Pergamon

Tetrahedron Vol. 50, No. 30, pp. 9051-9060, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00500-1

New Routes to 1,4- Benzodiazepin-2,5-diones

M. Akssira*, M. Boumzebra, H. Kasmi, A. Dahdouh
Laboratoire de Chimie Organique, Université Abdelmalek Essaadi,
Faculté des Sciences , M' Hannech BP2121 Tetouan - Maroc -

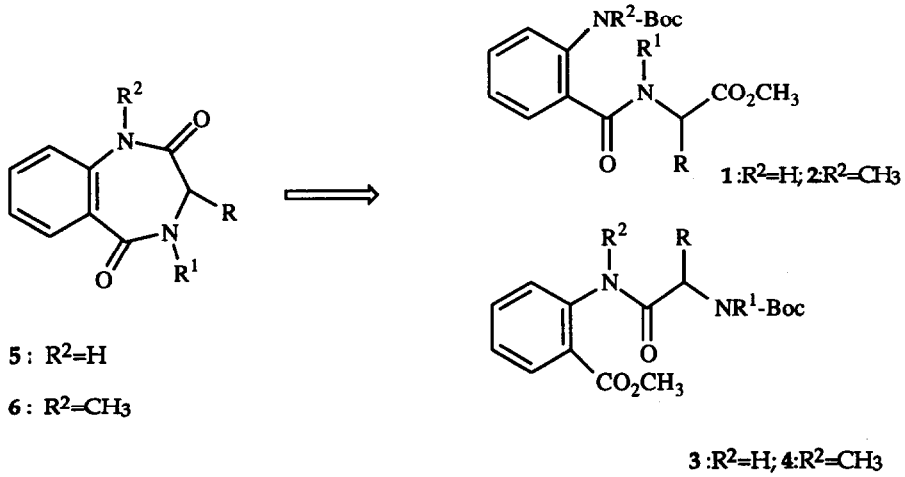
M.-L. Roumestant, Ph. Viallefont
Laboratoire d'aminoacides et Peptides, Université Montpellier II, Sciences et Techniques du Languedoc, Place E. Bataillon, 34095 Montpellier Cédex 5

Abstract : 1,4-benzodiazepin-2,5-diones have been synthesized in good overall yields by two routes, the first one by cyclisation of dipeptides prepared from Boc anthranilic acid and α-amino acid methyl esters, the second one by reaction of N-carboxy α-amino acid anhydrides with Boc anthranilic acid.

Benzodiazepines (BZD), agents widely used as anxiolytics and hypnotics could be regarded as "natural" drugs since they have been found in trace amounts in plants, various tissues of different animal species and even humans ; the biosynthesis of such compounds is still unknown[1].

We have recently reported[2,3] on the synthesis of 1,4-benzodiazepin-2,5-diones and we want to describe here our full results on this topic.

Mainly two routes have been explored, the first one is a classical one, cyclisation of dipeptides (**1-4**)[4] obtained by coupling anthranilic acid and α-amino acids (L or DL).



5 : R^2=H

6 : R^2=CH_3

a : R = R^1 = H; **b** : R = H, R^1= CH_3 ; **c** : R= CH_3 , R^1 = H

Scheme 1

Cyclisation to BZDs was accomplished by heating the dipeptides **1** and **2** in DMF (60-70°C) in the presence of hydrogen chloride gas catalyst (Scheme 1). In a typical reaction the dipeptide **1a** was dissolved in DMF and HCl gas was allowed to bubble during 5 to 10 min. Evolution of the reaction was followed by TLC and after heating for 24 h at 60°C the BZD **5a** was obtained in 62% yield.

Under the same conditions, precursors **1(b-c)** and **2(a-c)** led to the corresponding BZDs in satisfactory yields (62 to 87%). The results reported in Table 1 show that the yields are better with the compounds substituted on the nitrogen atom, N-alkylation causing the folding of the peptide chain and favouring the cyclisation in agreement with results of the literature[5].

Table 1 : Synthesis of 1,4-benzodiazepin-2,5-diones from precursors 1 and 2

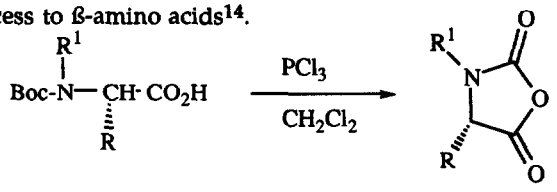
Dipeptide	Reaction Conditions Δ/t	BZD	Yield %
1a	60°/24h	**5a**	62
1b	60°/7h	**5b**	87
1c	60°/24h	**5c**	64
2a	70°/12h	**6a**	69
2b	60°/8h	**6b**	87
2c	70°/16h	**6c**	80

Optical purity (~30%) was checked using as chiral shift reagent Eu(hfc)$_3$ (Tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]europium) in $CDCl_3$ [0.1 to 0.5 eq. of Eu(hfc)$_3$] at room temperature on compound **6c** ($R=R^2=CH_3$). Reaction of the Vilsmeier complex (DMF, HCl) with the ester **2c** led to the acid chloride and probably to the oxazolone which explains the racemisation obtained. In the hope to minimize the racemisation, precursors **3** and **4** were submitted to cyclisation to the BZDs under the same conditions as peptides **1** and **2**, but without any success. Theoritical calculations[6] confirm these results.

The second route begins with N-carboxy α–amino acid anhydrides. These compounds appear to be reagents of considerable utility since their preparation achieves both amino group protection and carboxylate activation in one step. Most frequently N-carboxyanhydrides (NCA's) have been prepared by treatment of an amino acid with large excesses of phosgene gas at elevated

temperatures[7]. The use of standardized phosgene solution in the preparation of NCA's has been reported by FULLER et al.[8] ; furthermore, trichloromethyl chloroformate (diphosgene)[9] and bis -trichloromethyl carbonate (triphosgene)[10] have both been used also in the synthesis of NCA's. JOHNSTON[11] prepared these compounds by reaction of a Boc (tert-butyloxycarbonyl) amino acid, triethylamine and tert-butyldimethyl silyl chloride. Alternative procedures include reaction of the N-protected amino acids with PBr_3[12] but it is reported that this method suffers from the need for very long reaction times, extensive product purification and frequently very poor yields.

In our hands, action of PCl_3 in dichloromethane on Boc α–amino acids at 10°C during 4 h led to NCA's[13] in nearly quantitative yields. The data in Table 2 suggest that this approach may be expected to provide routinely the NCA's of most amino acids in very good yields and it was extended with success to ß-amino acids[14].



7 8

a: R = R^1= H ; **b** : R = H, R^1 = CH_3 ; **c** : R=CH_3, R^1=H ; **d** : R = $C_6H_5CH_2$, R^1 = H ; **e** : R = C_6H_5, R^1 = H ; **f** : R = C_9H_8N, R^1 = H ; **g** : R = i-C_3H_7, R^1=H ; **h** : R = R^1 = $(CH_2)_3$; **i** : R = R^1 = CH_3.

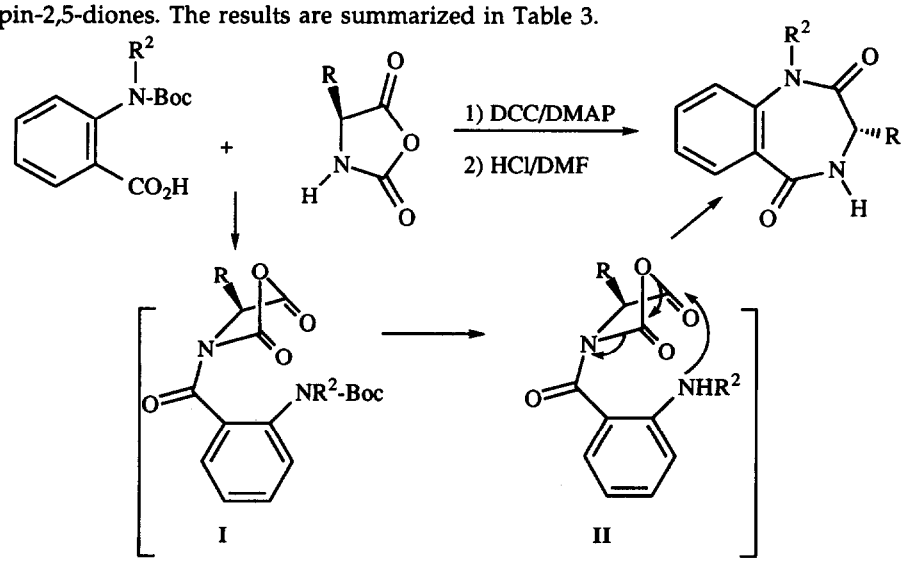
Scheme 2

Amongst the different methods reported in the literature for the preparation of 1,4-benzodiazepin-2,5-diones KIM's[15] method involving reaction of isatoic anhydride and ethyl glycinate is by far the simplest, but the reaction fails with N-substituted isatoic anhydrides. RATNAM[16] described a modification which works for simple N-methyl, N-ethyl, N-benzyl and N-phenyl isatoic anhydrides, but the reaction conditions were drastic. So we have projected to synthesize these products by a mild method using NCA's. Coupling reaction between NCA's with anthranilic acid derivatives activated by dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) gives the intermediate I (scheme 3).

Table 2 : Synthesis of N-carboxy anhydrides

Boc Amino Acid	NCA	Yield (%)	mp (Lit.) °C	IR
7a Boc Gly	8a	98	112-114(96-98)[7m]	3400,1870,1780
7b Boc Sar	8b	100	94-96(95-97)[7m]	1860,1765
7c (L) Boc Ala	8c	100	89-90(88-90)[11]	3335,1840,1760
7d (L) Boc Phe	8d	98	130-132(119-125)[11]	3400,1830,1730
7e Boc Phg	8e	95	128-130(127-129)[7g]	3400,1860,1765
7f (L) Boc Trp	8f	95	188-190(145-146)[7j]	3300,1850,1760
7g (L)BocVal	8g	100	114-116(115-116)[11]	3400,1840,1730
7h (L) Boc Pro	8h	96	82-83(45)[7l]	1840,1750
7i (L) Boc Ala (N.Me)	8i	100	78-79(75-76)[7k]	1850,1760

Deprotection of the Boc group, ring expansion and decarboxylation led to 1,4-benzodiazepin-2,5-diones. The results are summarized in Table 3.



Scheme 3

Table 3 : Synthesis of 1,4-Benzodiazepin-2,5-diones from NCA's

BZD	R	R_2	Yield %	mp °C
5a	H	H	60	328-329
6a	H	CH_3	65	194-195
5c	CH_3	H	58	336-337
6c	CH_3	CH_3	68	245-246
5d	$C_6H_5CH_2$	H	62	278-280
6d	$C_6H_5CH_2$	CH_3	70	210-212
5e	C_6H_5	H	62	291-293
6e	C_6H_5	CH_3	66	181-183
5f	C_9H_8N	H	65	215-218
6f	C_9H_8N	CH_3	68	188-189

Contrarily to the first method, for the benzodiazepin-2,5-dione **6c** obtained from the NCA only one product was detected in the ^1H NMR spectrum recorded under the same conditions showing that with this method no notable racemisation took place.

In conclusion we have described two efficient routes for the obtention of substituted benzodiazepin-2,5-diones. The first method permits the synthesis of differently substituted (N_1, C_3, N_4) compounds but the cyclisation step is racemising ; in the second method we have reported the facile synthesis of N-carboxyanhydrides which react with anthranilic acid without notable racemisation.

Experimental :

All melting points were taken for samples in capillary tubes with an electrothermal apparatus and are not corrected. IR spectra were determined on a Shimadzu spectrophotometer IR-435 and ^{1}HNMR spectra were recorded on a VARIAN 360 EM or a VARIAN XL 250

spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a JEOL D100 spectrometer. Elemental analyses were carried out at the University of Montpellier II (France). Methylene chloride was distilled from calcium hydride and stored over 3Å molecular sieves. Tetrahydrofuran was distilled from sodium. Thin layer chromatography was performed on Merck 60 F254 sheets (0,2 mm).

General Procedure for the preparation of N-carboxy α-amino acid anhydrides.

To a solution of N-tert-butyloxycarbonyl α-amino acid (0.005 mol) in methylene chloride (25 ml) at 0°C, was added under nitrogen 1.2 equivalent of phosphorus trichloride. The reaction mixture was stirrred for 2h at 0°C, the solvent was removed under reduced pressure and the residue washed with carbon tetrachloride (3 x 20 ml) affording the corresponding N-carboxy α-amino acid anhydride. Yields, Melting points and IR bands are given in Table 2.

1,3-oxazolidine-2,5-dione : 8a

^{1}HNMR ($CDCl_3$-DMSO-d_6) δ : 4.25(s,2H); 6.9(m,1H).

(L)-3-methyl-1,3-oxazolidine-2,5-dione : 8b

^{1}HNMR ($CDCl_3$-DMSO-d_6) δ : 2.8(s,3H); 2(s,2H).

(L)-4-methyl-1,3-oxazolidine-2,5-dione : 8c

^{1}HNMR ($CDCl_3$) δ : 1.5(d,1H,J=7Hz) ; 2,8(s,3H); 4.4(q,1H,J=7Hz).

(L)-4-benzyl-1,3-oxazolidine-2,5-dione : 8 d

^{1}HNMR ($CDCl_3$-DMSO-d_6) δ : 2.95(dd,1H,J=7Hz,J=14 Hz); 3.2(dd,1H,J=7Hz,J=14 Hz); 4.50(m,1H), 6.5(br s,1H); 7.2-7.4 (m,5H).

(L) -4-phenyl-1,3-oxazolidine-2,5-dione : 8e

^{1}HNMR ($CDCl_3$) δ : 4.5(m,1H); 6.8-7.0(m,5H); 9.4(br s,1H).

(L)-4-(ß-indolmethyl)-1,3-oxazolidine-2,5-dione : 8f

^{1}HNMR ($CDCl_3$) δ : 2.4(d,2H,J=7Hz); 4.25(m,1H); 7.3-7.8(m,6H); 8.9(br s,1H).

(L)-4-isopropyl-1,3-oxazolidine-2,5-dione : 8g

^{1}HNMR ($CDCl_3$-DMSO-d_6) δ : 1(d,3H,J=6.5Hz),1.1(d,3H,J=6.5Hz); 2.20(m,2H); 4.45(d,1H,J=4Hz).

(L)-pyrrolo-[1,2-c]-1,3-oxazolidine-2,5-dione : 8h

^{1}HNMR ($CDCl_3$) δ : 2.20(m,4H); 3.50(m,2H); 4.15(m,1H,). MS: 141 (M^+).

(L)-3,4-dimethyl-1,3-oxazolidine-2,5-dione : 8i

^{1}HNMR ($CDCl_3$) δ : 1.5(d,3H,J=7Hz); 2.8(s,3H); 4.3(q,1H,J=7Hz).

General Procedure for the synthesis of 1,4-benzodiazepin-2,5-diones.

First method :

To a stirred solution of dipeptide **1** or **2** (1.5 mmol) in dry DMF (40 ml) dry hydrogen chloride was bubbled over 15 to 20 min at r.t. The resulting reaction mixture was heated to 60°C and the reaction was monitored by TLC. After completion of the reaction (7 to 24 h) the mixture was concentrated, the residue was triturated with H_20 (20 ml) and dried to give **5** or **6** (white solids), respectively.

Second method :

To a cold solution (0°C) of Boc-anthranilic acid (0.05 mol) dicyclohexylcarbodiimide (0.05 mol) and dimethylaminopyridine (0.05 mol), N-carboxy α-aminoacid anhydride (0.05 mol) was added.

The mixture was stirred for 2h at 0°C and for 4 h at room temperature. Dicyclohexylurea was filtered and the filtrate evaporated under reduced pressure. The residue was taken up in anhydrous DMF (25 ml) and the solution treated with HCl gas for 4 h. at 60°C After evaporation of the solvent, H_20 (25 ml) was added and the benzodiazepine filtered off.

Yields and melting points are reported in table 3.

1,4-benzodiazepin-2,5-dione : 5a

^{1}HNMR (DMSO-d_6) δ : 3.55(d,2H, J=4.5 Hz); 7.1(m,1H) ; 7.1-7.7 (m,4H) ; 10.5 (m,1H). IR (KBr) : 3285, 1690, 1665 . Anal. Calcd for $C_9H_8N_2O_2$: C, 61.33 ; H, 4.59 ; N, 16.08. Found : C, 61.36 ; H, 4.45 ; N, 15.90.

4-methyl-1,4-benzodiazepin-2,5-dione : 5b

m.p. = 250-252°C (acetone). ^{1}HNMR (DMSO-d_6) δ : 3.12(s,3H); 3.85(s,2H); 7.10 (d,1H,J=7.8Hz); 7.21 (t,1H,J=7.8Hz); 7.48(t,1H,J=7.8Hz); 7.74(d,1H,J=7.8Hz); 10.48(s,1H). IR (KBr) : 3248, 1700, 1633. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.30; N, 14.73. Found : C, 63.24; H, 5.39; N, 14.66.

3-methyl-1,4-benzodiazepin-2,5-dione : 5c

^{1}HNMR (DMSO-d_6) δ : 1.5(d,3H,J=6Hz); 3.95(q,1H,J=6Hz); 6.65(m,1H); 7.2-7.9(m,4H); 9.2(m,1H). IR

(KBr) : 3250, 1690,1660 . MS : 191 (M^+ +1). HRMS: calcd: 190.0743, found : 190.0740.

3-benzyl-1,4- benzodiazepin-2,5-dione : 5d

^{1}HNMR(DMSO-d_6) δ : 3.1(dd,2H,J=14Hz,J=8Hz); 3.45(dd,1H,J=14Hz,J=8Hz); 6.95(m,2H,NH); 7.2-7.9(m,9H). IR (KBr): 3275, 1700, 1685. MS (M^+ +1): 267. Anal. Calcd for $C_{16}H_{14}N_2O_2$, 0.25 H_20: C,70.97; H,5.36; N,10.35. Found : C, 71.13; H,5.33; N,10.3.

3-phenyl-1,4-benzodiazepin-2,5-dione : 5e

^{1}HNMR (DMSO-d_6) δ : 4.9(d,1H,J=4.5Hz) ; 7.1(m,1H); 7.3-8(m,9H); 9(m,1H). IR (KBr) : 3250, 1700, 1685. MS : 253 (M^+ +1).

3-(ß-indolmethyl)-1,4-benzodiazepin-2,5-dione : 5f

^{1}HNMR(DMSO-d_6)δ: 3.25(dd, 1H,J=14Hz,J=8Hz); 3.5(dd,1H,J=14Hz,J=8Hz); 4.05(m,1H); 6.9(m,1H); 7-7.6(m,8H); 7.8(dd,1H,J=9Hz,J=2.25Hz); 8.25(m,1H); 9.6(s,1H). IR (KBr) : 3300, 1700, 1685. MS : 306 (M^+). Anal. Calcd for $C_{18}H_{15}N_3O_2$: C,70.81; H,4.93; N,13.73. Found: C,70.81; H,4.93; N,12.46.

1-methyl-1,4-benzodiazepin-2,5-dione : 6a

^{1}HNMR ($CDCl_3$) δ : 3.45 (s,3H); 3.55(d,2H,J=4.5Hz); 6.9(m,1H); 7.7-7.8(m,4H). IR (KBr) : 3290, 1695, 1668. HRMS : calcd: 190.0743, found: 190.0743.

1,4-dimethyl-1,4-benzodiazepin- 2,5-dione : 6b

^{1}HNMR ($CDCl_3$) δ : 3.17(s,3H); 3.29(s,3H); 3.78(AB, 2H,J=14.4Hz); 7.10(d,1H,J=7.80Hz); 7.19(t,1H, J=7.80Hz);7.6(t,1H,J=7.80Hz);7.75(d,1H,J=7.80Hz).MS: 205(M^++1,100), 409($2M^+$+1,5), 162(4), 134(10), 106(8).

1,3-dimethyl-1,4-benzodiazepin-2,5-dione : 6c

$[\alpha]_D$ = 155.8 (c=1.2, CH_3OH)

^{1}HNMR($CDCl_3$) δ: 1.5(d,3H, J=6Hz); 3.45(s,3H); 3.95(q,1H,J=6Hz); 6.7(m,1H); 7.2-7.9(m,4H).IR (KBr) :3550, 1690,1665. MS : 205 (M^+ +1). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 63.3; H, 5.99 ; N, 13.43. Found: C, 63.12 ; H, 5.55 ; N, 13.19.

1-methyl-3-benzyl-1,4-benzodiazepin-2,5-dione : 6d

$[\alpha]_D$ = 88.7 (c=1.2, CH_3OH)

^{1}HNMR ($CDCl_3$) δ :3.1(dd,1H,J=14Hz,J=8Hz);3.45(dd,2H,J=14Hz,J=8Hz);3.45(s,3H);6.9 (m,1H); 7.2-7.9(m,9H). IR (KBr) : 3275, 1700, 1685. MS : 281(M^++1). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C,72.86; H,5.71 ; N,10.00. Found: C,72.56; H,5.67; N,9.8.

1-methyl-3-phenyl-1,4-benzodiazepin-2,5-dione : 6e

$[\alpha]_D$ = 92.5 (c=1.2, CH_3OH)

^{1}HNMR ($CDCl_3$) δ: 3.5(s,3H); 4.95(d,1H,J=4.5Hz) 7.2(m,1H); 7.3-8.0(m,9H). IR (KBr) : 3300, 1670, 1650. MS : 267(M^++1) ; Anal. Calcd for $C_{16}H_{14}N_2O_2$: C,69.82; H,5.45; N,10.18. Found :C,70.09; H,5.44; N,9.52.

1-methyl- 3-(ß-indolmethyl)-1,4- benzodiazepin-2,5-dione : 6f

$[\alpha]_D$ = 83.3 (c=1.2, CH_3OH)

^{1}HNMR (DMSO-d_6) δ : 3.25(dd,1H,J=14Hz,J=8Hz); 3.45(s,3H); 3.5(dd,2H,J=14Hz,J=8Hz);4.5(m,1H); 7.35 (m,1H); 7.0-7.6 (m,8H); 8.25(s,1H). IR (KBr) : 3260, 1700, 1680. MS : 320(M^++1). Anal. Calcd for $C_{19}H_{17}N_3O_2,H_2O$: C,67.55; H,5.44; N,12.46. Found: C,67,84; H,5.55; N,12.52.

REFERENCES and NOTES

1. Klotz, U. *Life Sciences* **1991,** *48* , 209.

2. Akssira, M.; Kasmi, H.; Dahdouh, A.; Boumzebra, M. *Tetrahedron Lett.* **1992,** *33* , 1887.

3. Akssira, M.; Kasmi, H.; Dahdouh, A.; Boumzebra, M. ; Roumestant, M.L. ; Viallefont, Ph. *Synthetic Commun.* **1993,** *23* , 2265.

4. Peptides **(1-4)** were obtained in good yields by coupling the corresponding α–amino acids with the methyl ester of anthranilic acid using as coupling agent DCC, DMAP in dichloromethane.

5. Cavelier-Frontin, F. ; Achmad, S. ; Verducci, J.; Jacquier R., Pepe G. ; *J. Mol. Struct. Theochem, in press.*

6. Akssira, M., Boumzebra, M.; El Bergmi, R., Molina J.M. ; *Results to be published .*

7.a) Fuchs, R. *Chem. Ber.* **1922,** *55* , 2943 ; b) Levy, A.L. *Nature* **1950,** *165,* 142 ; c) Farthing, A.C.; Reynolds, R.J. ibid **1950,** *165* , 647 ; d) Farthing, A.C. *J. Chem. Soc.* **1950,** 3213; e) Patchorknitk, A. ; Sila, M., Katchalski, E. *J. Am. Chem. Soc.* **1954,** *76,* 299; f) Grant, N.H.; Clark, D.E. ; Alburn, H.E. *J. Am. Chem. Soc.* **1966,** *88,* 4071; g) Dvonch, W. ; Fletcher, H.; Alburn, H.E. *J. Org. Chem.* **1964,** *29,* 2764 ; h) Grant, N.H. ; Alburn, H.E. *J . Am. Chem. Soc.* **1964,** 3870; i) Hayakawa, T.; Harada, K. *Bull. Chem. Soc. Jpn.* **1965,** *38,* 1354 ; j) Fasman, G.D.; Landsberg, M.; Buchwald, M. *Can. J. Chem.* **1965,** 43, 1588 ; k) Hanby, W.E.; Waley, S.G.; Watson, J. *J. Chem. Soc.* **1950,** 3009; l) Randall, A.A. *J. Chem. Soc.* **1962,** 374; m) Kricheldorf, H.R. *Chem. Ber.* **1970,** *103,* 3353.

8. Fuller, W.D.; Verlandier, M.S.; Goodman, M. Biopolymers, **1976,** *15* , 1869.

9. Oya, M.; Katakai, R. ; Nakai, H. *Chem. Lett.* **1973,** 1143.

10. a) Daly, W.H. ; Poche, D. *Tetrahedron Lett.* **1988,** *29,* 5859 ; b)Wilder, R., Mobashery, S. *J. Org. Chem.* **1992,** *57,* 2755.

11. Mobashery, S. ; Johnston, M. *J. Org. Chem.* **1985**, *50* , 2200.

12. a) Leuchs, H. *Chem. Ber.* **1906**, *39*, 857; b) Ben-Ishai, D.; Katchalski, E. *J. Am. Chem. Soc.* **1952**, *74* , 3688 ; c) Berger, A. ; Kurtz, J. ; Katchalski, E. ibid, **1954**, *76*, 5552.

13. We have not been able to determine the optical rotations of the NCA's because of their relatively low solubility in most organic solvents and their lability in polar solvents such as alcohols. However, the ^{1}HNMR spectrum of **8i** using Eu(hfc)$_3$ as chiral reagent shows only one product.

14. Akssira, M.; Kasmi, H.; Dahdouh, A.; Boumzebra, M. *Results to be published.*

15. Kim, D.H. *J. Heterocycl. Chem.* **1975**, *12* , 1323.

16. Mohiuddin, G.; Reddy, P.S.N.; Khalid Ahmed, L.; Ratnam, C.V. *Indian J. Chem.* **1985**, *24B*, 905.

(*Received in Belgium* 17 *June* 1993; *accepted* 12 *April* 1994)