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Stereoselective routes to 3-hydroxy and 3,4-dihydroxy derivatives of 2-aminocyclohexanecarboxylic acid

Ishmael B. Masesane[a,*] and Patrick G. Steel[b]

[a]*Department of Chemistry, University of Botswana, P/Bag UB 00704, Gaborone, Botswana*
[b]*Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK*

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Abstract—The Diels–Alder adduct of ethyl (*E*)-3-nitroacrylate and furan provides a versatile template for the stereoselective synthesis of mono and dihydroxylated derivatives of 2-aminocyclohexanecarboxylic acid (ACHC). The hydroxylated ACHC derivatives can be considered to be useful building blocks for β-peptides.

There is a great deal of interest in cyclic β-amino acids as these compounds exhibit promising structural and biological properties.[1] Pioneering work by Gellman has shown that oligomeric structures derived from 2-aminocyclohexane-1-carboxylic acid (ACHC) adopted defined secondary structures comparable to those observed in proteins.[2–4] Oligomers of ACHC and its derivatives therefore have a particular appeal for extending the understanding of protein structure and stabilization.

In view of the importance of oligomers of ACHC, there is a need for development of stereoselective synthetic routes to substituted ACHC derivatives. This would set the stage for further studies on the effects of the substituents on the stability of the oligomers. Consequently, we report in this Letter the synthesis of 3-hydroxy and 3,4-dihydroxy derivatives of ACHC based on the Diels–Alder reaction of ethyl (*E*)-3-nitroacrylate **1** and furan.

In our early work, we explored the Diels–Alder reaction of β-nitroacrylate **1** with furan.[5] Carrying out the reaction in chloroform at room temperature gave a 2:1 mixture of cycloadducts favouring the *endo* nitro isomer **2**. Selectivity was increased in favour of the *endo* nitro isomer by running the reaction in $CHCl_3$ at −20 °C to give a 4:1 mixture of the two isomers in over 90% yield.

The two isomers were easily separated by column chromatography. Nitro group reduction and protection of the resultant amines of **2** and **3** gave carbamates **2a** and **3a**, respectively. The relative stereochemistry of carbamate **2a** was confirmed by X-ray crystallography. Subsequent β-elimination of the oxygen bridge of carbamates **2a** and **3a** gave dihydroanthranilates **4** and **5**, respectively. Subsequent acetylation of **4** and **5** afforded acetates **4a** and **5a**, respectively. Reduction of these acetates proved to be highly *facio* selective and afforded 3-hydroxy ACHC derivatives *anti–anti* **6** from **4a** and *syn–syn* **7** from **5a**. The stereoselectivity of the reduction of the $\Delta^{1,2}$ double bond is consistent with reported observations[6,7] and the overall stereochemistry was confirmed by 2D NMR experiments, particularly NOESY (Scheme 1).

The extension of the above methodology to the preparation of the 3,4-dihydroxy derivatives of ACHC was based on reductive opening of epoxide intermediates derived from cyclohexadienes **4** and **5**. We have recently shown that treatment of **4** with *m*CPBA in dichloromethane gave a separable 9:1 mixture of epoxides **8**:**9**.[8] Exposure of epoxide **8** to the action of Pd–C under a hydrogen atmosphere afforded the *anti–anti–anti* dihydroxy ACHC derivative **10** as the only detectable isomer.[9] The *anti–anti–anti* configuration of **10** was confirmed by NOESY experiments. Reductive opening of vinylic epoxides was described by Danishefsky et al.[10] and on the basis of this precedent, the above results were not surprising. It is noteworthy that the addition of the hydride took place on the more hindered diastereo-face

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* Corresponding author. Tel.: +267-3552495; fax: +267-3552836; e-mail: masesane@mopipi.ub.bw

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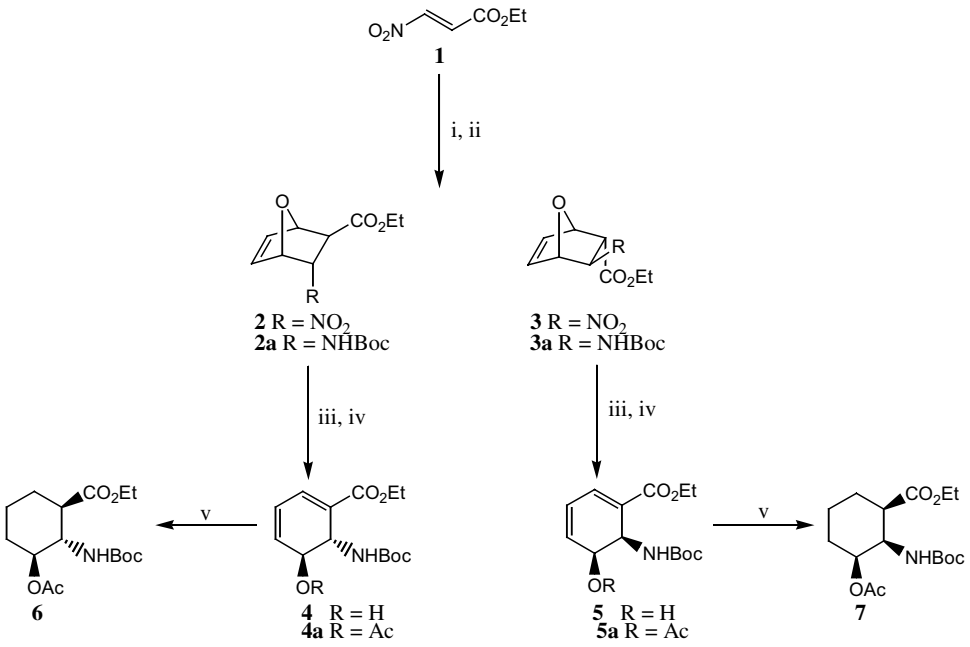
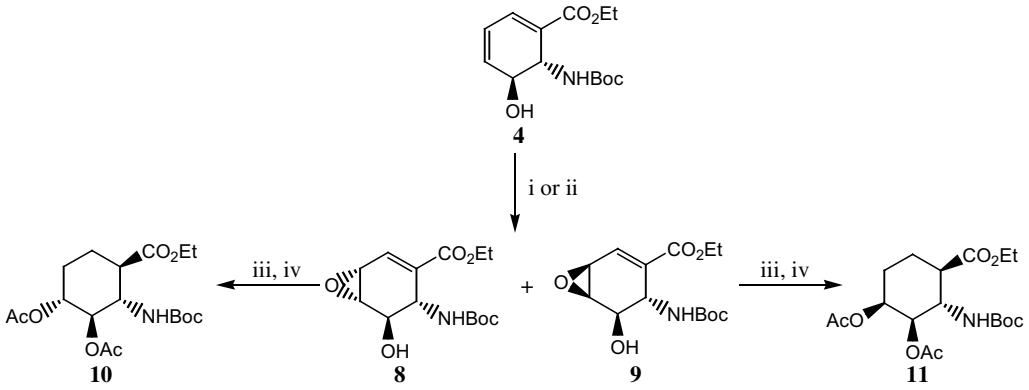


Scheme 1. Reagents and conditions: (i) furan, $CHCl_3$, 25 °C, (**2**:**3** 2:1), 90%; (ii) Zn, HCl, EtOH then Boc_2O, Et_3N, 25 °C, **2a** 77%, **3a** 75%; (iii) KHMDS, THF, −50 °C, **4** 71%, **5** 69%; (iv) Ac_2O, pyridine, **4a** 77%, **5a** 76%, (v) H_2, Pd–C, EtOH, **6** 98%, **7** 98%.

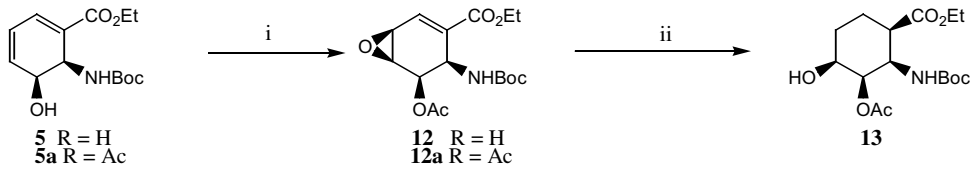
of the alkene probably due to the coordination of the palladium–hydride complex to the carbamate.

Repeating the epoxidation of **4** in acetonitrile instead of dichloromethane reversed the stereoselectivity and gave a 2:1 mixture of isomers favouring the *syn* epoxyalcohol **9**.[8] Reductive opening of the epoxide in the presence of Pd–C under a hydrogen atmosphere gave the *anti–anti–syn* dihydroxy ACHC derivative **11**.[9] The *anti–anti–syn* configuration of **11** was confirmed by NOESY experiments (Scheme 2).

Having used cyclohexadiene **4** in the synthesis of ACHC derivatives **10** and **11** we then set out to elaborate **5** into the corresponding ACHC derivatives. It was anticipated that substrate-stereocontrolled processes would secure the vicinal stereochemical relationships. With both the carbamate and the hydroxy groups on the same face of cyclohexadiene **5** and therefore operating in cooperation, it was presumed that epoxidation would occur preferentially on the upper face. Indeed, exposure of **5** to the action of *m*CPBA proved to be highly stereoselective and afforded epoxide **12** as the only product in 82% yield. All attempts at the use of polar solvents or acetate **5a** failed to give the *anti* epoxyalcohol. Treatment of epoxide **12a** with Pd–C under a hydrogen atmosphere afforded the *syn–syn–syn* isomer **13**[9] in excellent yield and interestingly as the only detectable isomer. Contrary to the systems above, the addition of hydride during reduction took place on the less hindered side of the alkene. The ability of the γ-acetate or hydroxy group of **12** to completely switch off the directing ability of the β-carbamate when the two are on the same face of the molecule is an interesting observation (Scheme 3).



Scheme 2. Reagents and conditions: (i) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 25 °C, (**8**:**9** 9:1), 77%; (ii) *m*CPBA, MeCN, $NaHCO_3$, 25 °C, (**8**:**9** 1:2), 95%; (iii) H_2, Pd/C, 25 °C; (iv) Ac_2O, pyridine, 25 °C, **10** 88% from **8**, **11** 84% from **9**.



5 R = H
5a R = Ac

12 R = H
12a R = Ac

13

Scheme 3. Reagents and conditions: (i) *m*CPBA, CH_2Cl_2, $NaHCO_3$, 25 °C, **12** 82%, **12a** 81%; (ii) H_2, Pd/C, EtOH, 25 °C, 98%.

In summary, we have amplified the utility of the Diels–Alder adduct of ethyl (*E*)-3-nitroacrylate and furan by obtaining a range of mono and dihydroxylated derivatives of ACHC through simple substrate-stereocontrolled operations. Whilst the chemistry described above was conducted on a racemic series, it is pertinent to note that the oxanorbornene adduct **2a** is amenable to an efficient enzyme mediated kinetic resolution and chiral HPLC resolution.[5] Ongoing work in our laboratory involves the use of these cyclic β-amino acids in the synthesis of short peptides and this will be reported in due course.

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9. Satisfactory spectroscopic and analytical data have been obtained for all new compounds. **10**: Colourless gum; ν_{max} (KBr disk): 3319, 2979, 1732, 1692, 1543 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.23 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.37 (9H, s, $OC(CH_3)_3$), 1.70 (1H, m, H-6), 1.94 (1H, m, H-6), 2.00 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.14 (2H, m, HH-5), 2.47 (1H, dt, $J = 9.0$ and 3.0 Hz, H-1), 3.88 (1H, m, H-2), 4.13 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.88 (1H, d, $J = 9.5$ Hz, H-3), 4.98 (1H, m, H-4); δ_C (125 MHz, $CDCl_3$): 14.3 (OCH_2CH_3), 20.9 and 21.2 ($2\times CH_3CO$), 24.9 (C-6), 28.4 ($OC(CH_3)_3$), 28.8 (C-5), 48.5 (C-1), 54.1 (C-2), 61.3 (OCH_2CH_3), 72.6 (C-3), 75.0 (C-4), 79.9 ($OC(CH_3)_3$), 155.0 (NCO_2), 170.3, 171.0, 172.2 (CO_2 and $2\times CH_3CO$); *m*/*z* (CI): 405 (MNH_4^+, 71%), 388 (MH^+, 36%), 349 (100%). Found: C, 55.83; H, 7.52; N, 3.59. $C_{18}H_{29}NO_8$ requires C, 55.80; H, 7.54; N, 3.62. **11**: White gum; ν_{max} (KBr disk): 3385, 2975, 1737, 1525 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.25 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 1.39 (9H, s, $OC(CH_3)_3$), 1.64 (1H, m, H-5), 1.81 (1H, m, H-6), 1.95 (2H, m, H-5 and 6), 2.01 (3H, s, CH_3CO), 2.13 (3H, s, CH_3CO), 2.51 (1H, t, $J = 11.5$ Hz, H-1), 4.16 (3H, m, OCH_2CH_3 and H-2), 4.45 (1H, d, $J = 9.5$ Hz, NH), 4.86 (1H, dd, $J = 11.5$ and 2.5 Hz, H-3), 5.32 (1H, br, H-4); δ_C (125 MHz, $CDCl_3$) 14.4 (OCH_2CH_3), 21.0 (CH_3CO), 21.5 (CH_3CO), 23.1 (C-6), 27.8 (C-5), 28.5 ($OC(CH_3)_3$), 48.8 (C-1), 50.7 (C-2), 61.2 (OCH_2CH_3), 69.4 (C-4), 73.3 (C-3), 79.7 ($OC(CH_3)_3$), 155.1 (NCO_2), 170.6, 171.0, 172.8 (carbonyls); *m*/*z* (CI): 388 (MH^+, 100%); Found: C, 55.81; H, 7.55; N, 3.65. $C_{18}H_{29}NO_8$ requires C, 55.80; H, 7.54; N, 3.62. **13**: colourless gum; ν_{max} (KBr disk): 3438, 3374, 2975, 1729, 1699, 1513 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.23 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.40 (9H, s, $OC(CH_3)_3$), 1.57 (1H, m, H-5), 1.63 (1H, m, H-6), 2.02 (2H, m, H-5 and 6), 2.07 (3H, s, CH_3CO), 2.60 (1H, m, $J = 11.5$ and 3.5 Hz, H-1), 4.07 (2H, m, H-4 and OH), 4.13 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.52 (1H, br, H-2), 4.85 (1H, m, H-3), 5.72 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 14.3 (OCH_2CH_3), 17.4 (C-6), 21.2 (CH_3CO), 28.5 ($OC(CH_3)_3$), 28.9 (C-5), 44.4 (C-1), 50.0 (C-2), 61.0 (OCH_2CH_3), 68.9 (C-4), 72.6 (C-3), 79.4 ($OC(CH_3)_3$), 155.9 (NCO_2), 170.2 (CO_2), 172.3 (CH_3CO); *m*/*z* (ES^+): 368 (MNa^+, 100%). HRMS (ES^+) found M^+, 368.3821. $C_{16}H_{27}NO_7$ requires 368.3826.
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