Straightforward Synthesis of Non-Natural Selenium Containing Amino Acid Derivatives and Peptides

Antonio L. Braga,*[a] Diogo S. Lüdtke,[a] Márcio W. Paixão,[a] Eduardo E. Alberto,[a]
Hélio A. Stefani,[b] and Luiz Juliano[c]

Keywords: Selenium / Peptides / Selenoamines / Organoselenium / Chiral pool

A series of non-natural selenium-containing amino acid derivatives and peptides have been synthesized, in a flexible and modular strategy. The peptide coupling reaction between *N*-protected amino acids and chiral β-seleno amines afforded the desired products in high yields.

1. Introduction

The field of amino acids has gained enormous popularity and relevance in recent years, particularly with the emergence of unnatural analogs as components of molecules with therapeutic potential.[1] Recently, the replacement of natural amino acids in peptides with non-proteinogenic derivatives in order to obtain drug-like target molecules has become an important goal in synthetic organic chemistry.[2]

One of the more exciting areas of research in drug design has been the synthesis of so-called peptidomimetic molecules that are expected to have the same therapeutic effects as natural peptide counterparts, with the added advantage of metabolic stability.[3]

On the other hand, organoselenium chemistry has continued to attract considerable attention due to its pivotal role in the synthesis of a large number of biological compounds (e.g., selenocarbohydrates, selenoamino acids, and selenopeptides). Dietary selenium is an essential element in human nutrition, playing important roles in cancer prevention, immunology, aging, male reproduction and other physiological processes.[4] Indeed, organoselenium compounds have also emerged as an exceptional class of structures that exemplify a role in biochemical processes, serving as important therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements.[5] In particular the synthesis of peptides containing selenium or sulfur atom is rapidly gaining interest with the discovery of an increasing number of proteins containing these compounds.[6,7] However, despite the growing importance of this field, the incorporation of the selenium atom in amino acids and peptides is much restricted to selenocysteine derivatives and there is still a need for further developments towards the synthesis of amino acid-derived chiral selenium compounds, potentially candidates for biological evaluations.

As part of our growing interest in using α-amino acids as chiral building blocks in organic synthesis,[8] and in connection with the increasing importance of the synthesis of small libraries of compounds with programmed variations of substituents, we describe herein an easy, inexpensive and straightforward synthetic route for the preparation of a series of chiral selenium and sulfur containing amino acids. Our approach to the preparation of these peptide-like compounds having a chalcogen atom incorporated in their structures consists in a peptide coupling between a β-seleno amine and an activated *N*-protected amino acid, as depicted in the proposed retrosynthetic analysis (Scheme 1). For the preparation of the key chiral β-seleno amines, we took advantage of a strategy recently developed by us,[9] which explores the regioselective ring opening of chiral aziridines, prepared from the readily accessible *N*-Boc-protected amino alcohols.[10]

2. Results and Discussion

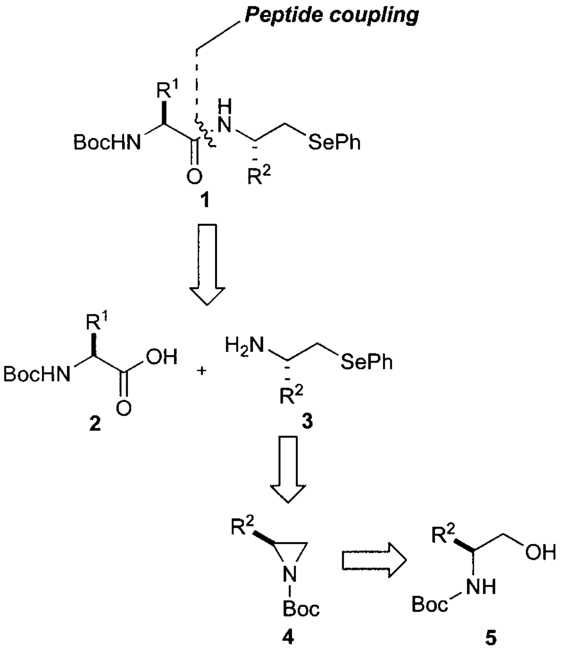
As the starting point for the synthesis of compounds of type **1**, we had to find an efficient way to prepare β-seleno amines in a short and high yielding sequence. To accomplish this task, we took advantage of our previous strategy for the synthesis of chiral β-amino diselenides, which

---

[a] Departamento de Química, Universidade Federal
de Santa Maria,
97105-900, Santa Maria, RS, Brazil
[b] Department of Pharmacy, Faculdade de Ciências
Farmacêuticas, USP,
São Paulo, SP, Brazil
[c] Department of Biophysics, Escola Paulista de Medicina,
UNIFESP,
São Paulo, SP, Brazil
E-mail: albraga@quimica.ufsm.br

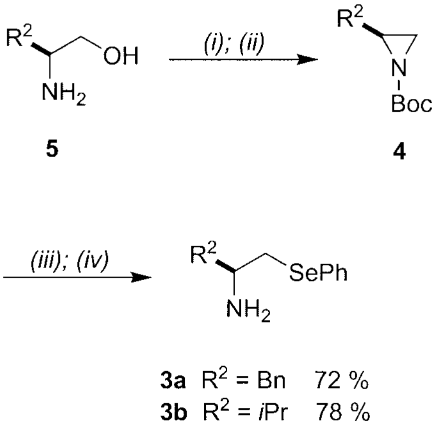
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

DOI: 10.1002/ejoc.200500530



Scheme 1. Retrosynthetic analysis.

employs a nucleophilic ring opening of *N*-Boc aziridines with lithium diselenide.[8] By this time, we changed the selenium nucleophile from Li_2Se_2 to the phenyl selenide anion, which is easily generated by reaction of diphenyl diselenide with $NaBH_4$ in a mixture of THF and ethanol. Regioselective nucleophilic ring opening at the less hindered carbon of the *N*-Boc aziridines proceeded in good yields and the target β-seleno amines were obtained after removal of the Boc protecting group with trifluoracetic acid (Scheme 2).



Scheme 2. Synthesis of β-seleno amines **3**. Reagents and conditions: (i) Boc_2O, CH_3CN, room temp., 3 h; (ii) KOH, TsCl, THF, reflux, 4 h; (iii) PhSeSePh/$NaBH_4$, THF/EtOH (3:1), room temp., 24 h; (iv) TFA, CH_2Cl_2, room temp., 1 h.

With the desired seleno amines in hands, we turned our attention to couple them with *N*-Boc amino acids. To accomplish this transformation, the mixed anhydride was the method of choice, because it has already been successfully employed in our laboratory in a previous work.[11] Coupling condition consists in treatment of the amino acid with *N*-methylmorpholine in chloroform, followed by the addition of ethyl chloroformate to afford the mixed anhydride "in situ" which was then allowed to react with the seleno amine to form the peptide bond in high yields and under very mild conditions (Scheme 3). Gratifyingly, we did not observe any epimerization at the original chiral center from **2**. This was stablished by ^1H NMR experiments where a single set of signals for **1a** were observed. Additionally, **3a** was treated with racemic **2a** to produce a mixture of diastereoisomers, which was also analyzed by ^1H NMR spectroscopy. By comparison of both NMR spectra, we could then confirm the absence of appreciable epimerization. The amino acids of choice were L-valine, L-phenylalanine, and L-proline and they were conveniently protected by reaction with Boc_2O in dioxane, with aqueous $NaHCO_3$ as base.[12]

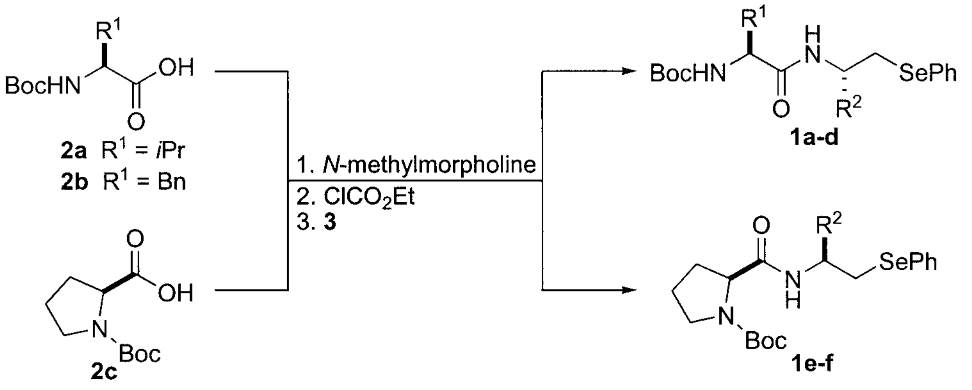
The coupling reaction could be applied to a range of substrates, thus allowing the synthesis of small libraries of compounds with variations of substituents in either, R^1 or R^2, which is of high interest for an efficient biological screening and in structure-activity relationship study, directed towards the design of best combination of substituents in both positions.

Seleno amines **3a** furnished product **1** in essentially quantitative yields when submitted to reaction with the acids **2a** and **2b** (Table 1, entries 1 and 2). On the other hand, when amine **3b** was employed in the combination with the above mentioned acids, yields of **1c** and **1d** are still high, but showed a slightly decrease in comparison to **1a**–**b** (Table 1, entries 3 and 4).

The coupling between the seleno amines with *N*-Boc-proline was also successfully performed, furnishing the desired products in high yields (Table 1, entries 5 and 6). Worth to mention is that the structures of these proline-derived compounds with the selenium atom incorporated in their structures shows some resemblance with the known captopril,[13] which is known for their ability in lowering blood pressure by binding to the active site of angiotensin converting enzyme.[14] The structural features of these proline based seleno peptoids makes them attractive compounds for pharmacological studies.

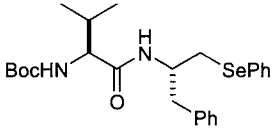
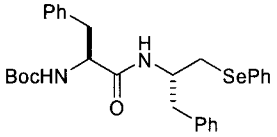
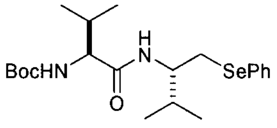
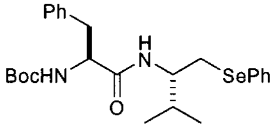
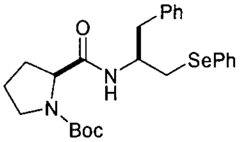
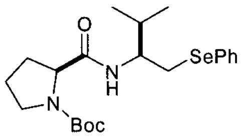
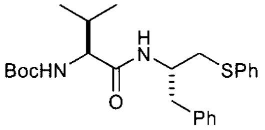
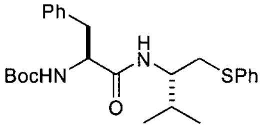
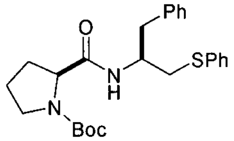
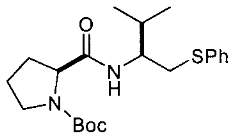
Due to the success obtained with the preparation of the seleno peptoids, we decided to extend our studies to sulfur analogs, in order to prepare some sulfurated amino acids derivatives, different from those which are directly prepared from the natural sulfur-containing amino acids cysteine and methionine (Scheme 4). The preparation of these compounds was analogous to the parent selenium derivatives, by ring opening of aziridines **4**, Boc deprotection and followed by coupling with the protected amino acids, leading to sulfurated peptoids **1g**–**j** in good yields (Table 1, entries 7–10).

As a further extension of the present methodology we attempted to convert the protected **1** to the free amine to make possible to attach another amino acid unit and obtain a tripeptide-like structure bearing either an organoselenium or an organosulfur group. Deprotection was conveniently performed with usual procedure, using trifluoracetic acid in

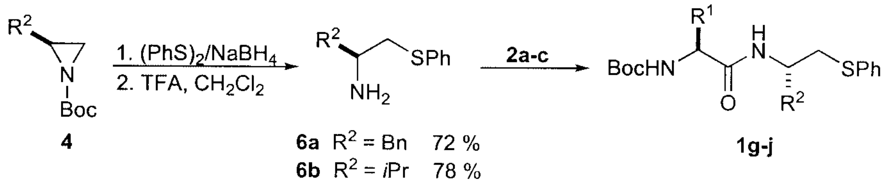


Scheme 3. Preparation of **1**.

Table 1. Synthesis selenium-containing amino acid derivatives 1.[a]

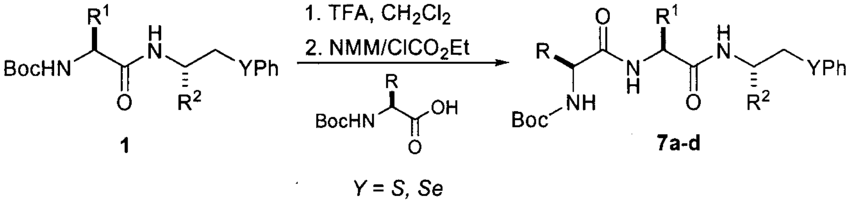
Entry	Acid	Amine	Product	Yield (%)[b]
1	**2a**	**3a**	 **1a**	98
2	**2b**	**3a**	 **1b**	97
3	**2a**	**3b**	 **1c**	85
4	**2b**	**3b**	 **1d**	83
5	**2c**	**3a**	 **1e**	82
6	**2c**	**3b**	 **1f**	84
7	**2a**	**6a**	 **1g**	90
8	**2b**	**6b**	 **1h**	71
9	**2c**	**6a**	 **1i**	67
10	**2c**	**6b**	 **1j**	68

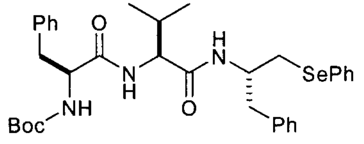
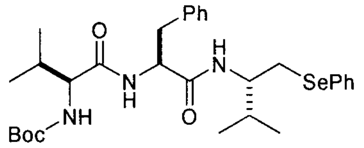
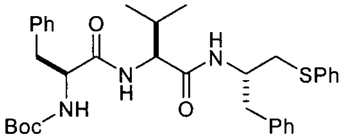
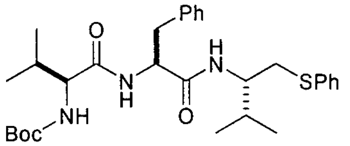
[a] Reaction performed on a 0.5 mmol scale with *N*-Boc amino acid **2**, NMM (1 equiv.), $ClCO_2Et$ (1 equiv.) and the seleno amine **2** (1 equiv.), in chloroform (5 mL). [b] Yields of isolated materials.



Scheme 4.

Table 2. Synthesis of selenium-containing peptides 7.



Entry	Acid	Amine	Product	Yield (%)[a]
1	**2b**	**1a**	 **7a**	92
2	**2a**	**1d**	 **7b**	87
3	**2b**	**1g**	 **7c**	83
4	**2a**	**1h**	 **7d**	89

[a] Yields of isolated materials.

dichloromethane at room temperature, followed by neutralization of the resulting TFA salt with K_2CO_3. With the free amine in our hands, we carried out the chain extension using the same protocol employed earlier. Indeed, tripeptide-like **7** could be smoothly obtained in high yields under our standard coupling conditions and the results are depicted in Table 2. The reaction worked very well for both, sulfur and selenium derivatives.

3. Conclusions

In summary, we have described herein a new class of chiral selenium-containing amino acid derivatives and peptides, which were prepared in a concise and flexible synthetic route in good yields and that permits the preparation of a wide range of compounds with a highly modular character, thus allowing the synthesis of small libraries of new chiral selenium compounds.

We also believe that this modular approach may have significant importance in the design of new selenium-containing compounds for biological screenings and as a chiral pool to the design of new ligands for asymmetric catalysis as well.

Experimental Section

General Procedure for the Synthesis of 1: Under an argon atmosphere, *N*-methylmorpholine (50 mg, 0.5 mmol) was added to a solution of the *N*-Boc-protected amino acid **2** (0.5 mmol) in chloroform (5 mL) at 0 °C. After stirring for 15 minutes at this temperature, ethyl chloroformate (54 mg, 0.5 mmol) was added and stirring was prolonged for additional 30 minutes at 0 °C before addition of **3** (0.5 mmol). The resulting reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 16 h. After this time it was diluted with chloroform and washed with 1 M NaOH (2 × 10 mL), 1 M HCl (2 × 10 mL), and brine (10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography, when required, eluting with a mixture of hexanes/ethyl acetate (80:20).

***tert*-Butyl *N*-<(1*S*)-1-{[(1*S*)-1-Benzyl-2-(phenylselanyl)ethyl]aminocarbonyl}-2-methylpropyl>carbamate (1a):** Yield 98%; $[\alpha]_D^{20}$ = +22 (c = 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.49–7.48 (m, 2 H), 7.25–7.11 (m, 8 H), 6.10 (br., 1 H), 4.96 (br., 1 H), 4.39–4.38 (m, 1 H), 3.80–3.76 (m, 1 H), 3.02–3.01 (m, 2 H), 2.92–2.90 (m, 2 H), 2.01–2.11 (m, 1 H), 1.43 (s, 9 H), 0.97–0.80 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 171.0, 155.8, 137.2, 135.3, 132.8, 129.8, 129.3, 128.7, 126.7, 126.4, 79.8, 60.1, 50.3, 40.0, 32.2, 30.6, 28.3, 19.3, 17.5. HRMS: m/z calcd. for $C_{25}H_{34}O_3N_2Se + Na^+$ 513.1619, found 513.1626.

Supporting Information (see also footnote on the first page of this article): Full experimental procedures and characterization of compounds are provided.

Acknowledgments

The authors are indebted to CAPES, CNPq and FAPERGS for financial support. CAPES and CNPq are also acknowledged for providing PhD fellowships to D.S.L. and M.W.P., respectively.

---

[1] a) S. Hanessian, G. McNaughton-Smith, H.-G. Lombart, W. Lubell, *Tetrahedron* **1997**, *53*, 12789–12854; b) T. K. Chakraborty, S. Ghosh, S. Jayaprakash, *Curr. Med. Chem.* **2002**, *9*, 421–435; c) M. Rainaldi, V. Moretto, M. Crisma, E. Peggion, S. Mammi, C. Toniolo, C. Cavicchioni, *J. Pept. Sci.* **2002**, *8*, 241–252; d) E. Mann, A. Chana, F. Sanchez-Sancho, C. Puerta, A. Garcia-Merino, B. Herradon, *Adv. Synth. Catal.* **2002**, *344*, 855–867; e) S. Kee, S. D. S. Jois, *Curr. Pharm. Des.* **2003**, *9*, 1209–1224.

[2] a) S. Saitton, A. L. Del Tredici, N. Mohell, R. C. Vollinga, D. Boström, J. Kihlberg, K. Luthman, *J. Med. Chem.* **2004**, *47*, 6595–6602; b) Y. Lu, *Curr. Opin. Chem. Biol.* **2005**, *9*, 118–126.

[3] a) A. Giannis, F. Rubsam, *Advances in Drug Research*; Academic Press: London, **1997**; pp. 1–78; b) A. S. Ripka, D. H. Rich, *Curr. Opin. Chem. Biol.* **1998**, *2*, 441–452.

[4] a) G. V. Kryukov, S. Castello, S. V. Novoselov, A. V. Lobanov, O. Zehtab, R. Guigó, V. N. Gladyshev, *Science* **2003**, *300*, 1439–1443; b) L. C. Clark, G. F. Combs, B. W. Turnbull, E. H. Slate, D. K. Chalker, J. Chow, L. S. Davis, R. A. Glover, G. F. Graham, E. G. Gross, A. Krongrad, J. L. Lesher, H. K. Park, B. B. Sanders, C. L. Smith, J. R. Taylor, *J. Am. Med. Assoc.* **1996**, *276*, 1957–1996.

[5] a) K. C. Nicolaou, N. A. Petasis, in: *Selenium in Natural Products Synthesis* CIS, Inc.: Pennsylvania **1984**; and references cited therein; b) A. Krief, M. Derock, *Tetrahedron Lett.* **2002**, *43*, 3083; c) D. L. Klayman, W. H. H. Günter, in: *Organoselenium Compounds: Their Chemistry and Biology*, Wiley-Interscience: New York, **1973**; d) R. J. Shamberger, *Biochemistry of Selenium*, Plenum Press: New York, **1983**; e) For a review on the chemistry of biologically important synthetic organoselenium compounds, see: S. W. May, S. H. Pollock, *Drugs* **1998**, *56*, 959–964; f) G. Mugesh, W.-W. du Mont, H. Sies, *Chem. Rev.* **2001**, *101*, 2125–2179; g) C. W. Nogueira, G. Zeni, J. B. T. Rocha, *Chem. Rev.* **2004**, *104*, 6255–6286.

[6] a) T. C. Stadtman, *J. Biol. Chem.* **1991**, *266*, 16257–16260; b) T. C. Stadtman, *Annu. Rev. Biochem.* **1996**, *65*, 83–100; c) T. C. Stadtman, *Annu. Rev. Biochem.* **2002**, *71*, 1–16; d) Y. Ogasawara, G. M. Lacourciere, K. Ishii, T. C. Stadtman, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 1012–1016.

[7] For recent reviews concerning thiopeptides and lanthibiotics, see: a) M. C. Bagley, J. W. Dale, E. A. Merritt, X. Xiong, *Chem. Rev.* **2005**, *105*, 685–714; b) C. Chatterjee, M. Paul, L. Xie, W. A. van der Donk, *Chem. Rev.* **2005**, *105*, 633–683.

[8] For selected examples, see: a) A. L. Braga, H. R. Appelt, P. H. Schneider, C. C. Silveira, L. A. Wessjohann, *Tetrahedron: Asymmetry* **1999**, *10*, 1733–1738; b) A. L. Braga, S. J. N. Silva, D. S. Lüdtke, R. L. Drekener, C. C. Silveira, J. B. T. Rocha, L. A. Wessjohann, *Tetrahedron Lett.* **2002**, *43*, 7329–7331; c) A. L. Braga, P. Milani, M. W. Paixão, G. Zeni, O. E. D. Rodrigues, E. F. Alves, *Chem. Commun.* **2004**, 2488–2489; d) P. H. Schneider, H. S. Schrekker, C. C. Silveira, L. A. Wessjohann, A. L. Braga, *Eur. J. Org. Chem.* **2004**, 2715–2722; e) A. L. Braga, M. W. Paixão, P. Milani, C. C. Silveira, O. E. D. Rodrigues, E. F. Alves, *Synlett* **2004**, 1297–1299; f) A. L. Braga, D. S. Lüdtke, E. E. Alberto, L. Dornelles, W. A. Severo Filho, V. A. Corbellini, D. M. Rosa, R. S. Schwab, *Synthesis* **2004**, 1589–1594; g) A. L. Braga, D. S. Lüdtke, F. Vargas, M. W. Paixão, *Chem. Commun.* **2005**, 2512–2514; h) A. L. Braga, J. A. Sehnem, D. S. Lüdtke, G. Zeni, C. C. Silveira, M. I. Marchi, *Synlett* **2005**, 1331–1333.

[9] A. L. Braga, M. W. Paixão, D. S. Lüdtke, C. C. Silveira, O. E. D. Rodrigues, *Org. Lett.* **2003**, *5*, 2635–2638.

[10] Chiral amino alcohols were easily obtained by reduction of the corresponding amino acids following the procedure described by Meyers. M. J. McKennon, A. I. Meyers, K. Drauz, M. Schwarm, *J. Org. Chem.* **1993**, *58*, 3568–3571.

[11] a) A. L. Braga, F. Vargas, C. C. Silveira, L. H. Andrade, *Tetrahedron Lett.* **2002**, *43*, 2335–2337. See also: b) J. Eilers, J. Wilkens, J. Martens, *Tetrahedron: Asymmetry* **1996**, *7*, 2343–2357.

[12] T. W. Greene, P. G. M. Wuts, in: *Protective Groups in Organic Synthesis* 3rd ed.; John Wiley and Sons: New York, **1999**.

[13] G. Bashiardes, S. G. Davies, *Tetrahedron Lett.* **1987**, *28*, 5563–5564.

[14] a) M. A. Ondetti, D. W. Cushman, *Science* **1977**, *196*, 441–444; b) D. W. Cushman, H. S. Cheung, E. F. Sabo, M. A. Ondetti, *Biochemistry* **1977**, *16*, 5484–5491.

Received: July 14, 2005