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Ionic liquid supported organotin reagents to prepare molecular imaging and therapy agents

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Efficiency of ionic liquid supported organotin reagents in dehalogenation reaction has been investigated. High radiochemical yields of astatinated and iodinated compounds have been obtained using simple work-up procedure. This methodology represents a straightforward approach for the preparation of molecular imaging and therapy agents in nuclear medicine.

Introduction

The use of radiopharmaceuticals in nuclear medicine is opening significant perspectives for diagnostic and functional imaging of tumors. Indeed, the characterization (phenotype, proliferation, response to treatment) and the better comprehension of tumor environment (vascularization, hypoxia, inflammation, and immune response) can be crucial for personalized therapy, another valuable application for radiopharmaceuticals. Various radionuclides may be used, especially radioactive isotopes of halogens (i.e. radiohalogens).1 Radiohalogens are widely represented in nuclear medicine as Fluorine-18 is the most common used radioisotope for PET imaging.2,18 F-FDG is considered now as a standard with applications not only for oncology but also for neurology or cardiology. Another heavy radiohalogen, astatine, is currently gaining attention. Indeed, astatine with its isotope 211 is considered as one of the most promising radionuclides for the development of targeted alpha-radionuclide therapy of disseminated cancerous cells considering its physical properties (T 1/2: 7.2 hours; E ave.: 6.79 MeV (100%); LET: 99 keV.m μ).3 Its chemistry is similar to the one of iodine which radioisotopes are applicable for both targeted β-therapy (I-131) more convenient for larger tumors, SPECT (I-125, I-123,) and PET (I-124).4 Theranostic (diagnostic and therapy with the same or similar molecule(s) radiolabeled with a pair of radionuclide) for personalized medicine can then be considered with the astatine/iodine pair.5 Except for [I-131/I-123]NaI for thyroid diseases imaging, radiopharmaceuticals labeled with radiohalogens are generally constituted by two entities: the vector and the radionuclide. Vectors may be antibodies and derivatives, peptides or small organic molecules targeting tumors. The labeling of the vector may be performed either directly or requires the use of a small radiolabeled organic compound (prosthetic group) bearing a reactive function able to link the vector. Among the direct radiolabeling strategies, electrophilic substitution of organometallic precursors with heavy radiohalogens represents one of the most convenient methods. Based on the high reactivity of carbon-metal bond, organometallic derivatives allow fast and regioselective reactions on a wide variety of substrates with high yields under mild conditions. In addition, these reactions display a good tolerance towards functionalities present in the substrate (e.g. esters, activated esters). Halodemetation reaction for the preparation of radiohalogenated compounds have been studied with organometallics7 containing mercury,8 boron,9 tin,10 silicon,11 germanium,12 thallium13 and lead.14 Triorganotin derivatives display thus great potential for demetaltion reaction. Unfortunately, drawbacks such as contamination of halogenated products by tin residues limit the scope of these reagents. Efforts have been made to overcome these problems, leading, for example, to the development of solid-phase synthesis methods,15 and fluoruous phases.16 As a part of our ongoing research program on the discovery of potentialities of TSILs (Task Specific Ionic Liquids),16 we decided to investigate organotin reagents supported on ionic liquids in demetaltation reactions to produce radiohalogenated compounds. The use of organotin reagents immobilized on ionic liquids would have the combined advantages of safe handling (non-volatile properties) and minimizing the product contamination by tin.
Results and discussion

The first part of this study relies on the preparation of organotin reagents immobilized on ionic liquids bearing an ester function or an activated ester group. In this context, starting from organotin chloride derivative \( 1,^{18} \) new organotin reagent supported on ionic liquid \( 2 \) has been isolated in 70% yield after reaction of 3-(ethoxycarbonyl)phenyl zinc reagent. To avoid any side reactions involving the bromide counter anion instead of the radiohalogen, anionic metathesis reaction between bromide and hexafluorophosphate anions has been achieved to lead \( 3 \) in 94% yield (Scheme 2). Succinimidyl ester \( 4 \) was obtained in 55% yield by saponification of precursor \( 2 \) using NaOH aqueous solution in EtOH followed by esterification with N-hydroxysuccinimide. Bromide anion was exchanged with PF\(_6\) to afford \( 5 \) in a good yield. All new compounds \( 2-5 \) were fully characterized with conventional methods (Scheme 3).

The reactivity of ionic liquid supported organotin reagents in halodemetalation reactions was first evaluated with the organotin derivative \( 3 \) and carrier-added iodine-125. In that case, the halodemetalation reaction occurred quantitatively in only five minutes to form the ethyl \([\text{I-125}/\text{I-127}]\)iodobenzoate \( 6 \).

using an equimolar ratio between the oxidant (N-Chlorosuccinimide) and the ionic liquid supported tin precursor \( 3 \) (Scheme 4). Pure product was then easily obtained with simple filtration on silica cartridge which was validated with HPLC control of the purified product \( 6 \) (Fig. 1). Contrarily to conventional radiolabeling techniques,\(^{17} \) it is noteworthy that purification was facilitated here since the by-product \( 7 \) can be easily separated from \( 6 \) limiting also the tin contamination.

We were then interested in the radiolabeling with astatine-211 for the synthesis of the SuccinimidylAstatobenzoate ([At-211]SAB) which is the most frequently described prosthetic group for astatine radiolabeled vectors (Scheme 5).\(^{18} \)

Scheme 1 General strategy for a “clean” synthesis of radiolabeled compounds and making the purification easier, by filtration (Scheme 1).

Scheme 2 Synthesis of Ethyl 3-(dibutylstannyl)benzoate supported on ionic liquid. Reagents and conditions: (a) 3-(ethoxycarbonyl)phenylzinc, THF, room temperature, overnight; (b) NaPF\(_6\), acetone, 24h.

Scheme 3 Preparation of 3-(Dibutylstannyl)succinimidyl ester supported on ionic liquid. Reagents and conditions: (a) i) aq NaOH (15% w/w), EtOH, 78°C, 2h; ii) N-hydroxysuccinimide, DCC, THF, overnight; 55 %; (b) NaPF\(_6\), acetone, 24h.

Scheme 4 Radiolabeling of Ethyl 3-(dibutylstannyl)benzoate supported on ionic liquid 3. Reagents and conditions: [I-125/127]NaI, N-chlorosuccinimide, MeOH/AcOH, 5 min., 20°C.

Fig. 1 HPLC chromatogram of cold ethyl iodobenzoate (A), and purified [I-125/127]iodobenzoate (B).
Scheme 5 Radiolabeling of 3-(Dibutylstannyl)succinimidyl ester supported on ionic liquid 5. Reagents and conditions: N-chlorosuccinimide, MeOH/AcOH, 30 min., 20°C.

Table 1 Radiochemical yields (RCY) and concentration in oxidant for production of [At-211]SAB from organotin supported ionic liquid 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>NCS (mg mL⁻¹)</th>
<th>RCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>1.00</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>1.35</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>2.70</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>4.05</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>5.40</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 2 Radiochemical yields and concentration in ionic liquid supported organotin 5 for production of [At-211]SAB.

<table>
<thead>
<tr>
<th>Entry</th>
<th>5 (mg mL⁻¹)</th>
<th>RCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>10.0</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>20.0</td>
<td>64</td>
</tr>
</tbody>
</table>

The demetalation reaction involving organotin derivative 5 and no-carrier-added astatine-211 was completed in 30 minutes in MeOH / AcOH (95/5) mixture at 20 °C. Unsurprisingly, previous reaction time with carrier-added radiodine is shorter as the carrier generally enhanced reaction kinetics. However, it should be noted that astato-demetalation with a conventional tin derivative and our astatine source generally required heating at 60°C.¹⁹ This decrease of reaction temperature is likely due to the fact that ionic liquid can act as a catalyst or can enhance the reactivity of radiohalogen.²⁰

We then studied the influence of NCS (N-Chlorosuccinimide) concentration on the astato-demetalation reaction. Results are summarized in Table 1. This study shows that optimal concentration of NCS is 2.70 mg mL⁻¹ and leads to [At-211]SAB in 62 % radiochemical yield (Table 1, entry 5). Below this value the yield is lower (Table 1, entries 1-4) and higher concentration does not afford better performance (Table 1, entries 6-7).

To further optimize reaction conditions, the influence of concentration of ionic liquid supported organotin reagent 5 was investigated (Table 2). Using an organotin 5 concentration of 5.0 mg mL⁻¹ with a NCS concentration of 2.70 mg mL⁻¹, the reaction proceeded with 64% optimized radiochemical yield (Table 2, entry 4).

Interestingly, no time-consuming purification protocols such as HPLC technique was required to isolate the reaction product from tin precursors and unreacted astatine species. The pure [At-211]SAB was conveniently isolated by filtration through silica gel cartridge from the crude mixture. This single purification led to a time saving estimated about 2 hours compared with conventional methodologies. RP-HPLC analysis of the purified product shows that hydrophilic species such as free astatine was also eliminated during the fast filtration (Fig. 2). According to the analytical HPLC, the [At-211]SAB 8 was obtained up to 91% radiochemical purity (Fig. 2).

Purified [At-211]SAB allowed successfully the astatine radiolabeling of the 9E7 mAb in 76% yields with good immunoreactivity.²¹ Similarly, halodemetalation optimized conditions were directly applied to reaction with iodine-125 and 5 (Scheme 5). [I-125]SIB 9 was thus obtained with 67% RCY and coupled to bovine serum albumin modified with about 50 Di-HSGL heteropeptide²² residues per protein (BSA-Di-HSGL) after purification (Fig. 3). The coupling yield was interestingly good (54%) despite the low protein concentration (1.5 mg mL⁻¹, 20 μM). Moreover, the immunoreactivity test has demonstrated that recognition of HSG residues on the radiolabeled BSA-Di-HSGL is maintained for mAb-679 (anti-HSG)²³.

Fig. 2 HPLC chromatogram of [At-211]SAB 8 (tₚ: 15.34 min.) after purification.¹⁷

Fig. 3 TLC of [I-125]SIB 9 before (A) and after (B) purification, (C) ITLC-SG of radiolabeled BSA-Di-HSGL.

Conclusion
In summary, we have developed a new ionic liquid–solution phase radiolabeling method avoiding time consuming purification methods, leading to astatinated and radioiodinated radiopharmaceuticals compounds in good yields and purities. Interestingly, halodehalomethylation radiochemical yields are similar to those obtained with conventional tin precursors (trimethylstannyl derivatives). It is noteworthy that this new original methodology led to final products with higher global yields since no product was lost neither by decay (thanks to this time-saving process) nor by undesirable retention on chromatographic systems. An innovative automated system based on this methodology is currently underway to routine production.

**Experimental section**

**General Information**

Commercially available reagents and solvents were purified and dried, when necessary, by standard methods prior to use. $^1$H (300 MHz), $^{13}$C (75 MHz) NMR spectra were recorded on a Bruker Avance 300 spectrometer. The compounds studied were measured in CDCl$_3$ and $^1$H and $^{13}$C chemical shifts, reported in ppm, were referred to the central signal of the solvent. $^{13}$C NMR spectra were recorded with complete proton decoupling. High resolution mass spectra measurements were recorded on Waters-Micromass GCT Premier spectrometers. Analytical thin layer chromatography was performed on precoated silica gel 60 F254 plates. For cold references, methyl-iodoethylbenzoate is commercially available and methyl-succinimidyl iodobenzoate has been previously described.

Radioactive materials. All radioactive materials were handled according to the approved protocols at the Centre de Recherche en Cancérologie Nantes/Angers. Astatine-211 was produced at the CEMTHI, Orléans, France using the Recherche en Cancérologie Nantes/Angers. Astatine-211 was recovered from targets by sublimation and subsequent purification methods, leading to astatinated and undesirable retention on chromatographic systems. A new innovative automated system based on this methodology is currently underway to routine production.

1-(6-dibuty1-[3-(ethoxy carbonyl)phenyl]stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium bromide 2. Commercially available (3-ethoxy carbonyl)phenyl)zinc bromide (0.5 M in THF, 12.8 mL, 6.4 mmol, 5.6 eq) was introduced dropwise to the iodic liquid (529 mg, 1.15 mmol, 1 eq) in solution in anhydrous THF (6 mL). After 18 h of stirring at room temperature, the resulting mixture was filtered through a short pad of silica gel then extracted with CH$_2$Cl$_2$ (3 $\times$ 100 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (CH$_2$Cl$_2$ to CH$_2$Cl$_2$/MeOH 90:10) to afford compound 2 as a viscous yellow oil (450 mg, 70%).$^1$H NMR (CDCl$_3$, ppm) δ 10.17 (s, 1H), 8.00 (bs, 1H), 7.86-7.81 (m, J = 7.8 Hz, 1H), 7.58 (bs, 1H), 7.55-7.50 (m, J ≈ 7.5 Hz, 1H), 7.37 (bs, 1H), 7.32-7.25 (m, 1H), 4.38-4.17 (m, 6H), 1.81-1.70 (m, 2H), 1.55-1.38 (m, 9H), 1.35-1.18 (m, 11H), 1.02-0.90 (m, 6H), 0.77 (t, J = 7.2 Hz, 6H).$^{13}$C NMR (CDCl$_3$, ppm) δ 167.1, 142.2, 140.9, 137.1, 136.2, 129.6, 129.0, 120.7, 122.2, 122.1, 60.8, 50.0, 45.3, 33.6, 30.2, 28.9, 27.2, 26.5, 25.7, 15.7, 14.3, 13.6, 9.6, 9.5. HRMS (FAB) calcd. for C$_{38}$H$_{62}$N$_2$O$_2$Sn $\{M-Br\}^+$; found 563.2675.

1-(6-dibuty1-[3-(ethoxy carbonyl)phenyl]stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium hexafluorophosphate 3. Compound 2 (150 mg, 0.233 mmol, 1 eq) was dissolved in NaPF$_6$ (78 mg, 0.464 mmol, 2 eq) at room temperature for 24 h to exchange the anion. The reaction mixture was filtered and the acetone was evaporated at room temperature. The crude product was purified by silica gel chromatography (CH$_2$Cl$_2$ to CH$_2$Cl$_2$/MeOH 90:10) to afford compound 3 as a viscous yellow oil (156 mg, 94%).$^1$H NMR (CDCl$_3$, ppm) δ 8.55 (bs, 1H), 8.10 (s, 1H), 7.95-7.91 (m, 1H), 7.69-7.55 (m, 1H), 7.42-7.26 (m, 3H), 4.35 (q, J = 7.3 Hz, 2H), 4.21 (q, J = 7.3 Hz, 2H), 4.10 (t, J = 7.2 Hz), 1.89-1.75 (m, 2H), 1.61-1.49 (m, 9H), 1.41-1.24 (m, 12H), 1.11-0.99 (m, 5H), 0.87 (t, J = 7.2 Hz, 6H).$^{13}$C NMR (CDCl$_3$, ppm) δ 167.5, 142.5, 141.2, 137.4, 135.1, 129.9, 129.3, 128.1, 122.4, 122.3, 61.2, 50.3, 45.5, 33.7, 30.1, 29.2, 27.5, 26.8, 25.9, 15.3, 14.6, 13.9,
residue was acidified with 3 mL of HCl 1M, and then extracted and the ethanol was removed under reduced pressure. The resulting mixture with CH₂Cl₂ was stirred for 20 min at room temperature, then refluxed 2 h.

J = 7.3 Hz, 6H).

1.58-1.45 (m, 9H), 1.38-1.21 (m, 9H), 1.13-1.00 (m, 5H), 0.87 (t, J = 7.4 Hz, 2H), 1.58-1.45 (m, 9H), 1.38-1.21 (m, 9H), 1.13-1.00 (m, 5H), 0.87 (t, J = 7.4 Hz, 2H).  

Succinimidyl 3-[At-211]iodobenzoate [At-211]-8. To astatine (50 µl, 4.2 MBq) in methanol was added to NCS (4 µl, 81 nmol.) in MeOH/AcOH (95/5). The solution was stirred 30 s at 20°C. 5 (20 µl, 130 nmol) in MeOH/AcOH (95/5) was then added. After 30 minutes stirring, 2 µl of an aqueous solution of sodium metabisulphite (20 mg/ml) were added. The succinimidyl m-astatobenzoate [At-211]-8 was obtained (64% RCY). The solution was evaporated to dryness and recovered in 400 µl of diethyl ether. After filtration using a silica gel cartridge and diethyl ether as eluent, the product [At-211]-8 was obtained with a good RCP (90%). Volatiles were evaporated under argon and the purified [At-211]SAB was obtained as a dry residue ready for the coupling to the vector. Rf (CHCl₃/AcOEt 9:1) : 0.4, t₅₀ : 15.3 min.

Succinimidyl 3-[I-125/127]iodobenzoate [I-125/127]-9. To NaI (1 µl, 46.2 pmol (3.7 MBq) of [I-125/127]NaI) in NaOH 0.048 M was added NCS (4 µl, 81 nmol.) in MeOH/AcOH (95/5). The solution was stirred 30 s at 20°C. 5 (20 µl, 130 nmol) in MeOH/AcOH (95/5) was then added. After 30 minutes stirring, the radiiodinated succinimidyl iodobenzoate was obtained (67% RCP). The solution was evaporated to dryness and the crude product was recovered in 400 µl of diethyl ether. After filtration using a silica gel cartridge and diethyl ether as eluent, the product was obtained with a good RCP (100%). Volatiles were evaporated under argon and the purified [I-125/127]-9 was obtained as a dry residue ready for the coupling to the vector. Rf (CHCl₃/AcOEt 8:2) : 0.5.

Radioimmunoassay for the radiolabeled mAb-9E7. Radioimmunoassay was assessed using magnetic beads coated with the synthetic mucus CD138 peptide (SNTETAFSSLVPGKPEEGPVLHVAAEPGFTARDKEKE-Ahx-C-NH₂). 2 µl of astatinated 9E7 (mouse anti-CD138) were diluted with 1 mL of PBS/BSA 0.5%. Series of 20 µl (200 µg) aqueous suspension of magnetic beads were aliquoted in an Eppendorf vial, washed 4 times with PBS/BSA 0.5% and then suspended in 120 µl of PBS/BSA. 50 µl of the diluted solution of astatinated 9E7 (0.45 pmol) were then added and stirred for 1 h. at 20°C (A). Supernatants were separated and magnetic beads were washed twice with 200 µL of PBS/BSA 0.5%. Finally, 600 µL of PBS/BSA 0.5% were added to the washed magnetic beads (B). Activities contained in (A) and (B) were determined using a γ-counter (Wallac 1480-Wizard³, Perkin-Elmer, Paris) and immunoreactivity was calculated as the ratio between (A) and (B). The [At-211]SAB-9E7 exhibits a good immunoreactivity (78%).
buffer pH 8.6 300 mM) was added to the dry \([\text{I}^{-125}]\)-
500
9
11
Recherche (grant n° 11-BSV5-016-03, grant n° 07-JCJC-0026-
6
1
Notes and references
provided by a grant from the French National Agency  for
and Atlanpole Biotherapies. Astate-211 has been par tially
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production.

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Notes and references
1  M. J. Adam and D. S. Wilbur, Chem. Soc. Rev., 2005, 34, 153-
163.
2015, 26, 1-18.
3  (a) F. Guérard, J.-F. Gestin and M. W. Brechbiel, Cancer
Biother. Radiopharm., 2013, 28, 1-20; (b) D. S. Wilbur, Nat.
4  (a) E. B. Silberstein, Semin. Nucl. Med., 2012, 42, 164-170. (b)
V. V. Belov, A. A. Bonab, A. J. Fischman, M. Heartlein, P.
7  A. I. Kassis, C. F. Foulon, and S. J. Adelstein, PCT Int. Appl.,
8  D. S.Wilbur, M.-K. Chyan, D. K. Hamlin and M. A. Perry,
9  F. Dolle, S. Demphel, F. Hinnen, D. Fournier, F. Vaufrey and C.
10  M. Speranza, C.-Y. Shue, A. P. Wolf, D. S. Wilbur and G.
13  M. J. Adam, M. M. Berry, L. D. Hall, B. D. Pate and T. J. Ruth,
14  (a) A. N. Gifford, S. Kuschel, C. Shea and J. S. Fowler, Bioconjugate Chem., 2011, 22, 406-412; (b) G. W. Kabalka, V.
Namboodiri and M. R. Akula, J Labelled CpdRadiopharm.,
2001, 44, 921-929; (c) G. Vaidyanathan, D. J. Affleck, K. L.
Alston, X.-G. Zhao, M. Hens, D. H. Hunter, J. Babich and M.
15  (a) A. Donovan, J. Forbes, P. Dorff, P. Schafer, J. Babich and J.
F. Vaillan, J. Am. Chem. Soc., 2006, 128, 3536-3537; (b) J.
W. McIntee, C. Sundararajan, A. C. Donovan, M. S. Kovacs, A.
Capretta and J. F. Vaillant, J. Org. Chem., 2008, 73, 8236-
8243.
16  (a) J. Vitz, D. H. Mac and S. Legoupy, Green Chem., 2007, 9,
431-433; (b) P. D. Pham and S. Legoupy, Tetrahedron Lett.,
2009, 50, 3780-3782; (c) P. D. Pham, P. Bertus and S.
Legoupy, S. Chem. Commun., 2009, 6207-6209; (d) P. D.
Pham, J. Vitz, C. Chamignon, A. Martel and S. Legoupy, Eur.
J. Org. Chem., 2009, 3249-3257; (e) N. Louaisil, P. D. Pham, F.
Chem.2011, 143-149; (f) D. Faye, M. Vybornyi, F. Boeda and S.
Legoupy, Tetrahedron2013, 69, 5421-5425.
17  G. Vaidyanathan and M. R. Zalutsky, Nat. Protoc., 2006, 1,
707-713.
1008; (b) M.R. Zalutsky and A.S. Narula, Appl. Radiat. Isot.,
19  Unpublished results: to 500 µl (40-200 MBq) of astatin-211 in
MeOH were added 39 µl (598 nmol.) of NCS in MeOH/Ac.
acid (95/5) and 60 µl (156 nmol.) of N-succinimidyl-3-
(trimethylstannyl)benzoate in MeOH/Ac. Acid (95/5). The
reaction was heated 30 min. at 60°C under stirring. [At-
211]SAB was obtained in 60-90% RCY. The crude product
was purified using normal phase HPLC (HR silica NovaPrepcolumn, isocratic Hept/AcOEt (80/20), 1.5 µl.min-
1). Fractions of interest were collected and evaporated
leading to pure [At-211]SAB ready to be coupled to vectors.
After coupling, typical global yields for astatinated Mab are
9-30 %.
20  J. Pavlinac, M. Zupan, K. K. Laali and S. Stavber, Tetrahedron,
21  N. Fichou, S. Gouard, C. Maurel, J. Barbet, L. Ferrer, A.
Morgenstern, F. Bruchertseifer, A. Faire-Chauvet, E. Bigot-
Corbel, F. Davodeau, J. Gaschet and M. Chérel, Front. Med.,
22  L. Morandeau, E. Benoist, A. Loussouarn, A. Ouadi, P. Lesaec,
M. Mougin, A. Faire-Chauvet, J. Le Boterff, J. F. Chatal, J.
23  J.-M. Le Doussal, M. Martin, E. Gautherot, M. Delaage and J.