

Bidirectional asymmetric allylboration and the synthesis of C_2 symmetric 3-methylenepentane-1,5-diols

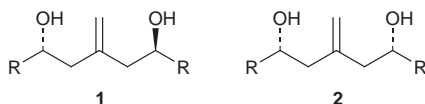
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Received (in Liverpool, UK) 16th October 1998, Accepted 27th January 1999

The double allylboration of aldehydes using 1,3-bis(diisopinocampheylboryl)-2-methylenepropane under Brown's salt-free conditions provides C_2 symmetric 3-methylenepentane-1,5-diols in excellent enantiomeric excess.

C_2 Symmetric 3-methylenepentane-1,5-diols **1** are versatile synthetic intermediates¹ and a number of procedures have been reported for their synthesis.^{2,3} Most of these methods entail the



double addition of an aldehyde to the 2-methylpropene dianion, or a synthetic equivalent. However, the reported syntheses are neither diastereo- nor enantio-selective as only 1 : 1 mixtures of the C_2 **1** and *meso* **2** diastereomers were obtained. As an extension of the Brown asymmetric allylboration reaction,⁴ we were interested in preparing the enantiomeric bis(diisopinocampheylboryl)s (*S,S*)- and (*R,R*)-**4** and investigating their double allylboration reactions. In this regard, we were encouraged by a report detailing the use of 1,3-bis(dipropylboryl)-2-methylenepropane in double allylboration reactions, affording 1 : 1 mixtures of the desired 3-methylenepentane-1,5-diols **1** (racemic) and **2** (*meso*).³

Treatment of an ethereal suspension of 1,3-dilithio-2-methylenepropane, prepared from 2-methylpropene **3**, BuⁿLi and TMEDA in hexane,⁵ with 2 equiv. of the commercially

available (1*S*)-(+)-*B*-chlorodiisopinocampheylborane (DIP-ClTM) afforded the corresponding bis(diisopinocampheylborane) (*S,S*)-**4** (Scheme 1). The corresponding enantiomeric borane (*R,R*)-**4** was prepared from (1*R*)-(-)-DIP-ClTM.[†] *In situ* reaction with benzaldehyde followed by an alkaline H₂O₂ work-up gave an inseparable mixture of 3-methylene-1,5-diphenylpentane-1,5-diols **1** and **2** (R = Ph) (60%), which were readily separated from the accompanying product of mono-allylboration, 3-methyl-1-phenylbut-3-en-1-ol (**5**) (R = Ph) (30%) (Scheme 1). The diastereomeric ratio (dr) of the mixture of diols **1** and **2** (R = Ph) was estimated to be 8 : 2 (by ¹H NMR spectroscopy), in favour of the desired C_2 symmetric isomer **1**.

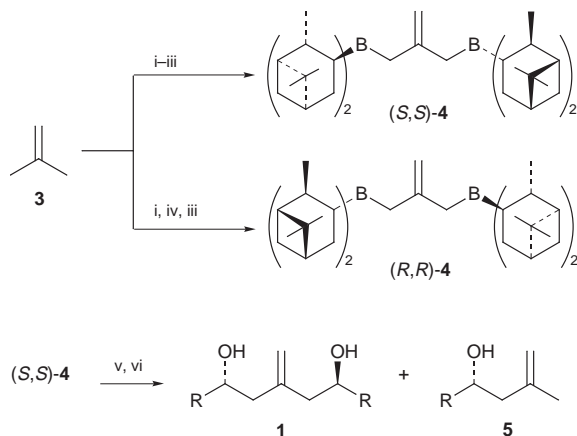
While this was a promising result, the moderate dr of the C_2 symmetric diol **1** as well as the significant amount of alcohol **5** formed necessitated changes to the reaction conditions. Reasoning that alcohol **5** arose from 3-lithio-2-methylpropene as a result of incomplete dianion formation,^{5,6} the 1,3-dilithio-2-methylenepropane was isolated by filtration (35–50%) prior to the addition of the DIP-ClTM. The subsequent allylboration reaction was conducted under Brown's 'salt-free' conditions⁷ in order to improve the selectivity. Gratifyingly, these modifications afforded the desired product **1** (R = Ph) with excellent diastereo- and enantio-selectivity (see Table 1, entry 1), and reduced the yield of the alcohol by-product **5** to less than 5%.

A range of aldehydes were allowed to react with both enantiomers of reagent **4**[‡] to afford the corresponding C_2 symmetric 3-methylenepentane-1,5-diols **1** in moderate yields (Table 1)[§] but with excellent diastereoselectivities (> 80% de)

Table 1 Preparation of C_2 symmetric 3-methylenepentane-1,5-diols **1**

Entry	Reagent	Aldehyde	Yield (%)	Dr ^a	Ee (%) ^a	Config.
1	(<i>S,S</i>)- 4	PhCHO	55 R = Ph	84 : 16	> 95	(<i>R,R</i>)
2	(<i>S,S</i>)- 4	Pr ⁱ CHO	41 R = Pr ⁱ	93 : 7	> 95	(<i>R,R</i>)
3	(<i>R,R</i>)- 4	Pr ⁱ CHO	38 R = Pr ⁱ	91 : 9	> 95	(<i>S,S</i>)
4	(<i>S,S</i>)- 4	EtCHO	45 R = Et	93 : 7	> 95	(<i>S,S</i>)
5	(<i>S,S</i>)- 4	Bu ⁱ CHO	53 R = Bu ⁱ	93 : 7	> 95	(<i>S,S</i>)
6	(<i>S,S</i>)- 4	C ₅ H ₁₁ CHO	43 R = C ₅ H ₁₁	92 : 8	> 95	(<i>S,S</i>)
7	(<i>S,S</i>)- 4	4-O ₂ N-C ₆ H ₄ CHO	51 R = 4-O ₂ N-C ₆ H ₄	95 : 5	> 95	(<i>R,R</i>)
8	(<i>S,S</i>)- 4	4-MeO-C ₆ H ₄ CHO	55 R = 4-MeO-C ₆ H ₄	95 : 5	> 95	(<i>R,R</i>)
9	(<i>S,S</i>)- 4	3-O ₂ N-C ₆ H ₄ CHO	47 R = 3-O ₂ N-C ₆ H ₄	94 : 6	> 95	(<i>R,R</i>)
10	(<i>S,S</i>)- 4		38 R =	66 : 14.5 : 1	—	(<i>R,R</i>) ^b
11	(<i>R,R</i>)- 4		50 R =	160 : 22 : 1	—	(<i>S,S</i>) ^b
12	(<i>R,R</i>)- 4	(<i>S</i>)-citronellal	57 (<i>S</i>)-Me ₂ C=C(CH ₂) ₂ CHMeCH ₂	46 : 6 : 1	—	(<i>R,R</i>) ^b
			R =			
13	(<i>S,S</i>)- 4	2-O ₂ N-C ₆ H ₄ CHO	0 R = 2-O ₂ N-C ₆ H ₄	—	—	—
14	(<i>S,S</i>)- 4	Bu ⁱ CHO	0 R = Bu ⁱ	—	—	—

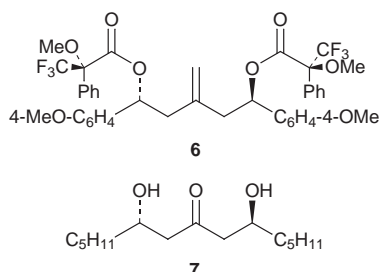
^a The diastereomeric ratio (dr) is the ratio **1** : **2**. Both the dr and the ee are estimated from the corresponding bis-Mosher esters (ref. 8). ^b The stereochemical descriptor refers to the central 3-methylenepentanediol entity.



Scheme 1 Reagents and conditions: i, BuⁿLi, TMEDA, hexane; ii, (+)-DIP-ClTM, Et₂O; iii, pentane, filtration; iv, (–)-DIP-ClTM, Et₂O; v, RCHO, Et₂O or THF, –78 °C; vi, 30% H₂O₂, 4 mol dm^{–3} NaOH, 20 °C.

and enantioselectivities (>95% ee).[¶] Both pivaldehyde and 2-nitrobenzaldehyde failed to provide the corresponding adducts **1** presumably on account of steric congestion (Table 1, entries 13 and 14). In the case of the homochiral aldehydes (Table 1, entries 10, 11 and 12) substantial reagent control of the selectivity was observed, with largely a single isomer being isolated in both the mismatched (entry 10) and matched (entry 11) cases.

The absolute stereochemical course of the reaction was determined by an X-ray crystallographic analysis of the bis-(S)-(-)-Mosher ester **6**.^{||} This study unequivocally established both the relative and absolute stereochemistry of the diol and, by implication, all of the other diols in Table 1. Additional confirmation of the absolute stereochemistry was obtained from a comparison of the optical rotation of dihydroxy ketone **7**



{[α]_D²⁵ +45.8, (c 0.2 in CHCl₃)}, obtained *via* ozonolysis of diol **1** (R = C₅H₁₁) (97%), with that previously reported for the antipode {[α]_D²⁵ –40.4, (c 0.2 in CHCl₃)}.⁹

This study further demonstrates the utility of pinene-derived compounds in asymmetric synthesis. The direct conversion of aldehydes into highly enantiomerically enriched C₂ symmetric 3-methylenepentane-1,5-diols **1** *via* an experimentally simple procedure should be of considerable application in organic synthesis.

We thank Parke Davis Warner Lambert for generous support of this programme of research, Glaxo Wellcome Research Ltd. for the generous research endowment (to A. G. M. B.), the Wolfson Foundation for establishing the Wolfson Centre for

Notes and references

† A solution of the salt-free bis(diisopinocampheylborane) **4** in Et₂O was found to be stable for up to 3 days at room temperature under an argon atmosphere. After this time the reagent deteriorated markedly as evidenced by substantially reduced yields.

‡ In a typical procedure a solution of (1S)-(+)-*B*-chlorodiisopinocampheylborane (5.4 g; 16.8 mmol) in dry Et₂O (20 ml) was added to a vigorously stirred suspension of 1,3-dithio-2-methylenepentane-2 (TMEDA) (2.3 g; 7.7 mmol) in dry Et₂O (20 ml) at 0 °C and the mixture was stirred at 20 °C for 3 h under argon. The Et₂O was removed *in vacuo* and the residue was dissolved in dry pentane (50 ml) and filtered under argon. The residual salts were washed with a further portion of dry pentane (50 ml). The combined pentane extracts were evaporated under reduced pressure and the resulting oil was dissolved in dry Et₂O (50 ml) under argon and cooled to –78 °C. 4-Methoxybenzaldehyde (2.5 ml; 20.5 mmol) was added and the resulting solution was stirred for 3 h at –78 °C. H₂O₂ (30%; 4 ml; 32 mmol) and aqueous NaOH (4 mol dm^{–3}; 8 ml; 32 mmol) were added simultaneously and the mixture was stirred for 18 h at 20 °C. Water (20 ml) was added and the mixture was extracted with Et₂O (3 × 20 ml). The ethereal extracts were dried and concentrated to give a clear residue, which was chromatographed (EtOAc–hexanes, 2:3) to give (1*R*,5*R*)-1,5-bis(4-methoxyphenyl)-3-methylenepentane-1,5-diol (1.377 g; 55%) as a white solid.

§ The reported yields are relative to the amount of 1,3-dithio-2-methylenepentane. All new compounds were fully characterised by spectroscopic data, combustion analysis and HRMS.

¶ Diastereoselectivities and enantioselectivities were determined by preparation of the corresponding bis-Mosher esters (ref. 8) and ¹H NMR analysis.

|| Full details of the X-ray crystallographic study will be reported elsewhere.

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Communication 8/08070D