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Diastereoselective Cyclisation of 2-Hydroxypinan-3-onyl Amino Esters

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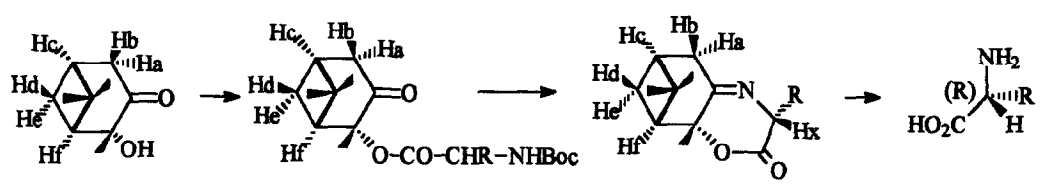
***Abstract** : A totally diastereoselective cyclisation of esters resulting from partial resolution during the condensation of 2-hydroxypinan-3-one with various racemic α-amino acids via Schiff bases has been observed and provides a route to homochiral α-amino acids.*

(1R,2R,5R) or (1S,2S,5S) 2-Hydroxypinan-3-one[1] is a very attractive chiral auxiliary widely used in asymmetric synthesis[2-5]. In particular, we have previously discovered that alkylation of the rigid 1,4-oxazinone formed by condensation of 2-hydroxypinan-3-one with glycine allows the synthesis of amino acids in high enantiomeric excess[2,4]. In order to achieve the asymmetric synthesis of various α-disubstituted amino acids by using the same procedure, we have studied the condensation of the same chiral auxiliary with four test racemic α-monosubstituted amino acids : Ala, Val, Leu, Phe. We wish to report the synthesis of these 1,4-oxazinone derivatives **3** which appears to be totally stereoselective.

Two strategies can be envisaged in order to form oxazinone **3** : (i) formation of a Schiff base between 2-hydroxypinan-3-one **1** and a racemic amino ester followed by ring closure; (ii) esterification of **1** with a racemic N-Boc amino acid and, after amine deprotection, ring closure by creation of a Schiff base. Unfortunately in the first case although the Schiff base was easily obtained[2,3], ring closure took place in very poor yield, undoubtedly due to the dominance of the E configuration of the Schiff base as already noted with glycine[2]. On the other hand, the second strategy readily gave rise to the desired compounds.

Esters **2** were prepared in 70-75% yields starting from racemic N-Boc amino acids by using dicyclohexyl carbodiimide (DCC) and a stoichiometric amount of 4-dimethylamino pyridine (DMAP). When DMAP was used in a catalytic amount, or when DCC / DMAP was replaced by other coupling reagents, the yields were drastically decreased (<5%).



1 **2** **3** **4**

a R=CH_3 **b** R=$CH(CH_3)_2$ **c** R= $CH_2C_6H_5$ **d** R=$CH_2CH(CH_3)_2$

Unfortunately the two diastereoisomeric esters **2** could not be distinguished by HPLC analysis. However, the ^{1}H-NMR spectra of the esters **2** exhibited a splitting of the H_f signal (δ ppm : **2a**, 2.86 and 2.89; **2b**, 2.79 and 2.90; **2c**, 2.82 and 2.88; **2d**, 2.86 and 2.94)[6] which showed that in each case a ca. 70/30 mixture of the two

epimers was obtained. This partial resolution could be evaluated more accurately by HPLC analysis after chiral derivatization with Marfey's reagent[7] of the crude amino acid obtained after acid hydrolysis (HCl 2N, reflux, 2h) of the ester mixture. We noted that no change of the epimeric ratio occurred when an excess of 2-hydroxypinan-3-one **1** and/or shorter or longer reaction times were used.

The N-protecting Boc group of the two diastereoisomeric amino esters **2** obtained in the form of an oily mixture, was next cleaved with 30% trifluoroacetic acid solution in CH_2Cl_2, and the resulting trifluoroacetic salts were neutralized with 10% diisopropyl amine in CH_2Cl_2. As in the case of the hydroxypinanonyl glycine ester[2], a spontaneous cyclisation took place on neutralization of the amine salts as shown by ^1H NMR study of crude products and mass spectrometry.

A careful study of the NMR spectrum of the reaction product showed that only one epimeric oxazinone derivative **3** was formed. Splitting of the H_x signal (δ ppm : **2a**, 4.15; **2b**, 3.86; **2c**, 4.26; **2d**, 3.98) demonstrates that H_x is situated on the same face as the gem-dimethyl bridge since it exhibits homoallylic coupling with H_a (J_{ax}=2.5Hz) and H_b (J_{bx}=4.2Hz) protons[2,5]. We did not observe a signal corresponding to the epimeric hydrogen of H_x which would not undergo homoallylic coupling[2].This proves that the cyclisation led only to the less hindered diastereoisomer in which the side chain of the amino acid moiety is situated on the face opposite to the gem-dimethyl bridge[2,5]. Molecular modelling confirmed that during imine formation, strong steric hindrance occurs between the methyl group in position two and the side chain of the amino acid moiety, thus preventing the cyclisation of one of the epimers.

The oxazinones **3** were isolated pure[8] after column chromatography in 48% yield from the corresponding starting racemic amino acids. Because of the many by-products, which were easily separated from **3**, we were not able to recover the uncyclised epimer.

In conclusion, during both steps of the one-pot process, two successive resolutions of the racemic mixture of amino acids occur : partial resolution during the ester formation followed by complete resolution during the cyclisation to form the oxazinone. Unlike the previous methodology using alkylation of the unsubstituted oxazinone[2], this method appears to be very general and can be applied to the preparation of all oxazinones **3.**

Finally the oxazinone ring can be cleaved by HCl solution according to Cativiela's procedure[5] thus affording the corresponding enantiomerically pure amino acids **4** (enantiomeric excesses were measured by reverse HPLC analysis after derivatization with Marfey's reagent[7]).

REFERENCES AND NOTES

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6. Resonances were assigned by using 250 MHz ^1H COSY and 2D $^1H/^{13}C$ Heteronuclear Correlation (HETCOR) NMR spectroscopy.
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8. The (R,R,R) 2-hydroxypinan-3-one was prepared according to H.Schmidt, *Chem. Ber.*, **1960**,*93*,2485. From (+) (1R,2R,5R) 2-hydroxypinan-3-one, **3a** : mp=67-68°C, $[\alpha]_D^{20°C}$ +214 (c=2, CH_2Cl_2); **3b** : mp=42-43°C, $[\alpha]_D^{20°C}$+215 (c=2, CH_2Cl_2); **3c** : mp=41-42°C, $[\alpha]_D^{20°C}$ +205 (c=2, CH_2Cl_2) ; **3d** : oil, $[\alpha]_D^{20°C}$+175 (c=2. CH_2Cl_2). Satisfactory elemental analyses were obtained for all compounds isolated.

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