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Chiral Cyclic β-Amino Esters. Part I : Synthesis by Diastereospecific Alkylation.

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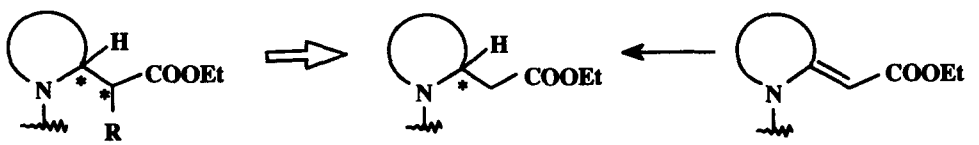
Abstract : Chiral cyclic β-amino esters can be enantiospecifically prepared by a kinetically controled alkylation of the ester function of β-amino esters.

β-Amino esters are important intermediates for the synthesis of natural products. In the case of alkaloids, these fragments may be excellent precursors of complex structures due to their different sites of reactivity.

Asymmetric cyclic β-amino ester **B**, easily obtained by reduction of corresponding trisubstituted β-enamino ester **C**, is a useful intermediate for the enantioselective synthesis of numerous alkaloids[1-5].



A **B** **C**

Scheme 1

This general strategy allows the sequential introduction of two stereogenic centers at Cα and Cβ next to the nitrogen atom. Herein, we report the alkylation study of compound **B** which allows the formation of a second stereogenic center, β to the amino function in cyclic β-amino ester **A**.

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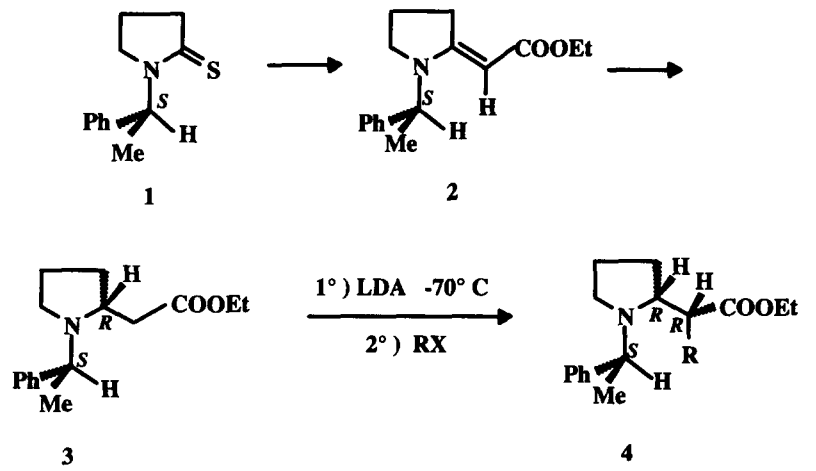
Chiral β-enamino ester **2** (R=H) was easily prepared by Eschenmoser condensation between enantiopure thiolactam **1** and ethyl bromoacetate in the presence of triphenylphosphine[6]. Catalytic hydrogenation of **2** over platinum oxide[6] led with a high selectivity to a major diastereomer **3** (de > 95 %). This product could be purified by critallization of its picrate in ethanol followed by deprotonation using an aqueous solution of K_2CO_3 led to the pure (*S,R*) diastereomer **3** with a 60% yield.



Scheme 2

Alkylation of **3** using a refluxing solution of sodium methylate in methanol afforded four diastereomers due to the reversibility of the Michael reaction which induced epimerization of the stereogenic centers. This result is in accordance with those of Davies *et al.* who have demonstrated that the Michael additions of disubstituted amides to acrylic systems followed by a quench of the intermediate with alkylating agents was not diastereoselective.[7]

On the contrary, deprotonation of **3** at low temperature followed by condensation of the resulting lithium enolate with different halides led, after work-up, only to one corresponding diastereomer **4a-i** as shown in Table 1. Similar results had already been observed with acyclic and cyclic β-amino esters.[8]

The (*S,R,R*) configuration of **4a** (R = CH_3) was unambiguously established by X-ray cristallography of the 2,6-dihydroxybenzoate derivative.[9,10]

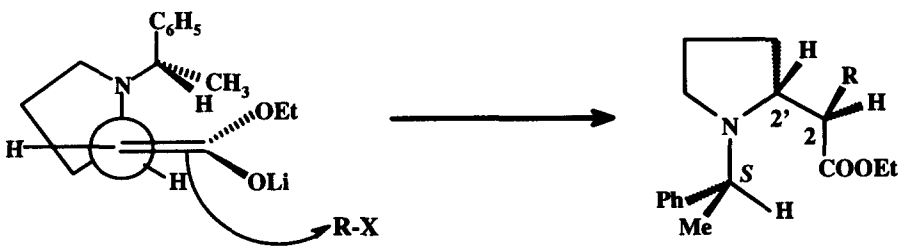
Table 1 : Alkylation of β-amino esters **3**.

Compound	R	X	Yield (%)
4a	Me	I	75
4b	Et	I	50
4c	nPr	I	26
4d	nBu	I	25
4e	nHex	I	9
4f	iPr	Br	---
4g	$PhCH_2$	Br	60
4h	CH_2=CH-CH_2	Br	68
4i	CH_3-CH=CH-CH_2[a]	Br	84[a]
4j	CH_2=C(CH_3)-CH_2	Cl	---

[a] As a mixture of *E* and *Z* isomers.

These results show that secondary halides did not react; besides, it can be noted that the yields of the alkylation reaction rapidly decrease with the length of the alkyl chain. However, allylic halides are good alkylating agents and can further be reduced into the alkyl substituents by catalytic hydrogenation over platinium oxide to lead to alkylated products. Thus, compounds **4c** and **4d** were obtained by this way respectively from **4h** and **4i** and in 68 and 84 % yields. Structures of compounds **4b-j** have been established by comparison with ^1H and ^{13}C NMR data of **4a**.

The very high diastereoselectivity of the alkylation can be explained by consideration of the *E* geometry[11] of the transient lithium enolate and the conformation **5** in which 1,3-allylic strain was minimized. In fact, the steric hindrance of the methybenzyl group induces a diastereofacial discrimination of the halide approach leading exclusively to one diastereomer.



5 **Scheme 3** 4

In conclusion, kinetic β-amino esters **4** with **2*R*,2'*R*** absolute configurations (*syn* relationship) can be prepared with a very high diastereoselectivity in two steps from cyclic β-enamino esters **2.**

References and Notes

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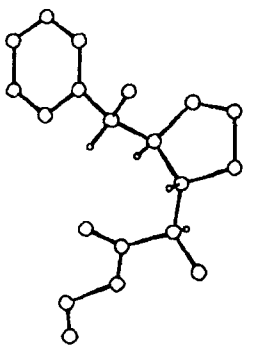
9. Satisfactory analytical and spectral data were obtained for (1*S*,2*R*,2'*R*) ethyl-2-[(1-phenylethyl)-pyrrolidin-2-yl] propionate. $[\alpha]^{20}_{D}$ -19 (c 0.99, EtOH). Anal. Calcd. For $C_{17}H_{25}NO_2$: C, 74.14 ; H, 9.15 ; N, 5.09. Found : C, 73.88 ; H, 9.02 ; N, 5.14. IR neat ν (cm^{-1}) 1730 ; 1495 ; 785 ; 705. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.00 (d, 3H, *J*=7Hz) ; 1.15 (t, 3H, *J*=7Hz) ; 1.29 (d, 3H, *J*=6Hz) ; 1.50-1.70 (m, 4H) ; 2.20-2.30 (m, 1H) ; 2.35-2.50 (m, 1H) ; 2.60-2.75 (m, 1H) ; 3.10-3.25 (m, 1H) ; 3.81 (q, 1H, *J*=6Hz) ; 4.00 (q, 2H, *J*=7Hz) ; 7.10-7.40 (m, 5H). ^{13}C NMR (64.25 MHz, $CDCl_3$) δ (ppm) 10.9 ; 14.2 ; 14.4 ; 24.3 ; 27.2 ; 42.9 ; 48.0 ; 58.6 ; 60.0 ; 62.5 ; 126.5 ; 127.5 ; 128.0 ; 145.1 ; 175.8.
10. X-Ray diagram of compound **4a** (R = CH_3) as a dihydroxybenzoate.



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