl_2 (0.26 ml, 3.94 mmol) in THF (10 ml) cooled to −100°C (ethanol/liquid N_2). After addition, the reaction mixture was stirred at −100°C for 20 min. To the resulting white suspension was added a solution of 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol cyclohexylboronate (1.42 g, 3.28 mmol) in Et_2O (5 ml) at −78°C. The clear solution was stirred at −100°C for another 20 min before anhydrous $ZnCl_2$ (0.360 g, 2.62 mmol) was added. The reaction mixture was gradually warmed to r.t. and stirred at r.t. for 24 h. The mixture was cooled to

−78°C and CH_3MgBr (2.84 ml, 8.52 mmol) was added. After stirring at r.t. for 24 h, the mixture was treated with 3 M NaOH (1.5 ml) and 30% H_2O_2 (0.8 ml) at 0°C and then stirred at r.t. overnight. After the usual work-up, chromatographic separation provided (*S*)-1-cyclohexyl-1-ethanol (0.299 g, 71%): $[\alpha]^3 = 3.51°$ (c 3.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 3.55 (quint, 1H, $J = 6.2$), 1.90–0.90 (m, 15H). ^{13}C-NMR ($CDCl_3$) δ 71.63, 44.54, 28.12, 27.75, 25.92, 25.63, 25.54, 19.83. An ee of 95% was determined by GC analysis of its (+)-menthyl chloroformate derivative, compared with the racemic samples. 1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol (0.936 g, 83%) was also recovered.

4.8. (S)-1-Phenyl-1-pentanol [15]

$[\alpha]^3 = -36.81°$ (C 3.97, benzene). ^{1}H-NMR ($CDCl_3$) δ 7.32 (m, 5H), 4.63 (*t*, 1H, $J = 6.34$), 2.00 (s, 1H), 1.75 (m, 2H), 1.31 (m, 4H), 0.88 (*t*, 3H, $J = 7.11$). ^{13}C-NMR ($CDCl_3$) δ 144.90, 128.37, 127.41, 125.86, 74.64, 38.76, 27.93, 22.56, 13.95.

4.9. (R)-2-Methyl-1-phenyl-1-propanol [16]

^{1}H-NMR ($CDCl_3$) δ 7.29 (m, 5H), 4.34 (d, 1H, $J = 6.84$), 1.93 (m, 2H), 0.99 (d, 3H, $J = 6.68$), 0.79 (d, 3H, $J = 6.79$).

4.10. (R)-2,2-Dimethyl-1-phenyl-1-propanol [16]

$[\alpha]^3 = 31.22°$ (C 4.4, Et_2O). ^{1}H-NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.40 (s, 1H), 1.35 (s, 1H), 0.92 (s, 9H).

4.11. (S)-1-Cyclohexyl-3-buten-1-ol [17]

$[\alpha]^3 = -10.15$ (C 4.0, EtOH). ^{1}H-NMR ($CDCl_3$) δ 5.82 (m, 1H), 5.15 (m, 2H), 3.40 (m, 1H), 2.45 (m, 1H), 2.15 (m, 1H) 1.90–1.00 (m, 12H). ^{13}C-NMR ($CDCl_3$) δ 135.47, 117.91, 74.75, 43.10, 38.82, 29.11, 28.12, 26.53, 26.29, 26.15.

4.12. (S)-1-Cyclohexyl-2-propen-1-ol [18]

$[\alpha]^3 = -14.32°$ (C 1.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 5.85 (m, 1H), 5.18 (d, 1H, $J = 17.50$), 5.3 (d, 1H, $J = 12.50$) 3.85 (*t*, 1H, $J = 7.30$). 1.90–0.90 (m, 12H). ^{13}C-NMR (CDClS) δ 139.81, 115.45, 77.76, 43.49, 28.75, 28.33, 26.51, 26.13.

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