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Carbamate-directed hydroboration: enantioselective synthesis of the excitatory amino acid 1-Aminocyclopentane-1,3-dicarboxylic acid

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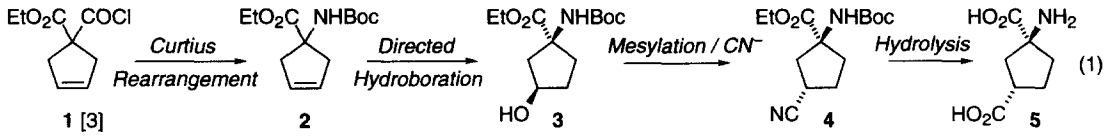
Abstract

Carbamate-directed hydroboration (using BH_3) of 1-substituted 3-cyclopentenes **2**, **6** and **9** and an enantioselective synthesis of the excitatory amino acid 1-aminocyclopentane-1,3-dicarboxylic acid *via* carbamate-directed asymmetric hydroboration [90% de, 45% ee using (+)-IpcBH$_2$] of cyclopentene **2** are described.

Keywords: Amino acids and derivatives; Carbamates; Cycloalkenes; Hydroboration

Ether and amide functionality in unsaturated substrates have been observed to direct hydroborations and transition metal-catalysed hydroborations respectively [1]. Here we communicate our preliminary results concerning a study of carbamate-directed hydroboration in the context of a synthesis of the excitatory amino acid 1-aminocyclopentane-1,3-dicarboxylic acid **5** (ACPD) [2] (eq. 1).



In order to examine this chemistry, cyclopentene **2** was prepared from the acid chloride **1** [3] *via* a Curtius rearrangement (NaN_3, acetone/H_2O, 5 °C, 30 min, then Bu^{t}OH, 4Å molecular sieves, cat. $SnCl_4$ [4], toluene, reflux, 3 h, 78% yield from **1**). Reaction of cyclopentene **2** with BH_3.THF (1 equiv., THF, 0 °C to 25 °C, 17 h) and oxidative work-up (1M NaOH, 30% H_2O_2) gave after chromatography the alcohol **3** (58%) and alcohol **12** (5%). The relative stereochemistry of alcohol **3** was initially assigned by NOE studies and ultimately by conversion to ACPD **5** (*vide infra*); the level of diastereoselectivity in the hydroboration was established as 95 : 5 (**3** : **12**) by ^{1}H NMR (and HPLC) analysis of the crude reaction mixture. The influence of the ester group on the stereoselectivity of the

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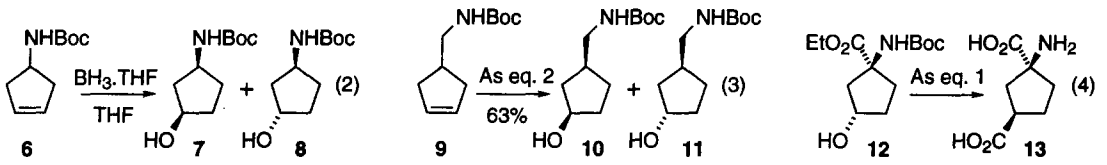
hydroboration was studied using alkene **6** {available from 3-cyclopentene carboxylic acid [3b] *via* a Curtius rearrangement} which after chromatography gave alcohols **7** (35%) and **8** (21%) (eq. 2), 75 : 25 respectively by ^{1}H NMR analysis of the crude reaction mixture. Consideration of the hydroboration results using **2** and **6** indicate that the 95 : 5 ratio of alcohols **3** and **12** obtained with **2** is due to a true carbamate-directing effect, but that this effect is significantly enhanced by the presence of the ester group. Interestingly, similar diasteroselectivity to that found in the hydroboration of alkene **6** was observed with alkene **9** [5](**10** : **11** = 79 : 21, by ^{1}H NMR analysis of the crude reaction mixture) (eq. 3).



Attempted asymmetric hydroboration of cyclopentene **2** with (−)-Ipc$_2$BH [6] (3 equiv., THF, 0 °C to room temperature, 17 h) followed by oxidation gave alcohols **3** (34%, racemic [determined by ^{1}H NMR using (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol]) and **12** (4%) (**3** : **12** = 81 : 19 by HPLC analysis of the crude reaction mixture). However, reaction of cyclopentene **2** with (−)-IpcBH$_2$ [6] (1 equiv., THF, 0 °C to room temperature, 17 h) gave the alcohol (−)-**3** in 42% yield and 34% ee ; reaction at −40 °C with (+)-IpcBH$_2$ gave the alcohol (+)-**3** in 45% ee (67% yield). The diastereoselectivities in these latter hydroborations were essentially identical (by ^{1}H NMR analysis of the crude reaction mixtures) to that observed earlier with cyclopentene **2** using BH_3. Alcohol (+)-**3** (45% ee) was converted to (1*S*,3*S*)-ACPD **5** {$[\alpha]_D^{23}$ +2.0 (*c* 0.41 in H_2O), lit. [2*a*] $[\alpha]_D^{20}$ +8.4 (*c* 1.0 in H_2O)} *via* mesylation (MsCl, Et_3N, CH_2Cl_2, 0 °C to room temperature, 17 h, 87%) and reaction with NaCN (3 equiv., DMF, 80 °C, 17 h) to give cyanide (+)-**4** (60% yield), followed by hydrolysis (6M HCl, reflux, 4 h) and ion-exchange [Dowex 50WX8-100, 2M aq. NH_3, 66% from (+)-**4**)] (eq. 1). Alcohol (+)-**3** (45% ee) was also converted into (1*S*,3*R*)-ACPD **13** {$[\alpha]_D^{23}$ −3.9 (*c* 0.26 in H_2O), lit. [2*a*] $[\alpha]_D^{20}$ −6.9 (*c* 1.0 in H_2O)} by the same sequence of transformations after first forming the inverted alcohol (−)-**12** (AcOH, PPh_3, DEAD, THF, 64%, then K_2CO_3, EtOH, 66%) (eq. 4).

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