

## DE NOVO SYNTHESIS OF RACEMIC ALTRONOLACTAM AND ARABINONOLACTAM AZASUGARS

Théophile Tschamber, Elsa-Maria Rodriguez-Perez, Patrick Wolf, and Jacques Streith (\*)

Ecole Nationale Supérieure de Chimie, Université de Haute-Alsace, 3, rue Alfred Werner, F-68093 Mulhouse Cédex, France

Dedicated to Professor Yoshio Ban, *in memoriam*.

**Abstract.** - Starting from the known peracetylated piperidinose derivatives (**7a**) and (**7b**), the corresponding *altrono*- and *arabino*-lactams (**4**) and (**5**) were obtained in a straightforward way. A selective two-step hydrolysis of the anomeric acetoxy groups gave the free hydroxyls (**8a**) and (**8b**) which were oxidised to the  $\delta$ -lactams (**9a**) and (**9b**), respectively. Deprotection of these latter compounds led to the target molecules.

**Introduction.** - The enzymatic glycosidase mechanism of pyranosic polysaccharides is believed to involve a transient type **A** half-chair oxocarbenium ion, which is stabilized by a complementary carboxylate anion of an active site catalytic residue.<sup>1,2</sup> Structural azanalogues of these glycosyl cations represent an attractive synthetic target for the design of potent glycoprocessing inhibitors.<sup>3,4</sup>  $\delta$ -Lactam azasugars like D-mannonolactam (**1**) and its D-rhamnose analogue (**2**), once protonated in the active site of the appropriate enzyme, should meet the conformational and electrostatic requirements as potential glycosidase inhibitors.<sup>5</sup> And indeed they do, since both **1** and **2** are better inhibitors of  $\alpha$ -mannosidase than DMJ (**3**), **1** being more powerful than the corresponding 6-deoxy compound (**2**) (*Scheme 1*). One may therefore surmise that the half-chair conformation of the lactams resembles more closely the structure of the transition state<sup>2</sup> for the enzymatic cleavage of the anomeric mannopyranoside. As to L-rhamnonolactam, *i.e.* (*ent-2*), it did not show any significant inhibition of any glycosidase, since its structure lacks the key stereochemical features at C(2), C(3) and C(4)

which are required for mannosidase inhibition (D-series).<sup>5</sup>

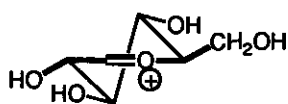
We describe herein the *de novo* synthesis of racemic *altronolactam* (**4**) and of *arabinonolactam* (**5**) from the corresponding 1,2-dihydropyridines (**6a**) and (**6b**).

### **Stereospecific Synthesis of (±)-Altronolactam (**4**) and of (±)-Arabinonolactam**

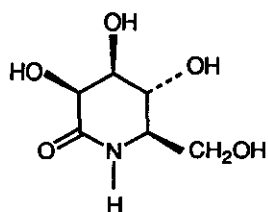
**(5)**. In a preceding publication we described the stereospecific synthesis of the tetraacetoxy-piperidinoses (**7a**) and (**7b**) from the corresponding dihydropyridines (**6a**) and (**6b**).<sup>6</sup> Selective removal of the anomeric acetyl groups was performed according to Fletcher's method (HBr/AcOH),<sup>7</sup> *i.e.* via the 1-bromo intermediates which were then hydrolysed to the expected hemiaminals (**8a**) (mp 160-161 °C) and (**8b**) (mp 149-150 °C), respectively. Hemiaminal (**8b**) could also be obtained directly in a one-pot procedure when **7b** was treated with the HBr/AcOH/H<sub>2</sub>O mixture. According to <sup>1</sup>H-nmr both hemiaminals occur as axial anomers since  $J_{1,2}=4.0$  for **8a**, and  $J_{1,2}=3.6$  for **8b**, a result which was anticipated for such *N*-acylpiperidinoses.<sup>6,8,9</sup>

Oxidation of hemiaminals (**8a**) and (**8b**) to the corresponding  $\delta$ -lactams with RuO<sub>4</sub>, as prepared from RuO<sub>2</sub>/H<sub>2</sub>O according to ref. 10, did not lead to any reproducible results, at least not in our hands.  $\delta$ -Lactam (**9a**) was obtained when **8b** was oxidised with PCC,<sup>11</sup> whereas **9b** formed when **8b** was oxidised with DMSO/Ac<sub>2</sub>O.<sup>12</sup> Removal of the remaining protection groups of **9a** and **9b** was performed in two steps : i) hydrogenolysis (H<sub>2</sub>, 5%Pd/C) of the benzyloxycarbonyl groups led to  $\delta$ -lactams (**10a**) and (**10b**) ; ii) reaction of these latter products with Amberlyst A-26 (OH<sup>-</sup>) led to the crystalline racemic  $\delta$ -lactams (**4**) and (**5**), respectively.

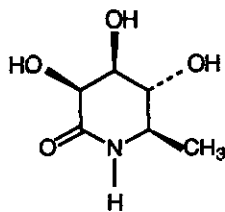
Glycosidase inhibitory assays with  $\delta$ -lactams (**4**) and (**5**) remain to be made.



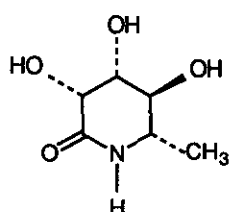
A (D- gluco)



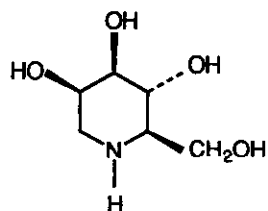
1 (D-manno)



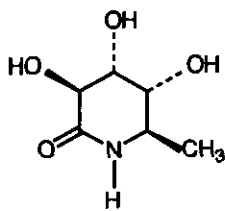
2 (D-rahmno)



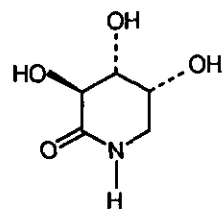
ent-2 (L-rhamno)



3 (DMJ)

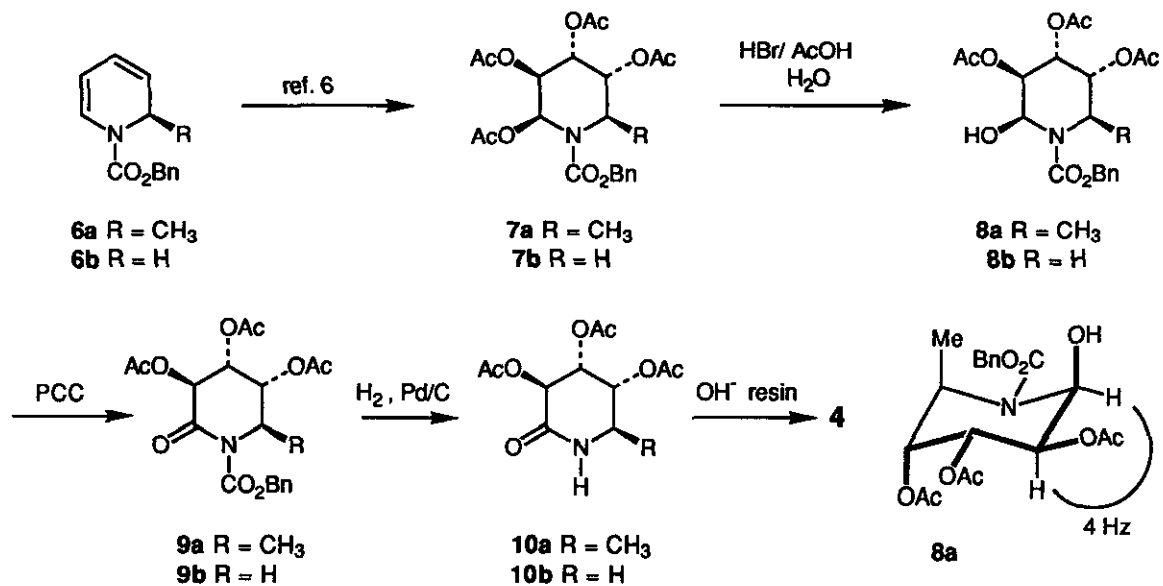


4 (altro)



5 (arabino)

Scheme 1



Scheme 2

## ACKNOWLEDGEMENTS

The support of the *Centre National de la Recherche Scientifique* (URA-135) is gratefully acknowledged. We also wish to thank the *Consejo Superior De Investigaciones Cientificas* for a post-doctoral grant to one of us (E.M.R.P.). Last but not least, we would like to express our thanks to diploma student Catherine N'Guyen who participated in part of the experimental work.

## EXPERIMENTAL PART

**General.** - Flash chromatography (FC) was performed on silica gel (Merck 60 ; 230-400 mesh) and tlc on silica gel HF254 plates (Merck) which were revealed with a solution of  $\text{KMnO}_4$  (2 g) and  $\text{Na}_2\text{CO}_3$  (4 g) in  $\text{H}_2\text{O}$  (100 ml) followed by heating. Mp : *Kofler* hot bench or *Büchi-SMP-20* apparatus, corrected ; ir spectra ( $\text{cm}^{-1}$ ) : *Nicolet 205*.  $^1\text{H}$ -nmr spectra were recorded at 250 MHz and  $^{13}\text{C}$ -nmr spectra at 62.9 MHz on a *Bruker AC-F-250* apparatus using double-irradiation techniques ; internal references : tetramethylsilane (TMS) ( $\delta = 0.00$ ) and  $\text{CD}_3\text{OD}$  ( $\delta = 3.30$  ppm) for  $^1\text{H}$ -nmr, and  $\text{CDCl}_3$  ( $\delta = 77.00$  ppm) and  $\text{CD}_3\text{OD}$  ( $\delta = 49.02$  ppm) for  $^{13}\text{C}$ -nmr. Microanalyses were carried out by the "Service Central de Microanalyses" of the CNRS at Vernaison.

Reagents : Amberlyst A-26 ( $\text{OH}^-$  form) was prepared from its chloride precursor A-26 ( $\text{Cl}^-$  form) by adding 1 N aq. NaOH and letting the ion exchange occur for 1 h.

( $\pm$ ) **Benzyl ester of [2*R*\*(2 $\alpha$ ,3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\alpha$ )]-2-hydroxy-3,4,5-tri-*O*-acetyl-6-methylpiperidine-1-carboxylic acid (8a).** - A solution of 33 % HBr/AcOH (10 ml) was added at 0 °C to **7a** (1.00 g, 2.15 mmol) and the mixture was stirred for 15 min at 0 °C. Ice water was added till the solution became colourless. After stirring for 5 min the solution was extracted with  $\text{CHCl}_3$  (2 x 30 ml). The organic phase was washed with sat. aq.  $\text{NaHCO}_3$ , dried over

MgSO<sub>4</sub> and evaporated. The yellowish residue was purified by FC (AcOEt/cyclohexane 5:5) to give an oil which crystallised in AcOEt/iPr<sub>2</sub>O (492 mg, 54 %). mp 160-161 °C (AcOEt/iPr<sub>2</sub>O). Ir(KBr) : 3370, 1747, 1681, 1438, 1423, 1374, 1344, 1321, 1288, 1243, 1227, 1140, 1122, 1098, 1071. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>, 338 K) : 7.36-7.29 (m, 5 arom. H) ; 6.08 (dd, J=4.0, 3.3, H-C(2)) ; 5.60 (dd, J=11.0, 3.0, H-C(4)) ; 5.28 (dd, J=3.0, 2.3, H-C(5)) ; 5.27 (dd, J=11.0, 4.0, H-C(3)) ; 5.17 and 5.20 (AB syst., J=12.3, CH<sub>2</sub>Ph) ; 4.37 (qd, J=7.4, 2.3, H-C(6)) ; 2.60 (br s, OH) ; 2.08, 2.04, 1.98 (3s, 3 x COCH<sub>3</sub>), 1.44 (d, J=7.4, CH<sub>3</sub>-C(6)). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) : 169.9 (2 x COCH<sub>3</sub>) ; 169.8 (COCH<sub>3</sub>) ; 155.6 (CO<sub>2</sub>) ; 136.1, 128.6, 128.3, 127.9 (6 C arom.) ; 76.4 (C(2)) ; 71.8 (C(3)) ; 68.7 (C(5)) ; 68.0 (CH<sub>2</sub>Ph) ; 65.4 (C(4)) ; 52.4 (C(6)) ; 20.7, 20.6, 20.5 (COCH<sub>3</sub>) ; 18.8 (CH<sub>3</sub>-C(6)). Anal. Calcd for C<sub>20</sub>H<sub>25</sub>NO<sub>9</sub> : C 56.73, H 5.95, N 3.31. Found : C 56.9, H 6.0, N 3.4.

(±) **Benzyl ester of [2*R*\*(2α,3α,4β,5β)]-2-hydroxy-3,4,5-tri-*O*-acetylpiperidine-1-carboxylic acid (**8b**).** - To a stirred heterogeneous solution of **7b** (1.67 g, 3.74 mmol) in H<sub>2</sub>O (18 ml) at 5-10 °C was added slowly a solution of 33 % HBr/CH<sub>3</sub>CO<sub>2</sub>H (20 ml) over a period of 80 min. The mixture became quasi homogeneous and was warmed to room temperature. To this mixture was added rapidly H<sub>2</sub>O (100 ml) whereby **8b** precipitated as a colourless solid. Filtration and drying gave analytically pure **8b** (1.21 g, 79 %); mp : 149-150°C. Ir(KBr) : 3500, 1748, 1683, 1667, 1445, 1375, 1320, 1272, 1244, 1221, 1197, 1151, 1132, 1103, 1071, 1033. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>, 335 K) : 7.32 (m, 5 arom. H) ; 6.06 (br d, J=3.6, H-C(2)) ; 5.38 (dd, J=10.4, 3.2, H-C(4)) ; 5.33 (ddd, J=3.2, 2.9, 1.6, H-C(5)) ; 5.21 and 5.12 (AB syst., J=12.4, CH<sub>2</sub>Ph) ; 5.20 (dd, J=10.4, 3.6, H-C(3)) ; 4.14 (ddd, J=14.6, 2.9, 1.1, Heq - C(6)) ; 3.47 (dd, J=14.6, 1.6, H<sub>ax</sub>-C(6)) ; 2.53 (br s, H-O) ; 2.08 (s, COCH<sub>3</sub>) ; 1.98 (s, 2 x COCH<sub>3</sub>). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) : 170.0, 169.9, 169.8 (COCH<sub>3</sub>) ; 155.1 (CO<sub>2</sub>) ; 136.2, 128.6, 128.3, 128.0 (6 C arom.) ; 75.7 (C(2)) ; 69.1 (C(2)) ; 68.1 (C(4) + C(5)) ; 67.9 (CH<sub>2</sub>Ph) ; 41.2 (C(6)) ; 20.6, 20.6,

20.5 (COCH<sub>3</sub>). Anal. Calcd for C<sub>19</sub>H<sub>23</sub>NO<sub>9</sub> : C 55.74, H 5.66, N 3.42. Found : C 55.7, H 5.8, N 3.3.

**(±) [3*R*\*(3α, 4β, 5β, 6α)]-3,4,5-Tri-*O*-acetyl-6-methyl-2-piperidinone (4).**

*Oxidation of 8a.* - To a solution of **8a** (1.79 g, 4.23 mmol) in anh. CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added PCC (1.95 g, 9.0 mmol). The mixture was stirred for 48 h at room temperature. Some more PCC (500 mg, 2.3 mmol) was added and the mixture was heated at reflux for 4 h. Filtration and evaporation of the solvent afforded crude **9a** which was recrystallised from decane leading to pure **9a** (650 mg, 36 %). <sup>1</sup>H-Nmr (CDCl<sub>3</sub>, 300 K) : 7.45-7.30 (m, 5 arom. H) ; 5.58 (dd, J=10.5, 2.9, H-C(4)) ; 5.44 (t, J=2.9, H-C(5)) ; 5.43 (d, J=10.5, H-C(3)) ; 5.30 (s, CH<sub>2</sub>Ph) ; 4.42 (qd, J=7.0, 2.9, H-C(6)) ; 2.17, 2.12, 2.05 (2 x COCH<sub>3</sub>) ; 1.48 (d, J=7.0, CH<sub>3</sub>-C(6)). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) : 169.9, 169.8, 169.6 (COCH<sub>3</sub>) ; 165.3 (CO<sub>2</sub>Bn) ; 153.4 (C(2)) ; 134.8, 128.6, 128.4, 128.0 (6 arom. C) ; 70.7 (C(5)) ; 69.9 (C(3)) ; 69.1 (CH<sub>2</sub>Ph) ; 67.1 (C(4)) ; 54.6 (C(6)) ; 20.8, 20.6, 20.5 (3 x COCH<sub>3</sub>) ; 18.8 (CH<sub>3</sub>-C(6)).

*N-Deprotection of 9a.* - A solution of **9a** (650 mg, 1.54 mmol) in AcOEt (15 ml) was stirred under H<sub>2</sub> in the presence of 5 % Pd/C (40 mg) for 2 h. Filtration and evaporation of the solvent gave a crude product which was purified by FC (AcOEt) leading to **10a** (418 mg, 94 %). <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) : 6.50 (H-N) ; 5.52 (dd, J=9.4, 2.6, H-C(4)) ; 5.39 (d, J=9.4, H-C(3)) ; 5.27 (td, J=2.6, 1.2, H-C(5)) ; 3.66 (qt, J=6.9, 3.0, H-C(6)) ; 2.15, 2.14, 2.07 (3s, 3 x COCH<sub>3</sub>) ; 1.40 (d, J=6.9, CH<sub>3</sub>-C(5)).

*O-Deprotection of 10a.* - A stirred solution of **10a** (418 mg, 1.46 mmol) in MeOH (3 ml) containing Amberlyst A-26 (OH<sup>-</sup>) (200mg) was allowed to react at room temperature for 1 h. Filtration and evaporation of the solvent gave an oil which crystallised slowly leading to **4** (110 mg ; 47 %). mp 176-177 °C (solid washed with MeOH and iPr<sub>2</sub>O). Ir (KBr) 3360, 3299, 3179,

3128, 2896, 2360, 2355, 1661, 1618, 1459, 1443, 1348, 1335.  $^1\text{H-Nmr}$  ( $\text{CD}_3\text{OD}$ ) : 4.03 (d,  $J=6.7$ , H-C(3)) ; 3.85 (dd,  $J=6.7$ , 2.5, H-C(3)) ; 3.75 (dd,  $J=5.2$ , 2.5, H-C(5)) ; 3.51 (qd,  $J=6.7$ , 5.2, H-C(6)) ; 1.24 (d,  $J=6.7$ ,  $\text{CH}_3\text{-C(6)}$ ).  $^{13}\text{C-Nmr}$  ( $\text{CD}_3\text{OD}$ ) : 173.6 (CO) ; 72.3, 72.1, 72.0 (C(3), C(4), C(5)) ; 52.1 (C(6)) ; 20.4 ( $\text{CH}_3\text{-C(6)}$ ). Anal. Calcd for  $\text{C}_6\text{H}_{11}\text{NO}_4$  : C 44.71, H 6.88, N 8.69. Found : C 44.7, H 7.3, N 8.5.

**( $\pm$ ) [3*R*\*(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ )]-3,4,5-Tri-*O*-acetyl-2-piperidinone (5).**

*Oxidation of 8b.* - To a stirred solution of **8b** (409 mg, 1.00 mmol) in anhydr. DMSO (4 ml, 56 mmol) at room temperature under Ar was added dropwise  $\text{Ac}_2\text{O}$  (15 ml, 159 mmol). After stirring for 16 h EtOH (10 ml) was added, stirring was continued for 30 min and the solution treated with  $\text{H}_2\text{O}$  (20 ml). After stirring for 20 min the mixture was extracted with  $\text{CHCl}_3$  (2 x 15 ml). Drying of the organic phase with  $\text{MgSO}_4$ , filtration and evaporation of the solvent gave a mixture (375 mg) of **9b** and **7b** (77/23 (nmr), 69 % and 21 % resp.) which was used without any purification.  $^1\text{H-Nmr}$  of **9b** ( $\text{CDCl}_3$ ) : 7.45-7.30 (m, 5 arom. H) ; 5.60 (ddd,  $J=3.4$ , 2.9, 2.4, (H-C(5)) ; 5.48 (d,  $J=10.4$ , H-C(3)) ; 5.35 (dd,  $J=10.4$ , 2.9, H-C(4)) ; 5.30 (s,  $\text{CH}_2\text{-Ph}$ ) ; 4.14 (dd,  $J=14.4$ , 3.4, H-C(6)) ; 3.76 (dd,  $J=14.4$ , 2.4, H-C(6)) ; 2.16, 2.13, 2.06 (3s, 3 x  $\text{COCH}_3$ ).

*N-Deprotection of 9b.* - A mixture of **9b** and **7b** (1.025 g ; 77/23) in AcOEt (8ml) was stirred under  $\text{H}_2$  in the presence of an excess of 5%Pd/C (30 mg) for 2 h. After removal of the catalyst and evaporation of the solvent, the residue was purified by FC (AcOEt). The major product (**10b**) was collected (370 mg, 71 % with respect to **9b**).  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ ) : 5.84 (br s, H-N) ; 5.54 (dt,  $J=3.0$ , 2.4, H-C(5)) ; 5.46 (d,  $J=10.0$ , H-C(3)) ; 5.38 (dd,  $J=10.0$ , 2.4, H-C(4)) ; 3.65 (dd,  $J=13.7$ , 2.4, H-C(6)) ; 3.44 (dt,  $J=13.7$ , 3.0, H-C(6)) ; 2.16 (s, 2 x  $\text{COCH}_3$ ) ; 2.07 (s,  $\text{COCH}_3$ ).

*O-Deprotection of 10b.* - Procedure as for **10a** : From **10b** (360 mg, 0.88 mmol) in MeOH (15 ml) with Amberlyst A26 ( $\text{OH}^-$ ) (1.5 g) **5** was obtained (115 mg, 50 %) as a resin which

crystallised slowly, mp 162-164 °C (solid washed with MeOH and  $i\text{Pr}_2\text{O}$ ). Ir(KBr) : 3400-3230, 1648, 1497, 1414, 1335, 1310, 1254, 1132, 1111, 1091, 1062.  $^1\text{H-Nmr}$  ( $\text{CD}_3\text{OD}$ ) : 4.11 (td,  $J=3.8, 2.4$ , H-C(5)) ; 4.10 (d,  $J=8.4$ , H-C(2)) ; 3.78 (dd,  $J=8.4, 2.4$ , H-C(3)) ; 3.38 (dd,  $J=13.0, 3.5$ , H-C(6)) ; 3.25 (dd,  $J=13.0, 3.8$ , H-C(6)).  $^{13}\text{C-Nmr}$  ( $\text{CD}_3\text{OD}$ ) : 174.4 (CO) ; 73.8, 71.5, 68.0 (C(3), C(4), C(5)) ; 46.0 (C(6)). HR-ms calcd for  $\text{C}_5\text{H}_9\text{NO}_4$  : 147.05315 ; found : 147.0530. Anal. Calcd for  $\text{C}_5\text{H}_9\text{NO}_4$  : C 40.81, H 6.17, 9.52. Found: C 40.6, H 6.5, N 9.3.

## REFERENCES

1. G. Legler, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 319.
2. M.J. Sinnott, *Chem. Rev.*, 1990, **90**, 1171.
3. G. Papandreou, M.K. Tong, and B. Ganem, *J. Am. Chem. Soc.*, 1993, **115**, 11682.
4. Y. Blériot, A. Genre-Grandpierre, and C. Tellier, *Tetrahedron Lett.*, 1994, **35**, 1867.
5. A.J. Fairbanks, N.C. Carpenter, G.W.J. Fleet, N.G. Ramsden, I.C. de Bello, B.G. Winchester, S.S. Al-Daher, and G. Nagahasdi, *Tetrahedron*, 1992, **48**, 3365.
6. T. Tschamber, F. Backenstrass, M. Neuburger, M. Zehnder, and J. Streith, *Tetrahedron*, 1994, **50**, 1135.
7. R.K. Ness, H.W. Diehl, and H.G. Fletcher, Jr., *J. Am. Chem. Soc.*, 1954, **76**, 763.
8. H. Paulsen and F. Leupold, *Chem. Ber.*, 1969, **102**, 2804, and references cited therein.
9. A. Defoin, H. Fritz, C. Schmidlin, and J. Streith, *Helv. Chim. Acta*, 1987, **70**, 554.
10. W.M. Parikh and J.K.N. Jones, *Can. J. Chem.*, 1965, **43**, 3452; L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 2, p. 358, Wiley-Interscience, New York 1969.
11. J.A. Seijas, M.P. Vasquez Tato, R. Estévez, L. Castedo, and R. Riguera, *Heterocycles*, 1989, **29**, 181.
12. P.-T. Ho, *Can. J. Chem.*, 1980, **58**, 858 ; Q. Meng and M. Hesse, *Helv. Chim. Acta*, 1991, **74**, 445.