

Stereoselective synthesis of 3,4,5,6-tetrahydroxycyclohexyl β -amino acid derivatives

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ABSTRACT

Stereoselective syntheses of racemic (1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)- and (1*S*,2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5,6-tetrahydroxy derivatives of 2-aminocyclohexanecarboxylic acid have been achieved by a stereospecific Diels–Alder reaction between furan and maleic anhydride, a Curtius rearrangement and hydroxylation reactions.

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The stereoselective synthesis of cyclic β -amino acids has attracted the attention of chemists due to their biological activities and the interesting structural properties of their oligomers.^{1–5} These compounds in which both the amino and the acid functionalities are vicinally attached to an aliphatic ring still present a demanding challenge to synthetic chemists. One of the major reasons for this challenge is the difficulty associated with controlling the absolute and relative stereochemistry of two adjacent stereocentres. The difficulty in controlling the relative stereochemistry is exacerbated by the introduction of other stereocentres on the ring carbon atoms.

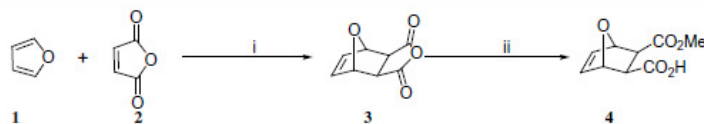
In view of the challenges involved in the synthesis of cyclic β -amino acids, we have been exploring the use of oxanorbornene adducts derived from the Diels–Alder reaction of ethyl (*E*)-3-nitroacrylate and furan as versatile intermediates in the synthesis of a range of novel mono-, di- and trihydroxy derivatives of 2-aminocyclohexanecarboxylic acid (ACHC).^{6,7} In this Letter, we report the use of an oxanorbornene adduct derived from the Diels–Alder reaction of furan and maleic anhydride as a useful intermediate in the synthesis of novel 3,4,5,6-tetrahydroxy derivatives of ACHC.

Our synthesis of tetrahydroxy cyclohexyl β -amino acid derivatives began with the Diels–Alder reaction of furan **1** and maleic anhydride **2**. When maleic anhydride was suspended in furan

and the mixture stirred for 16 h at room temperature, bicyclic adduct **3** was isolated exclusively in 98% yield, Scheme 1. This reaction can be considered to be green as no solvents were used. The stereochemistry of adduct **3** was assigned by 2D NMR experiments and by comparison with the relative stereochemistry of subsequent products. It is known from the literature that the Diels–Alder reaction between furan and maleic anhydride is reversible and gives the more thermodynamically stable *exo*-adduct.⁸ A prerequisite for the Curtius rearrangement on adduct **3** is solvolysis of the anhydride functionality. In the event, stirring a solution of adduct **3** in methanol at room temperature afforded half-ester **4** in 87% yield (Scheme 1).

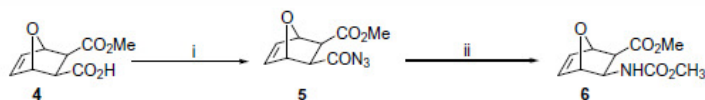
Next, half-ester **4** was converted into a form amenable to the crucial Curtius reaction. To this end, the free acid was activated using methyl chloroformate and then treated with sodium azide at 0 °C to give acyl azide **5**. To effect the Curtius rearrangement, acyl azide **5** was stirred at 50 °C in toluene for 10 h, cooled to room temperature, treated with methanol and stirred at room temperature to give carbamate **6** in 63% yield from **4** (Scheme 2).

We next set out to fragment the oxabicyclic adduct **6** by elimination of the oxygen bridge. There is extensive literature on both acid- and base-mediated elimination of the oxygen bridge of oxabicyclic rings.^{6,7,9,10} In our earlier work, we used a base for opening

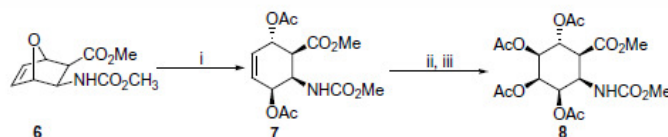


Scheme 1. Reagents and conditions: (i) 25 °C, 98%; (ii) MeOH, 25 °C, 87%

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Scheme 2. Reagents and conditions: (i) ClCO_2Me , NEt_3 , THF then NaN_3 , H_2O , 0°C ; (ii) toluene, 50°C then CH_3OH , 25°C , 63% from **4**.



Scheme 3. Reagents and conditions: (i) $\text{BF}_3\cdot\text{Et}_2\text{O}$, Ac_2O , 0°C , 61%; (ii) OsO_4 , $\text{Me}_3\text{NO}\cdot\text{H}_2\text{O}$, acetone; (iii) Ac_2O , py, 76% from **7**.

related oxabicyclic compounds.^{6,7} In this project, we investigated the ability of the Lewis acid $\text{BF}_3\cdot\text{Et}_2\text{O}$ in the presence of a nucleophile to open the oxabicyclic adduct **6**. In the event, a solution of carbamate **6** in acetic anhydride was treated with $\text{BF}_3\cdot\text{Et}_2\text{O}$ at 0°C to afford cyclohexene **7** in 61% yield (Scheme 3).

Elaboration of cyclohexene **7** through OsO_4 -mediated dihydroxylation followed by acylation afforded racemic (1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-3,4,5,6-tetraacetoxy-cyclohexyl β -aminocarboxylate **8**¹¹ as the only detectable isomer in 76% yield over the two steps. The relative stereochemistry of the product was assigned using NOESY NMR experiments (Fig. 1). The ability of cyclic homoallylic carbamates to give high levels of *syn* selectivity in osmium-mediated dihydroxylation reactions is well documented,^{6,7,12} therefore our results were not surprising.

An alternative oxygenation route involved an epoxidation reaction followed by acid-catalysed opening of the epoxide. Thus, when

cyclohexene **7** was treated with MCPBA, two isomeric epoxides **9** and **10** were isolated in 78% yield and 9:1 ratio with isomer **9** in excess. The epoxides were separated by column chromatography. The selectivity of the epoxidation reaction was consistent with reported literature.^{6,7,13,14} The major epoxide **9** was treated with perchloric acid followed by acylation to give racemic (1*S*,2*R*,3*R*,4*S*,5*S*,6*R*)-tetraacetoxy-cyclohexyl β -amino acid derivative **11**¹¹ as the only detectable product in 64% yield (Scheme 4). The relative stereochemistry of the product was assigned using NOESY NMR experiments (Fig. 2).

In conclusion, a stereoselective and effective route to tetrahydroxy derivatives of ACHC has been developed based on the oxabicyclic adduct derived from the Diels–Alder reaction of furan and maleic anhydride, a Curtius reaction and dihydroxylation reactions. On-going work in our laboratory includes testing these compounds for biological activity against bacteria.

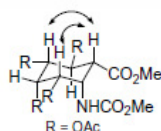


Figure 1. Selected NOESY interactions in **8**.

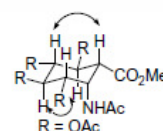
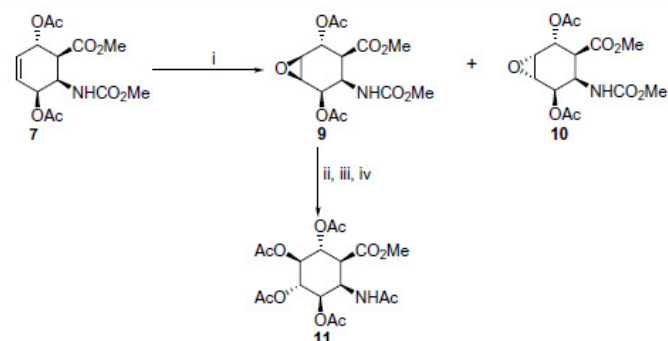


Figure 2. Selected NOESY interactions in **11**.



Scheme 4. Reagents and conditions: (i) MCPBA, CH_2Cl_2 , 25°C (**9**:**10**, 9:1) 78%; (ii) chromatography; (iii) HClO_4 , $\text{H}_2\text{O}/\text{acetone}$; (iv) Ac_2O , pyridine, 64% from **9**.

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11. Satisfactory spectroscopic and analytical data have been obtained for all new compounds. Compound **8**: white gum; ν_{max} (KBr disk): 3248, 2937, 1755, 1664, 1563 cm^{-1} ; δ_{H} (500 MHz, CDCl_3): 2.01 (3H, s, CH_3CO), 2.03 (6H, s, $2 \times \text{CH}_3\text{CO}$), 2.11 (3H, s, CH_3CO), 2.57 (1H, dd, $J = 3.5$ and 12.3 Hz, H-1), 4.12 (3H, s, OCH_3), 4.15 (3H, s, OCH_3), 4.33 (1H, m, H-2), 4.88 (1H, dd, $J = 3.5$ and 12.4 Hz, H-5), 4.96 (1H, t, $J = 3.5$ Hz, H-3), 5.21 (1H, br, H-4), 5.26 (1H, t, $J = 12.3$, H-6) 5.49 (1H, d, $J = 10.0$ Hz, NH); δ_{C} (125 MHz, CDCl_3): 20.8, 20.9 and 21.1 ($4 \times \text{CH}_3\text{CO}$), 44.7 (C-1), 53.5 (C-2), 62.8 (OCH_3), 65.1 (OCH_3), 70.6 (C-5), 72.9 (C-4), 73.2 (C-3), 75.3 (C-6), 169.8, 170.4, 170.8, 171.3 and 171.9 (carbonyls); m/z (CI): 448 (MH^+ , 100%); HRMS (ES^+): $\text{C}_{18}\text{H}_{25}\text{NO}_{12}\text{Na}$ requires M^+ , 470.1277. Found: 470.1267. Compound **11**: colourless gum; ν_{max} (KBr disk): 3271, 2986, 1747, 1651, 1556 cm^{-1} ; δ_{H} (500 MHz, CDCl_3): 1.91 (3H, s, CH_3CO), 1.97 (3H, s, CH_3CON), 2.03 (6H, s, $2 \times \text{CH}_3\text{CO}$), 2.16 (3H, s, CH_3CO), 2.77 (1H, dd, $J = 3.7$ and 12.7 Hz, H-1), 4.12 (3H, s, OCH_3), 4.50 (1H, m, H-2), 5.05 (2H, m, H-4 and 5), 5.50 (1H, t, $J = 12.4$ Hz, H-3), 5.53 (1H, t, $J = 11.9$ Hz, H-6), 5.56 (1H, d, $J = 8.0$ Hz, NH); δ_{C} (125 MHz, CDCl_3): 20.8 (CH_3CO), 21.2 (CH_3CO), 21.3 (CH_3CO), 23.3 (CH_3CON), 42.7 (C-1), 49.6 (C-2), 61.7 (OCH_3), 68.5 (C-5), 71.5 (C-3), 71.8 (C-4), 73.6 (C-6), 169.3, 169.9, 170.0, 170.1, 171.4, 171.7 (carbonyls); m/z (ES^+): 454 (MNa^+). HRMS (ES^+): $\text{C}_{18}\text{H}_{25}\text{NO}_{11}\text{Na}$ requires M^+ , 454.1328. Found: 454.1336.
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