ORGANIC LETTERS

2009
Vol. 11, No. 20
4760−4763

A Method for Parallel Solid-Phase Synthesis of Iodinated Analogues of the CB_1 Receptor Inverse Agonist Rimonabant

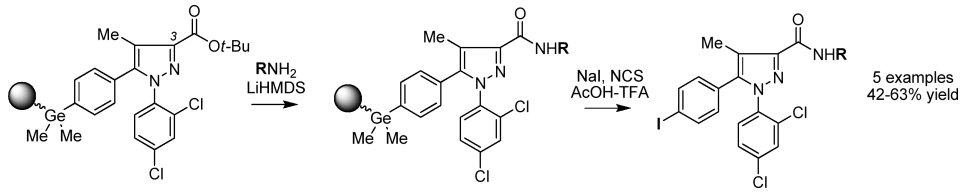
Alan C. Spivey,*,† Chih-Chung Tseng,† Teyrnon C. Jones,† Andrew D. Kohler,‡ and George J. Ellames‡

Department of Chemistry, Imperial College, London SW7 2AY, U.K., and Department of Isotope Chemistry and Metabolite Synthesis, Sanofi-Aventis, Willowburn Avenue, Alnwick, Northumberland NE66 2JH, U.K.

a.c.spivey@imperial.ac.uk

Received September 2, 2009

ABSTRACT



A method for the parallel solid-phase synthesis (SPS) of iodinated analogues of Sanofi-Aventis' type 1 cannabinoid (CB_1) receptor inverse agonist rimonabant (acomplia) has been developed. The method allows the synthesis of a range of C3 amide/hydrazide derivatives from a resin-bound C3 ester precursor. The C−Ge linkage to the Hypogel-200 resin is stable to the diversification conditions but allows *ipso*-iododegermylative cleavage using NaI/NCS even for the products containing the oxidatively labile hydrazide moiety.

Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) are noninvasive, high-resolution "molecular" imaging techniques used clinically for diagnosis and monitoring of many medical disorders.[1] The short-lived positron or γ-ray emitting nuclei required for these techniques [e.g., ^{124}I ($t_{1/2}$ 4.2 d) and ^{123}I ($t_{1/2}$ 13.2 h), respectively] must be incorporated into the appropriate imaging molecules regioselectively and rapidly.[2] For radio-iodinated aryl iodides this normally entails *ipso*-iododestannylation of an aryltrialkyltin precursor (e.g., $ArSnMe_3$ or $ArSnBu_3$) by radiolabeled KI or NaI in the presence of an oxidant followed by HPLC purification to remove all traces of toxic tin residues from the product.[3]

We envisaged that by employing an aryl-labeling precursor bound to an insoluble polymer via a trialkylgermane linker it would be possible to effect analogous *ipso*-iododegermylative labeling, thereby obviating the need for the radiochemist to handle tin-containing materials and also the requirement for any post-reaction purification.[4,5] Ge-containing compounds do not have the adverse toxicity profile of

† Imperial College.
‡ Sanofi-Aventis.

(1) (a) Ametamey, S. M.; Honer, M.; Schubijer, P. A. *Chem. Rev.* **2008**, *108*, 1501. (b) Willmann, J. K.; van Bruggen, N.; Dinkelborg, L. M.; Gambhir, S. S. *Nat. Rev. Drug Disc.* **2008**, *7*, 591.

(2) For an excellent overview of radiolabeling, see: (a) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998. For radioiodination, see: (b) Finn, R. Chemistry Applied to Iodine Radionuclides. In *Handbook of Radiopharmaceuticals: Radiochemistry and Applications*; Welch, M. J., RedvanlyC. S., Eds.; John Wiley and Sons: New York, 2003. (c) Bourdoiseau, M. *Int. J. Radiat. Applic. Instrument. Part B. Nucl. Med. Biol* **1986**, *13*, 83.

(3) (a) Kabalka, G. W.; Varma, R. S. *Tetrahedron* **1989**, *45*, 6601. (b) Glaser, M.; Luthra, S. K.; Brady, F. *Int. J. Oncol.* **2003**, *22*, 253.

(4) For pioneering studies on the use of arylgermanes for (radio)halogenation, see: (a) Moerlein, S. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1687. (b) Moerlein, S. M. *J. Org. Chem.* **1987**, *52*, 664. For the use of polymer-supported arylstannanes for radioiodination, see: (c) Culbert, P.; Hunter, D. H. *React. Polym.* **1993**, *19*, 247. (d) Hunter, D. H.; Zhu, X. *J. Labelled Compd. Radiopharm* **1999**, *42*, 653. Kabalka, G. F.; Namboodiri, V.; Akula, M. *J. Labelled Compd. Radiopharm* **2001**, *44*, 921.

10.1021/ol902038y CCC: $40.75
Published on Web 09/24/2009

their Sn congeners,[6] and the only molecules released into solution should be those of the labeled product. Moreover, unlike arylstannanes, arylgermanes are robust toward a wide range of conditions for chemical synthesis[7] and so afford the possibility to make a range of derivatives of an advanced precursor prior to final radioiodinative release; a potentially valuable feature during preclinical imaging agent development. Herein, we describe proof-of-concept for this approach as exemplified by the parallel, solid-phase synthesis (SPS) of a small array of iodinated analogues of the CB_1 receptor inverse agonist rimonabant.

Type 1 cannabinoid (CB_1) receptors belong to the rhodopsin family of G protein coupled receptors (GPCRs) and are widely distributed in the central nervous system (CNS).[8] Physiologically, they are implicated in regulation of pain, energy distribution, and metabolism. Drug candidates acting as antagonists/inverse agonists for these receptors have been/are in clinical trials for treatment of obesity, metabolic syndrome, and various addictions including smoking.[9] Rimonabant (**1a**, marketed as acomplia) is a CB_1 receptor inverse agonist first approved for treatment of obesity by the European Medicines Agency in 2006 and then withdrawn from the market in 2008 following the emergence of psychiatric disorders among patients.[10] Various ^{11}C-labeled,[11] ^{18}F-labeled,[12] and $I^{123/124}$-labeled[13] derivatives (e.g., **1b** [^{123}I]AM251 and **1c** [^{123}I]AM281, Figure 1) have proved to

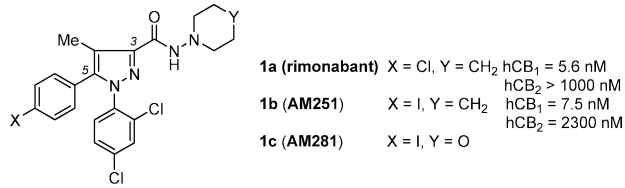
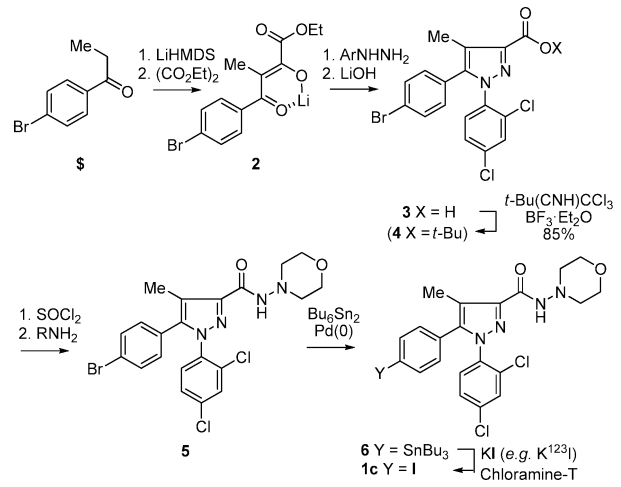


Figure 1. Structures of rimonabant, AM251, and AM281.

be viable for PET and SPECT imaging of CNS activity but an optimal ligand has yet to be identified.[14]

All reported rimonabant-derived radioiodinated ligands contain the labeled iodine atom in place of the chlorine atom in the C5 aryl ring; this substitution marginally reduces affinity but increases selectivity for binding at CB_1 vs CB_2. Their synthesis involves solution phase Pd(0)-mediated stannylation of an arylbromide late intermediate (e.g., **5** → **6**, Scheme 1)

Scheme 1. Standard Synthesis of a Radioiodinated Rimonabant Analogue (e.g., AM281)



then *ipso*-iododestannylation with a radiolabeled iodonium source (e.g., **6** → **1c**, Scheme 1).[13]

Experimental structure−activity relationship (SAR) data, particularly in the context of previous attempts to develop

(5) (a) For a review of solid-phase radiochemistry, see: Hockley, B. G.; Scott, P. J. H.; Kilbourn, M. R. In *Linker Strategies in Solid-Phase Organic Synthesis*; Scott, P. J. H., Eds.; Wiley: Chichester, 2009; Chapter 22. (b) For an overview of isotopic labeling employing phase-tagged Ge linkers, see: Spivey, A. C.; Martin, L. J.; Noban, C.; Jones, T. C.; Ellames, G. J.; Kohler, A. D. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 281.

(6) Lukevics, E.; Pudova, O. In *Chemistry of Organic Germanium, Tin and Lead Compounds*; Rappoport, Z., Ed.; Wiley: Chichester, 2002; Vol. 2 (Part2), p 1685.

(7) Spivey, A. C.; Tseng, C.-C.; Hannah, J. P.; Gripton, C. J. G.; Fraine de, P.; Parr, N. J.; Scicinski, J. J. *Chem. Commun.* **2007**, 2926, and references therein.

(8) Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol. Rev.* **2002**, *54*, 161.

(9) (a) Jagerovic, N.; Fernandez-Fernandez, C.; Goya, P. *Curr. Top. Med. Chem.* **2008**, *8*, 205. (b) Svíženská, I.; Dubový, P.; Šulcová, A. *Pharmacol., Biochem. Behav.* **2008**, *90*, 501. (c) Cota, D. *Diabetes Metab. Res. Rev.* **2007**, *23*, 507. (d) Mucciolo, G. G. *Chem. Biodivers.* **2007**, *4*, 1805. (e) Pagotto, U.; Marsicano, G.; Cota, D.; Lutz, B.; Pasquali, R. *Endocrine Rev.* **2006**, *27*, 73. (f) Ramos, J. A.; González, S.; Sagredo, O.; Gómez-Ruiz, M.; Fernández-Ruiz, J. *Mini-Rev. Med. Chem* **2005**, *5*, 609.

(10) Jones, D. *Nature Rev. Drug Disc.* **2008**, *7*, 961.

(11) Mathews, W. B.; Scheffel, U.; Rauseo, P. A.; Ravert, H. T.; Frank, R. A.; Ellames, G. J.; Herbert, J. M.; Barth, F.; Rinaldi-Carmona, M.; Dannals, R. F. *Nucl. Med. Biol.* **2002**, *29*, 671.

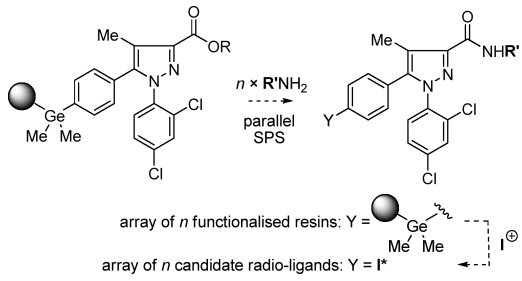
(12) (a) Liu, P.; Lin, L. S.; Hamill, T. G.; Jewell, J. P.; Lanza, T. J., Jr.; Gibson, R. E.; Krause, S. M.; Ryan, C.; Eng, W.; Sanabria, S.; Tong, X.; Wang, J.; Levorse, D. A.; Owens, K. A.; Fong, T. M.; Shen, C.-P.; Lao, J.; Kumar, S.; Yin, W.; Payack, J. F.; Springfield, S. A.; Hargreaves, R.; Burns, H. D.; Goulet, M. T.; Hagmann, W. K. *J. Med. Chem.* **2007**, *50*, 3427. (b) Burns, H. D.; Van Laere, K.; Sanabria-Bohórquez, S.; Hamill, T. G.; Bormans, G.; Eng, W.; Gibson, R.; Ryan, C.; Connolly, B.; Patel, S.; Krause, S.; Vanko, A.; Van Hecken, A.; Dupont, P.; De Lepeleire, I.; Rothenberg, P.; Stoch, S. A.; Cote, J.; Hagmann, W. K.; Jewell, J. P.; Lin, L. S.; Liu, P.; Goulet, M. T.; Gottesdiener, K.; Wagner, J. A.; de Hoon, J.; Mortelmans, L.; Fong, T. M.; Hargreaves, R. J. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 9800. (c) Li, Z.; Gifford, A.; Liu, Q.; Thotapally, R.; Ding, Y.-S.; Makriyannis, A.; Gatley, S. J. *Nucl. Med. Biol.* **2005**, *32*, 361. (d) Willis, P. G.; Pavlova, O. A.; Chefer, S. I.; Vaupel, D. B.; Mukhin, A. G.; Horti, A. G. *J. Med. Chem.* **2005**, *48*, 5813. (e) Mathews, W. B.; Scheffel, U.; Finley, P.; Ravert, H. T.; Frank, R. A.; Rinaldi-Carmona, M.; Barth, F.; Dannals, R. F. *Nucl. Med. Biol.* **2000**, *27*, 757.

(13) (a) Berding, G.; Schneider, U.; Gielow, P.; Buchert, R.; Donnerstag, F.; Brandau, W.; Knapp, W. H.; Emrich, H. M.; Müller-Vahl, K. *Psych. Res.: Neuroimaging* **2006**, *147*, 249. (b) Gielow, P.; Klinge, P.; Knapp, W. H.; Berding, G. *Appl. Radiat. Isot.* **2006**, *64*, 763. (c) Berding, G.; Müller-Vahl, K.; Schneider, U.; Gielow, P.; Fitschen, J.; Stuhrmann, M.; Harke, H.; Buchert, R.; Donnerstag, F.; Hofmann, M.; Knoop, B. O.; Brooks, D. J.; Emricj, H. M.; Knapp, W. H. *Biol. Psychiatry* **2004**, *55*, 904. (d) Lan, R.; Lu, Q.; Fan, P.; Gatley, J.; Volkow, N. D.; Fernando, S. R.; Pertwee, R.; Makriyannis, A. *AAPS Pharmsci.* **1999**, *1*, 4. (e) Gatley, S. J.; Lan, R.; Volkow, N. D.; Pappas, N.; King, P.; Wong, C. T.; Gifford, A. N.; Pyatt, B.; Dewey, S. L.; Makriyannis, A. *J. Neurochem.* **1998**, *70*, 417. (f) Lan, R.; Gatley, S. J.; Makriyannis, A. *J. Labelled Compd. Radiopharm.* **1996**, *38*, 875. (g) Gatley, S. J.; Gifford, A. N.; Volkow, N. D.; Lan, R.; Makriyannis, A. *Eur. J. Pharmacol.* **1996**, *307*, 331.

(14) (a) For reviews, see: Van Laere, K. *Eur. J. Nucl. Med. Mol. Imaging* **2007**, *34*, 1719. (b) Gifford, A. N.; Makriyannis, A.; Volkow, N. D.; Gatley, S. J. *Chem. Phys. Lipids* **2002**, *12*, 65.

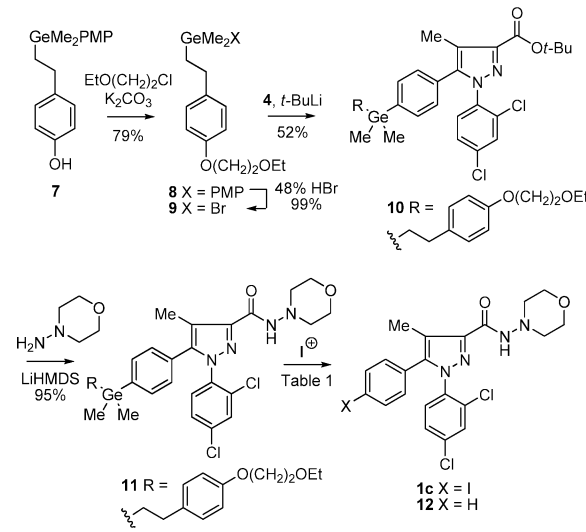
effective PET ligands, show that the nature of the C3 hydrazide moiety has a profound effect on the affinity and biodistribution of rimonabant analogues for the CB_1 receptor,[9a,15] making this unit an attractive target for variation to allow imaging agent optimization. Consequently, our plan was to prepare a 1,5-diarylpyrazole bound to an insoluble polymer support by a Ge linker (attached at the *para* position of the C5 aryl ring) and containing an ester at C3 that could be readily converted via parallel SPS into an array of hydrazide/amide derivatives. Such a strategy would allow the rapid preparation of an array of potential imaging agents from a single functionalized polymer *provided* that the Ge-linker was stable to the C3 diversification protocol and *ipso*-iododegermylation could be achieved in the presence of an oxidatively labile[16] hydrazide moiety. Arylgermanes are uniquely stable toward basic and nucleophilic conditions as compared to arylstannane and arylsilane congeners;[17] thus, we were confident of the former requirement but we were cognizant that arylgermanes undergo S_EAr reactions less rapidly than arylstannanes (due to their lesser β-effect)[18] and expected careful optimization of the cleavage conditions would be required to allow rapid clean cleavage without side reactions (Scheme 2).

Scheme 2. Planned Approach to an Array of Iodinated Rimonabant Analogues **1** via *ipso*-Iododegermylation of Functionalized Polymers Prepared by Parallel SPS



Our initial studies used a solution-phase model system **11** which was prepared by transmetalation of lithiated 1,5-diarylpyrazole *tert*-butyl ester **4** (Scheme 1) with germyl bromide **9** followed by LiHMDS-mediated amidation[19] with *N*-aminomorpholine. The ethoxyethyl group appended to the linker was present to mimic a PEG-grafted polymer support. A range of conditions was evaluated for *ipso*-iododegermylation of this model system to give AM281 (**1c**, Table 1).

Table 1. Synthesis of and Screening *ipso*-Iododgermylation Conditions on a Solution-Phase Germyl-AM281 Precursor



entry	conditions[a]	yield (%)
1	NaI, chloramine T, AcOH, rt, 16 h	0[c]
2	I_2, CCl_4, rt, 16 h	0[c]
3	NaI, $FeCl_3$, rt, 16 h	0[c]
4	ICl, rt, 16 h	0[c]
5	NH_4I, Oxone, rt, 16 h	0[c]
6	NaI, *m*-CPBA, rt, 16 h[b]	0[d]
7	NaI, AcO_2H, AcOH, rt, 16 h[b]	0[d]
8	NIS, TFA (cat.), AcOH, rt, 16 h	0[d]
9	I_2, AcOH, rt, 16 h	15[e]
10	I_2, TFA, AcOH, rt, 16 h[f]	63[e]
11	NaI, NCS,TFA, AcOH, rt, 30 min[f]	85

[a] All reactions were carried out with 2 equiv of reagents. [b] Slow addition of peracids. [c] No reaction occurred; recovery of S.M. [d] Decomposition of S.M. [e] Byproduct **12** also isolated (see text). [f] TFA−AcOH (1:3 v/v).

Subjection of arylgermane **11** to the conditions reported by Gatley[13d,f] for *ipso*-iododestannylation to give AM281 using NaI/chloramine-T/AcOH[4a] or I_2/CCl_4[4a,b] effected no reaction; starting material was recovered quantitatively (entries 1 and 2). Use of NaI/$FeCl_3$,[20] NH_4I/Oxone,[21] and ICl[4b] was similarly ineffective (entries 3−5). By contrast, use of NaI/*m*-CPBA,[22] NaI/AcO_2H,[23] and NIS/TFA[24] resulted only in decomposition of the starting material, even with slow addition of the oxidants (entries 6−8). However, the use of I_2/AcOH, as described by Moerlein for *ipso*-iododegermylation of aryltrimethylgermanes,[4b] resulted in a sluggish reaction (16 h) which yielded AM281 (**1a**) in 15% yield along with protonated byproduct **12** in 10% yield (entry 9). Using TFA in place of AcOH gave an improved outcome

(15) (a) Tobiishi, S.; Sasada, T.; Nojiri, Y.; Yamamoto, F.; Mukai, T.; Ishiwata, K.; Maeda, M. *Chem. Pharm. Bull.* **2007**, *55*, 1213. (b) Donohue, S. R.; Halldin, C.; Pike, V. W. *Bioorg. Med. Chem.* **2006**, *14*, 3712. (c) Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769. (d) Thomas, B. F.; Francisco, M. E. Y.; Seltzman, H. H.; Thomas, J. B.; Fix, E. E.; Schulz, A.-K.; Gilliam, A. F.; Pertwee, R. G.; Stevenson, L. A. *Bioorg. Med. Chem.* **2005**, *13*, 5463.

(16) (a) Amos, R. J. I.; Corulay, B. S.; Schiesser, C. H.; Smith, J. A.; Yates, B. F. *Chem. Commun.* **2008**, 1695. (b) Stieber, F.; Grether, U.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1073.

(17) Turner, D. J.; Anemian, R.; Mackie, P. R.; Cupertino, D. C.; Yeates, S. G.; Turner, M. L.; Spivey, A. C. *Org. Biomol. Chem.* **2007**, *5*, 1752.

(18) Eaborn, C.; Pande, K. C. *J. Chem. Soc.* **1960**, 1566.

(19) Cf.: Gustafsson, T.; Pontén, F.; Seeberger, P. H. *Chem. Comm.* **2008**, 1100.

(20) Mohanakrishnan, A.; Prakash, C.; Ramesh, N. *Tetrahedron* **2006**, *62*, 3242.

(21) Mohan, K. V. V. K.; Narrender, N.; Kulkarni, S. J. *Tetrahedron Lett.* **2004**, *45*, 8015.

(22) Sha, C.-K.; Young, J.-J.; Jean, T.-S. M. *J. Org. Chem.* **1987**, *52*, 3919.

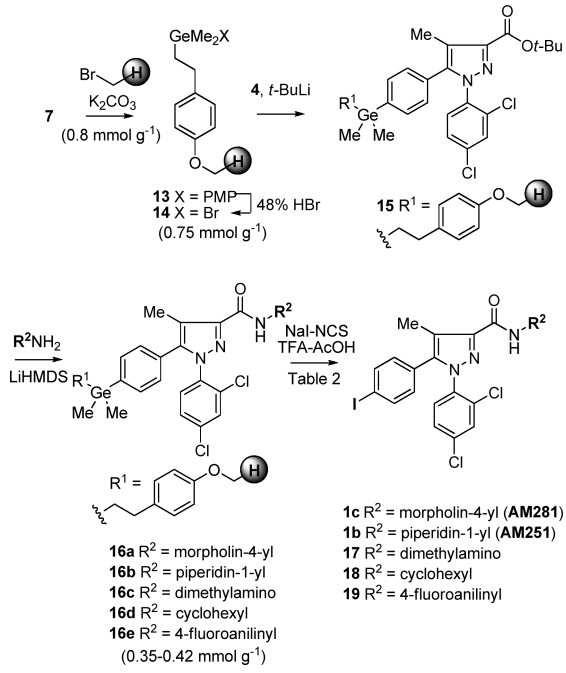
(23) Katsifis, A.; Mattner, F.; Zhang, Z.; Dikic, B.; Papazian, V. *J. Labelled Cpd. Radiopharm.* **2000**, *43*, 385.

(24) Castanet, A.-S.; Colobert, F.; Broutin, P. E. *Tetrahedron Lett.* **2002**, *43*, 504.

of **1a** (63%) and **12** (10%), but the reaction remained slow (16 h, entry 10). Further optimization of these conditions led to the use of NaI/NCS in a TFA/AcOH solvent system which gave AM281 (**1a**) in 85% yield with no byproduct **12** observed in just 30 min (entry 11). This protocol was considered sufficiently efficient to merit its deployment for our envisaged SPS for which we opted to employ the PEG-grafted, cross-linked polystyrene HypoGel-200 as the polymer support on account of its favorable swelling characteristics in hydrophilic solvents.

HypoGel-bound 1,5-diarylpyrazole *tert*-butyl ester **15** was prepared by an analogous protocol to that used for the solution model **10** but employing HypoGel-bound germanium bromide **14** (0.75 mmol g^{-1}) for the transmetalation. Parallel amidation of functionalized polymer **15** with 3 × hydrazines and 2 × amines gave HypoGel-bound 1,5-arylpyrazolyl hydrazides/amides **16a**−**e** (0.35−0.42 mmol g^{-1}, Table 2).

Table 2. Preparation of an Array of HypoGel-Bound Germyl Arylpyrazolyl Amides/Hydrazides and Their *ipso*-Iododegermylation[a]



entry	substrate	time	product	yield (%)
1	**16a**	1 h	AM281 (**1c**)	63
2	**16b**	1 h	AM251 (**1b**)	60
3	**16c**	1 h	**17**	60
4	**16d**	1 h	**18**	55
5	**16e**	6 h	**19**	42
6	**16b**	5 min	**1b**	8

[a] Reaction conditions: **16** (1.0 equiv), NaI (5.0 equiv), NCS (4.0 equiv), TFA−AcOH (1 mL, 1:3 v/v), rt.

Cleavage of the Ge linker with concomitant *ipso*-iodination was accomplished by mixing functionalized polymers **16a**−**e** with NaI in individual reaction cartridges, swelling the polymers in CH_2Cl_2, and then adding a solution of NCS in TFA/AcOH at rt. Iodinated rimonabant analogues **1c**, **1b**, and **17**−**19** were then isolated in 42−63% yields (based on polymer loading levels) following removal of the polymer by filtration and then flash chromatography (entries 1−5). The reactions in entries 1−4 were complete within 1 h, whereas that of entry 5 (the 4-fluoroanilino amide) required 6 h to reach completion. Exposure of polymer **16b** to the iodination conditions for just 5 min furnished AM251 (**1b**) in 8% yield after flash chromatography (entry 6). Analysis by HPLC with UV detection at 254 nm of the *crude* reaction mixture in the case of entry 2 revealed a purity of 80% due to contamination with succinimide (from the NCS). This impurity could be removed by briefly shaking the crude product mixture with a hydrazine-functionalized *Si*-propyl scavenger resin followed by filtration; this gave AM251 (**1b**) in a purity of 96% without recourse to chromatography (see the Supporting Information). These findings augur well for adaption of our approach to radio-iodination in a time-critical imaging context with the prospect of in-line purification through a scavenger cartridge for clinical application.[25]

In conclusion, a novel protocol for the rapid parallel SPS of iodinated 1,5-diarylpyrazole CB_1 receptor ligands has been developed. The method features the use of a Ge linker which is both robust enough to allow on-resin diversification by LiHMDS-mediated amidation and reactive enough to allow rapid and clean *ipso*-iododegermylative cleavage. In particular, the method obviates the use of toxic and labile arylstannane congeners in solution as is presently widely practiced in this type of chemistry. We believe the method holds promise for application in the development of radio-iodinated CB_1 receptor ligands as candidate PET/SPECT imaging agents for studying a range of CNS disorders and could be adapted to expedite development of other PET imaging ligands.

Acknowledgment. We thank the BBSRC and Sanofi-Aventis for provision of a studentship (T.C.J.).

Supporting Information Available: Experimental procedures and characterization for compounds/resins **1**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902038Y

(25) The preparation of no-carrier-added radioiodinated ligands requires very rapid kinetics even when employing a deficiency of the iodine donor at low concentration, and adsorption of the labeled product onto glass/plastic reaction vessels can be problematic. We have not yet adapted the cleavage conditions described here for this scenario but envisage that development of an appropriate microfluidic flow-cell should allow these potential problems to be circumvented.