Pergamon

Tetrahedron Letters 39 (1998) 3357–3358

TETRAHEDRON LETTERS

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

David M. Hodgson,*[a] Alison J. Thompson[a] and Sjoerd Wadman[b]

a Dyson Perrins Laboratory, Department of Chemistry, University of Oxford, South Parks Road, Oxford OX1 3QY, UK
b Glaxo Wellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK

Received 16 February 1998; accepted 27 February 1998

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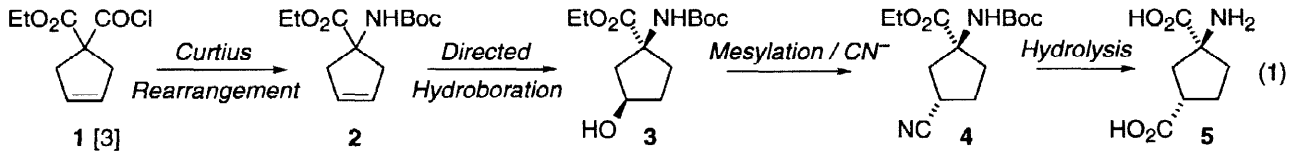
Keywords: Amino acids and derivatives; Carbamates; Cycloalkenes; Hydroboration

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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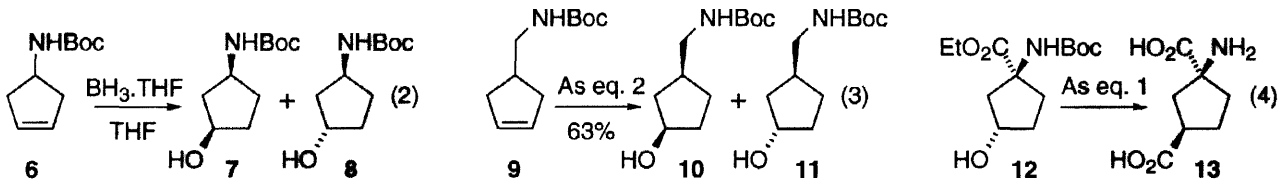
PII: S0040-4039(98)00490-0

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$_2$O), lit. [2*a*] $[\alpha]_D^{20}$ +8.4 (*c* 1.0 in H$_2$O)} *via* mesylation (MsCl, Et$_3$N, CH$_2$Cl$_2$, 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$_2$O), lit. [2*a*] $[\alpha]_D^{20}$ −6.9 (*c* 1.0 in H$_2$O)} by the same sequence of transformations after first forming the inverted alcohol (−)-**12** (AcOH, PPh$_3$, DEAD, THF, 64%, then K$_2$CO$_3$, EtOH, 66%) (eq. 4).

Acknowledgements

We thank the EPSRC and Glaxo Wellcome for a CASE award (to A. J. T.), and Zeneca (Strategic Research Fund) and Pfizer for additional financial support. We also thank E. McGuinness for expert assistance with the determination of stereochemistry and ee using NMR, and the EPSRC Mass Spectrometry Service Centre for mass spectra.

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