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Synthesis of Homochiral *R*-(+)-2-Methyl-1-butanol

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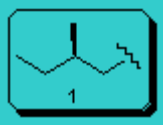
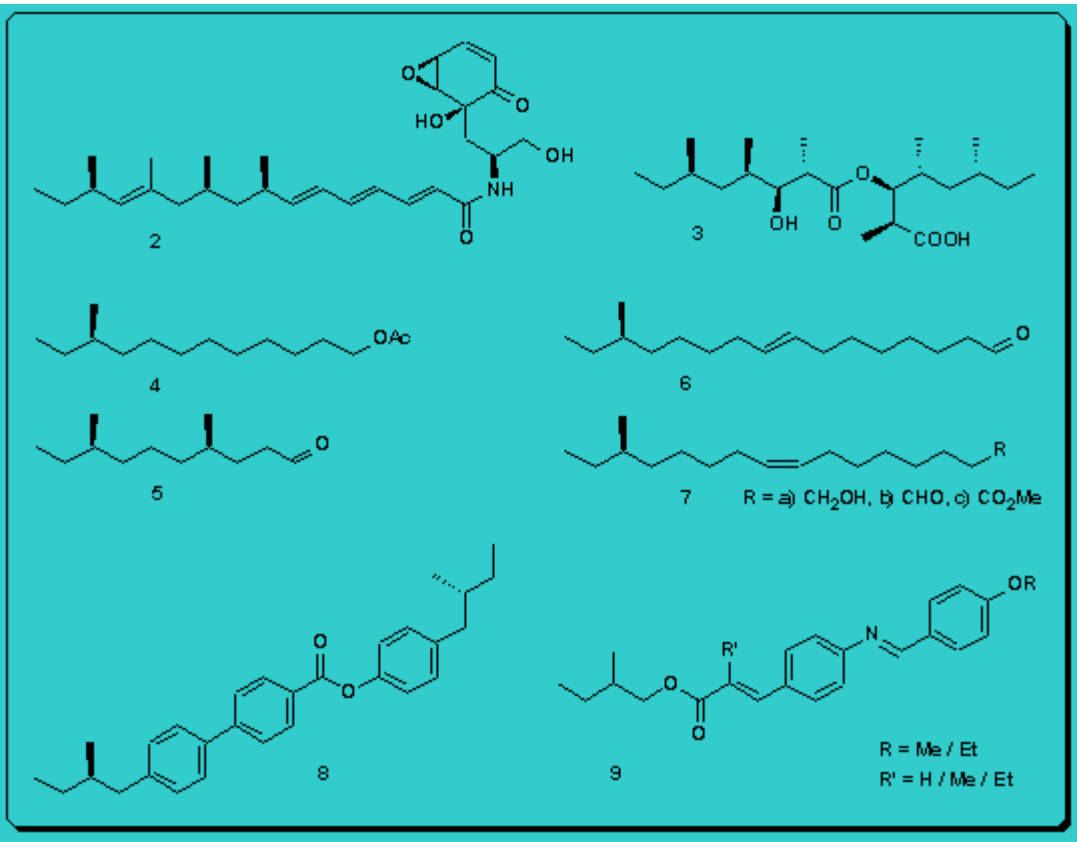
Abstract: *R*-(+)-2-Methylbutanol **10a,** a building block of several natural products, is commercially unavailable. The total synthesis of **10a** in four steps utilising the boronic ester homologation approach is described.

Keywords: boron, stereoselective synthesis, homologation, boronic esters, 2-methylbutanol

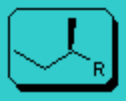
Introduction:



The *R*-2-methylbutyl motif **1** is present in a number of bio-active compounds found in nature. It forms part of scyphostatin **2**,[1] a highly potent sphingomyerinase inhibitor, appears in bourgeanic acid **3**,[2] a naturally occurring aliphatic depside found in lichens (*Ramalina* species), and also forms part in a series of optically active insect sex pheromones, *viz.* *R*-10-methyldodecyl acetate **4** (*Adoxophyes* species, lesser tea tortrix moth),[3,4] (4*R*,8*R*)-4,8-dimethyldecanal **5** (*Tribolium castaneum*),[3] (*R,E/Z*)-14-methyl-8-hexadecenal **6/7b** (*Trogoderma granarium, T. glabrum, T. inclusum* and *T. variabile*)[3,5] and (*R,Z*)-14-methyl-8-hexadecen-1-ol **7a** and methyl *(R,Z)*-14-methyl-8-hexadecenoate **7c** (*Trogoderma inclusum,* dermestid beetle).[5b,6] Also, optically active nematic liquid crystals exhibiting a cholesteric mesophase and containing the *R*-2-methylbutyl moiety **1** have been described, *viz.* homochiral **8**[7] and **9**[8].



It is of interest to note that compounds such as **10** corresponding to the *R*-2-methylbutyl motif are commercially not available and are sold as racemic mixtures (***RS*-10**) and/or as the *S* stereoisomers (***S*-10**). It is therefore not surprising that a number of research groups have been involved in both the synthesis of *R*-(+)-2-methylbutanol **10a**[9] and in the construction of substructure **1** as an intermediate *en route* to other target molecules.[2a,3,4,7,10]



R = CH_2R'

10a: R' = OH
10b: R' = NH_2
10c: R' = OMs
10d: R' = Cl
10e: R' = Br
10f: R' = I

R = *COR'*

10g: R' = OH
10h: R' = OMe
10i: R' = Cl

10j: *R* = *CHO*
10k: *R* = *CN*

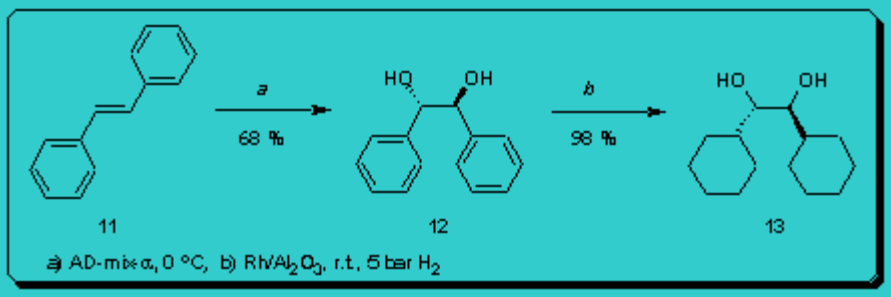
Prompted by the recent interest in the title compound, we have developed a new synthetic route towards **10a**. Herein, we wish to report a novel and straightforward total synthesis of *R*-(+)-2-methylbutanol **10a** utilising the boronic ester homologation approach and readily available starting materials.

Results and Discussion:

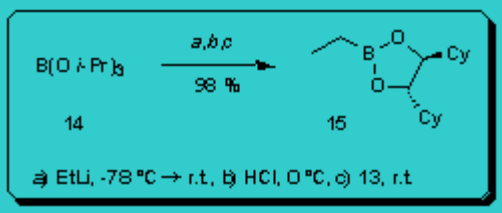
The one carbon-chain extension utilising asymmetric boronic ester chemistry has been developed and extensively reviewed by Matteson,[11] with mechanistic studies discussed by Corey *et al*.[12] This methodology allows complete control of the absolute configuration of each of the newly generated stereogenic centres. The use of homochiral C_2-symmetrical 1,2-diols and especially 1,2-dicyclohexyl-1,2-ethanediol (DICHED) as a chiral auxiliary permits the introduction of stereogenic centres via the a-chloroalkyl boronic ester approach in exceptionally high diastereoselectivities.

Retrosynthetic analysis of our target molecule **10a** resulted in a demand for (*S*,*S*)-DICHED **13**, which, unlike the enantiomer, is not yet commercially available and therefore had to be synthesised. *E*-stilbene **11** is converted with the AD-mix-a formulation to (*S*,*S*)-hydrobenzoin **12** following the asymmetric dihydroxylation protocol developed by Sharpless *et al*.,[13a] a procedure which has also been adapted for bulk amounts.[13b]

Catalytic reduction of the aromatic ring systems of **12** to yield (*S*,*S*)-DICHED **13** has been reported as troublesome and various attempts with different solvents, additives and reaction conditions exist.[14] However, the addition of glacial acetic acid (10 %) to the bulk solvent, methanol, provided a solvent system that allowed complete reduction of **12** at room temperature with a rhodium catalyst to form **13** at 5 bar hydrogen pressure in excellent yield. Hence, (*S*,*S*)-DICHED **13** is easily accessible in large quantities. The compound is stable for prolonged periods at room temperature. Furthermore, at the end of the reaction sequence leading to **10a**, it can be recovered without loss of optical quality and re-used after a single recrystallisation.



For the synthesis of the starting building block **15** we modified a route suggested by Brown *et al.*,[15] who used readily available organolithium compounds for related products, rather than persuing the route used by Matteson *et al*.,[16] who synthesised the antipode ***ent*-15** starting from dibutyl ethyl boronate or from Grignard reagents (EtMgCl plus **14**): Freshly prepared ethyl lithium[17] is added at –78 °C to an ether solution of triisopropyl borate **14**. After nucleophilic addition of the ethyl lithium-lithium bromide aggregate to the electron-deficient boron atom and subsequent anhydrous acidic cleavage of one isopropoxy group, simple transesterification with (*S*,*S*)-DICHED **13** led to (4*S*,5*S*)-4,5-dicyclohexyl-2-ethyl-1,3,2-dioxaborolane **15** in excellent yield. Impurities resulting from Wurtz-Fittig side-reactions could be easily removed by column chromatography.

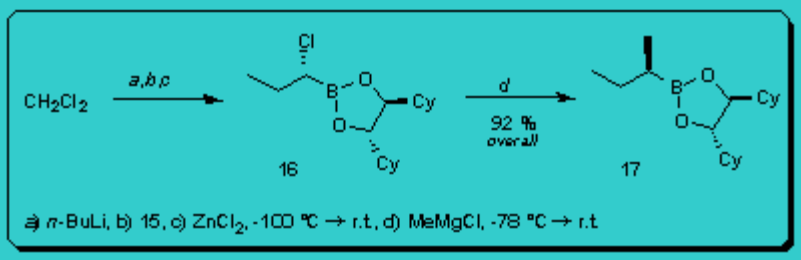


The introduction of the stereogenic centre starts with the generation of a carbenoid from dichloromethane and *n*-butyl lithium. The metallation reaction is exothermic, and the resulting lithiated species is stable only at temperatures below –65 °C, with the optimal temperature range for the generation below –100 °C.[11d,18] The preferred solvent is THF due to its enhanced polarity and Lewis basicity as well as its stabilising effect on dichloromethyl lithium. However, due to its high viscosity at these temperatures, a solvent mixture consisting of THF, diethyl ether and pentane 4:4:1 is used instead. This Trapp mixture possesses a much lower viscosity at very low temperatures and retains the desired properties of pure THF.[18c]

Thus, insertion of the chiral carbon unit into (4*S*,5*S*)-4,5-dicyclohexyl-2-ethyl-1,3,2-dioxaborolane **15** is achieved in absolute Trapp mixture under an inert gas atmosphere below –100 °C: **15** is added to dichloromethyl lithium followed after 30 min by the promoter, rigorously dried zinc dichloride. The reaction vessel was then allowed to warm to room temperature and stirred for an additional 18 hours. In this sequence the nucleophilic lithiodichloromethane binds to the electron-deficient boron atom and the formed intermediate rearranges under the influence of the zinc dichloride and under the stereochemical direction of the chiral auxilliary in high chemical and optical yield to (4*S*,5*S*)-2-[(1*R*)-1-chloropropyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane **16**.

As (4*S*,5*S*)-2-[(1*R*)-1-chloropropyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane **16** is prone to epimerisation, the crude oil obtained by extraction of the reaction mixture was used without further purification in the next step. Freshly prepared methyl magnesium chloride was added under inert gas atmosphere and in absolutely anhydrous solvents to the electrophilic boron atom in **16**. After warming the reaction mixture to room temperature, the intermediate rearranges

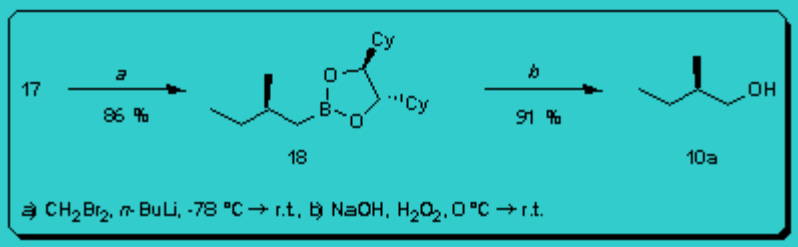
and the chlorine atom is substituted with complete inversion of configuration to yield (4*S*,5*S*)-4,5-dicyclohexyl-2-[(1*R*)-1-methylpropyl]-1,3,2-dioxaborolane **17** in high optical purity and chemical yield. NMR analyses of the crude and the purified (column chromatography) (4*S*,5*S*)-4,5-dicyclohexyl-2-[(1*R*)-1-methylpropyl]-1,3,2-dioxaborolane **17** showed the presence of only a single diastereomer.



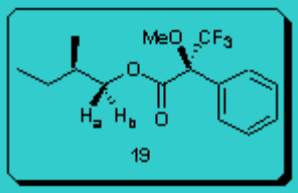
Insertion of the methylene unit into the carbon-boron bond is accomplished by a slightly modified procedure: Reaction of dibromomethane with *n*-butyl lithium leads via metal halogen exchange to labile bromomethyl lithium. In the presence of **17** this *in situ* generated nucleophilic lithiated species adds immediately to the elecron-deficient boron atom. The intermediate borate rearranges under extrusion of the remaining bromine atom to form (4*S*,5*S*)-4,5-dicyclohexyl-[(2*S*)-2-methylbutyl]-1,3,2-dioxaborolane **18** in good yield.

Cleavage of the boron-carbon bond is achieved through basic hydrogen peroxide at room temperature. The improved solubility of (*S*,*S*)-DICHED **13** in THF usually makes it the solvent of choice for this reaction. However, White *et al.*[2a] encountered problems while isolating the *R*-2-methylbutanol **10a** from toluene-THF solvent mixtures and therefore used it admixed with the solvent mixtures in subsequent reaction to from 1**0f**. Whitby *et al.*[9b] also describe the derivatisation of **10a** (tosylate and Mosher ester) as retained solvents precluded the determination of the specific rotation of **10a.**

Consequently, the boron-carbon bond cleavage procedure was modified by using diethyl ether as solvent. The suspension was allowed to react for 18 hours under vigorous stirring. The insoluble chiral auxiliary **13** precipitates and can easily be separated from the white suspension by filtration. The resulting emulsion is dried with anhydrous sodium sulfate in order to avoid any loss of **10a**, which is slightly soluble in the aqueous phase. Careful evaporation of the solvent via kugelrohr distillation yields a colourless liquid.



In contrast to preliminary experiments with racemic 2-methylbutanol on a 50 mmol scale, where evaporation of diethyl ether furnished a clean product with little or no loss of substance, on a small scale (1-3 mmol) the purification of **10a** proved to be extremely difficult, though, as the isolated liquid still contained some 10-20 % of diethyl ether.



Therefore, determination of the optical purity was carried out by analysis of the NMR data of the corresponding Mosher ester[19] *R*-2-methylbutyl *R*-a-methoxy-(a-trifluoromethyl)phenylacetate **19**. In the proton NMR, the diastereotopic protons H_a and H_b are diagnostic and the diastereomeric esters can be easily distinguished.[4,20] In the case of **19** two double doublets at d_H 4.25 and d_H 4.08, respectively, can be expected, whereas ***epi*-19** exhibits a doublet at d_H 4.17. In the present work, only the two double doublets at d_H 4.25 and d_H 4.08, respectively, are discernible, indicating that the precursor to **19**, the title compound *R*-(+)-2-methylbutanol **10a**, had an enantiomeric excess higher than 99 %. The e.e. of **19** was confirmed by the ^{19}F spectrum of **19** which showed a single signal at d_F –

72.07. The chemical shifts were also compared to spectra obtained from the Mosher ester of racemic 2-methylbutanol ***RS*-10a**, which exhibits signals at d_F –72.06 and d_F –72.07, respectively.

Summary:

R-(+)-2-Methylbutanol **10a** can be synthesised using the boronic ester homologation methodology. Starting from boron triisopropylate **14,** ethyl lithium and (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol **13,** the target molecule **10a** could be built up in four consecutive steps with a total yield of 71 % and particularly high enantiomeric excess.

Acknowledgements:

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His research interests are in the field of bio-organic chemistry and organic synthesis and are focussed on the structure elucidation, synthesis and biosynthesis of plant toxins and fungal metabolites which have deleterious effects on animal health.

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