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Stereoselective preparation of pyrrolidin-2-ones from a *Z*-enoate derived from D-(+)-mannitol

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Abstract—Chiral pyrrolidin-2-ones have been prepared through the reductive cyclisation of γ-nitro-esters. These intermediates were obtained by *syn*-stereoselective conjugate addition of nitronates to a *Z*-enoate derived from D-(+)-mannitol. This route was used to prepare the cognitive enhancer (*S*)-WEB-1868.

1. Introduction

The pyrrolidinone moiety is present in the structure of several bioactive compounds and the activity can be modulated by the ring substitution pattern. For example, (Fig. 1), (*R*)-Rolipram **1** is a potent and selective PDE4 inhibitor[1a] and a potent HIV-1 replication inhibitor in vitro,[1b] while (*R*)-HA-966 **2** is an antagonist at the glycine modulatory site of the NMDA sub-type of glutamate receptor.[1c] (±)-Nebracetam **3**, (±)-WEB-1868 **4** and NS-105 **5**, all act as cognitive enhancers.[1d]

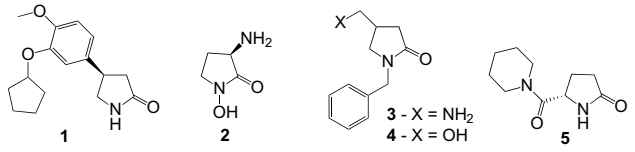

Figure 1. Examples of bioactive pyrrolidin-2-ones.

Substituted pyrrolidin-2-ones are also important because they can be used as intermediates in the preparation of γ-amino acids, such as (*R*)-Baclofen **6**,[2a] or pyrrolidines, such as Kainic acid **7**[2b] (Fig. 2).

Herein, we report the stereoselective synthesis of substituted pyrrolidin-2-ones, including (*S*)-WEB-1868, **4**.

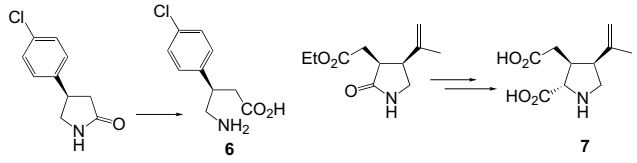

Figure 2. Pyrrolidin-2-ones as intermediates in syntheses.

2. Results and discussion

Stereoselective addition of $MeNO_2$ to enoate *Z*-**8** (Scheme 1) led to the *syn*-adduct **9**, (*syn*/*anti*, 9:1), as previously described.[3] Adduct **9** was reduced by catalytic transfer hydrogenation with ammonium formate and palladium in a closed vessel. Thus, a complex mixture of products was obtained by employing the reaction conditions described by Ehrenkaufer,[4] probably due to partial reduction of the nitro group. However, by increasing the (12 eq.) excess of NH_4HCO_2 and reaction time (4d), the resulting intermediate amino ester (detected by TLC) cyclised in situ (Scheme 1) to afford pyrrolidin-2-one **10** in 85% (dr 9:1). We also investigated the conjugate addition of ethyl α-nitro acetate to enoate *Z*-**8**. Good yield of **11** (90%) and good *syn*-selectivity at C-3 (10:1) was obtained in this reaction (^{13}C NMR),[3] however a mixture of diastereoisomers at the nitromethinic centre (C1′) was observed (55:45, Scheme 1). The configuration at C-3 in **11** was assigned,

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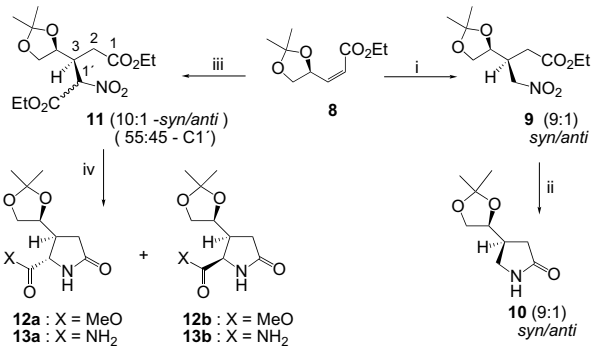
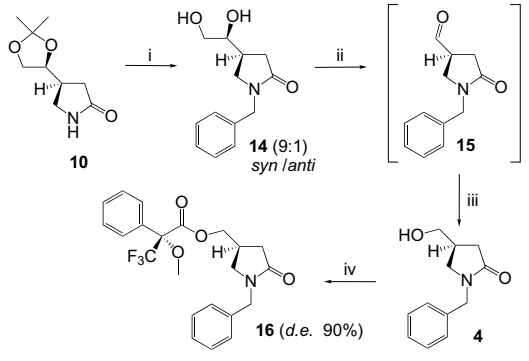


Scheme 1. Stereoselective synthesis of pyrrolidin-2-ones from enoate **8**. Reagents and conditions: (i) $MeNO_2$, DBU, MeCN, −30 °C, 70%; (ii) NH_4HCO_2, Pd–C 10%, MeOH, rt, 85%; (iii) $EtO_2CCH_2NO_2$, DBU, MeCN, rt, 90%; (iv) NH_4HCO_2, Pd–C 10%, MeOH, rt. (a) Closed vessel [**12a** (25%), **13a**+**13b** (37%, 23:77 or 77:23)]; (b) Open vessel [**12a** (35%), **12b** (20%)].

based on the comparison of its ^{13}C NMR spectrum with those of previously prepared *syn*-nitro-adducts.[3,4]

When compound **11** was reduced under the same conditions (closed vessel), compound **12a** could be easily obtained in pure form by flash chromatography, but in low yield (25%). This product was formed by the reduction of the nitro group, followed by cyclisation and transesterification with the solvent (not necessarily in this order). A polar fraction, consisting of a mixture of amides **13a** and **13b**, was also isolated in 37% yield, as the result of the substitution of the alkoxide group by ammonia, which is formed during the reduction (Scheme 1). These side products can be avoided when the reaction is run in an open vessel, where the ammonia concentration in solution is low. However, in this case, a mixture of epimers at the stereogenic centre substituted by the ester group was observed (**12a** and **12b**).

In order to prepare **4**,[5] compound **10** was *N*-benzylated with BnBr,[6] followed by acid hydrolysis of the dioxolan ring, leading to the diol intermediate **14**. After oxidative cleavage of **14** with $NaIO_4$,[7] $NaBH_4$ was added to the reaction medium (one-pot procedure, Scheme 2) leading to compound **4**.[8] The enantiomeric purity of **4** was evaluated by using Mosher's reagent.[9] The resulting compound **16** was homogeneous in ^1H and ^{13}C NMR, but ^{19}F NMR showed the presence of two compounds in a ratio of 95:5. This result indicates that aldehyde **15** did not epimerize under the reaction conditions.



Scheme 2. Stereoselective synthesis of (*S*)-WEB-1868 (**4**). Reagents and conditions: (i) (a) NaH, THF then BnBr, (b) 20% HCl aq, rt, 68%; (ii) $NaIO_4$, MeOH–H_2O, rt; (iii) $NaBH_4$, 0 °C, 69%; (iv) Mosher's acid chloride, Et_3N, DMAP, rt, quantitative.

3. Conclusion

Since enoate **8** can also be obtained in its enantiomeric form from vitamin C,[10] the presented synthetic strategy represents an easy access to pyrrolidin-2-ones with different patterns of substitution and chirality.

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8. Analytical data of (*S*)-**4**: $[\alpha]_{589} = -10.1$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.35–7.20 (sm, 5H), 4.48 (sd, 1H, $J = 15.0$ Hz), 4.40 (sd, 1H, $J = 14.7$ Hz), 3.66–3.50 (sm, 2H), 3.37 (dsd, 1H, $J = 9.9$ Hz, $J = 8.1$ Hz), 3.11 (dsd, 1H, $J = 9.9$ Hz, $J = 4.8$ Hz), 2.66–2.46 (sm, 1H), 2.36–2.18 (sm, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 173.93, 136.13, 128.58–127.50, 64.52, 49.14, 46.47, 33.84, 33.03; Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; O, 15.59. Found: C, 70.15; H, 7.40; N, 6.85.
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