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SmI_2-Mediated Couplings of α-Amino Acid Derivatives. Formal Synthesis of (−)-Pumiliotoxin 251D and (±)-Epiquinamide

Vagner D. Pinho,[†] David J. Procter,[‡] and Antonio C. B. Burtoloso*,[†]

Instituto de Química de São Carlos, Universidade de São Paulo, CEP 13560-970, São Carlos, SP, Brazil, and The School of Chemistry, University of Manchester, Manchester, M13 9PL, U.K.

antonio@iqsc.usp.br

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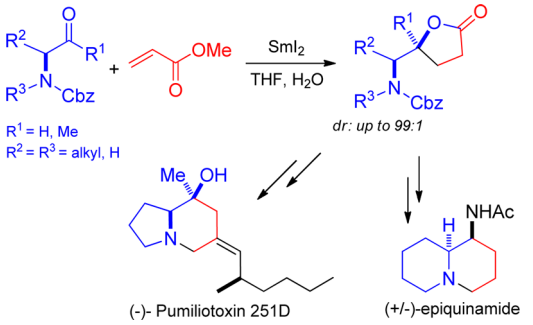
ABSTRACT



The coupling between cyclic and acyclic α-amino acid derivatives and methyl acrylate, mediated by samarium diiodide, is described. The method constitutes a powerful tool to construct indolizidine, quinolizidine, and piperidine systems in a straightforward two-step fashion. The formal synthesis of (−)-pumiliotoxin 251D and (±)-epiquinamide is achieved after two or three steps from these amino acid derivatives.

N-Heterocycles are of remarkable importance in the fields of asymmetric catalysis, chemical-biology, and medicinal chemistry, and they continue to inspire the development of new synthetic methodologies. Among them, indolizidine, quinolizidine, and piperidine alkaloids play an important role due to their interesting framework and biological activities. These compounds are very widespread in nature and are found in a myriad of organisms.[1] Although the literature describes plenty of methods to prepare these heterocyclic systems, short, direct, and diversity-oriented approaches are scarce.

Samarium(II) iodide (SmI_2) is a powerful reagent in organic synthesis[2] and has been applied with success in the synthesis of many nitrogen and oxygen heterocycles. Due to its great potential as a one electron donor, it is capable of mediating a wide range of transformations.[2,3]

The coupling between acrylates and aldehydes (or ketones) mediated by SmI_2 was first described by Fukuzawa[4] and Inanaga.[5] This reaction has proven to be one of the most

[†] Universidade de São Paulo.
[‡] University of Manchester.

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *25*, 139. (d) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603. (e) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625. (f) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458. (g) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719. (h) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520. (i) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 579 and references therein cited.

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(4) (a) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624. (b) Fukuzawa, S.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920. (c) Fukuzawa, S.; Seki, K.; Tasuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482.

(5) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763.

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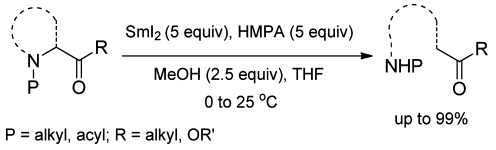
important transformations[3e,6] in the chemistry of SmI_2 and has been applied to the construction of a range of carbon frameworks in recent years.[7] However, a strong limitation of this method arises when α-amino-aldehydes/ketones are employed as substrates. As described by Honda,[8] the exposure of these aldehydes/ketones to SmI_2 is typically accompanied by C−N bond scission α to the carbonyl group (Scheme 1). Herein, we describe for the first time the Fukuzawa and Inanaga couplings of amino-aldehydes/ketones and methyl acrylate, without C−N bond cleavage, and the application of such couplings in the direct construction of functionalized indolizidine, quinolizidine, and piperidine systems (Scheme 2). In just two key transformations the method allows the synthesis of indolizidine **1** and quinolizidine **2**, advanced intermediates in the total syntheses of pumiliotoxin 251D[9,10] and epiquinamide,[11] respectively.

Scheme 1. Honda's Work on Reductive Deamination



We started our study by investigating the coupling between commercially and readily available (*S*)-*N*-Boc-prolinal or (*S*)-*N*-Cbz-prolinal[12] and methyl acrylate (Table 1).

As depicted in Table 1, the proton source, amount of methyl acrylate, and order of addition were investigated during the optimization of the reaction. The addition of 1−2 equiv of methyl acrylate in the presence of *t*-BuOH, MeOH, or H_2O as proton sources gave low yields of lactone products (23−31%, entries 1−6). Using 10 equiv of methyl acrylate, lactones **5** and **6** were provided in 43−75% yield (entries 7−11). For this case, the use of H_2O as the proton source[13] seemed to be the best choice. It is interesting to mention that lactones **5** and **6** were formed as single diastereomers[14] and that no products arising from C−N bond cleavage were observed.

Scheme 2. This Work: Sm(II)-Mediated Coupling Strategy for the Construction of Piperidines, Indolizidines, and Quinolizidines

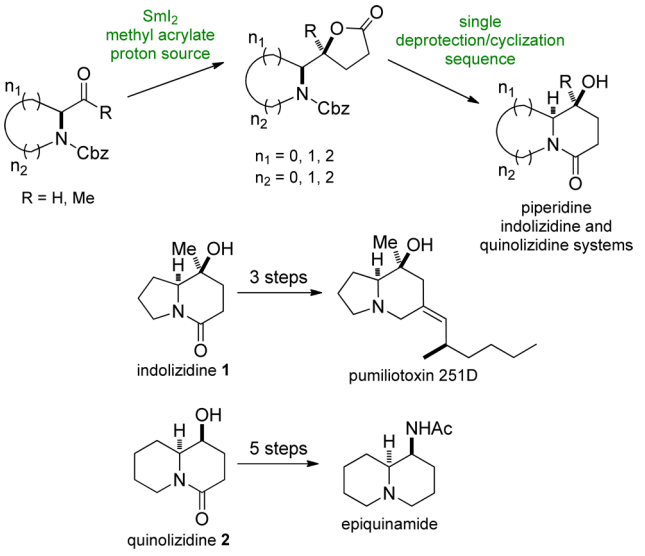
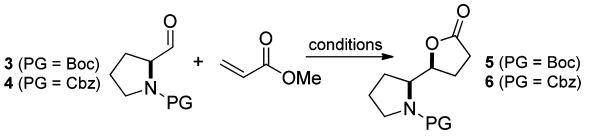


Table 1. Optimizing the Sm(II)-Mediated Couplings



entry	PG	acrylate (equiv)	SmI_2 (equiv)	proton source (equiv)	yield (%)
1	Cbz	2	2	*t*-BuOH (1)	23[a]
2	Boc	2	2	*t*-BuOH (1)	23[a]
3	Boc	2	2	*t*-BuOH (5)	31[a]
4	Boc	2	2	MeOH (5)	30[a]
5	Boc	1	3	*t*-BuOH (1)	27[a]
6	Boc	2	4	H_2O (5)	24[c]
7	Boc	10	2.5	MeOH (5)	43[b−d]
8	Boc	10	2.5	H_2O (5)	55[b,c]
9	Cbz	10	2.5	MeOH (5)	48
10	Boc	10	2.5	H_2O (5)	65[b−d]
11	Cbz	10	2.5	H_2O (5)	75[b−d]

[a] Recovery of starting aldehyde. [b] SmI_2 added to starting material. [c] H_2O added to SmI_2 before addition of starting material to SmI_2. [d] Syringe pump addition of SmI_2.

(6) (a) Vogel, J. C.; Butler, R.; Procter, D. J. *Tetrahedron* **2008**, *64*, 11876. (b) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Chem. Commun.* **2003**, 1402. (c) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Biomol. Chem.* **2004**, *2*, 2476. (d) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (e) Kerrigan, N. J.; Upadhyay, T.; Procter, D. J. *Tetrahedron Lett.* **2004**, *45*, 9087. (f) Xu, M.-H.; Wang, W.; Lin, G. *Org. Lett.* **2000**, *2*, 2229. (g) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G. *J. Org. Chem.* **2001**, *66*, 3953. (h) Wang, W.; Zhong, Y.; Lin, G. *Tetrahedron Lett.* **2003**, *44*, 4613. (i) Zhang, Y.; Wang, Y.; Dai, W.-M. *J. Org. Chem.* **2006**, *71*, 2445.

(7) (a) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140. (b) Kaname, M.; Yoshifuji, S. *Tetrahedron Lett.* **1992**, *33*, 8103. (c) Tadano, K.; Isshiki, Y.; Minami, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 6266. (d) Molander, G. A.; Sono, M. *Tetrahedron* **1998**, *54*, 9289. (e) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859–8862. (f) Carroll, G. L.; Little, R. D. *Org. Lett.* **2000**, *2*, 2873. (g) Shirahama, H.; Kamabe, M.; Miyazaki, T.; Hashimoto, K. *Heterocycles* **2002**, *56*, 105. (h) Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 3943. (i) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811.

(8) Honda, T.; Ishikawa, F. *Chem. Commun.* **1999**, 1065.

(9) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652–2656.

(10) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, *2002*, 3315.

(11) Wijdeven, M. A.; Wijtmans, R.; Van den Berg, R. J. F.; Noorduin, W.; Schoemaker, H. E.; Sonke, T.; Van Delft, F. L.; Blaauw, R. H.; Fitch, R. W.; Spande, T. F. *Org. Lett.* **2008**, *10*, 4001.

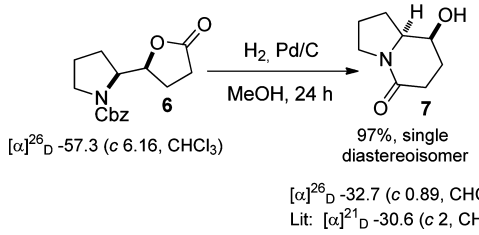
(12) Prolinals **3** and **4** can also be prepared in multigram quantities and in two or three steps from the cheap amino acid proline.

(13) Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012**, *48*, 330.

(14) Due the presence of rotamers in the NMR spectra of lactones, the diastereoselectivity was securely determined after the sequence of deprotection and lactamization.

The conversion of lactone **6** to an indolizidine system, as well as the proof of its stereochemistry, was accomplished after a one-pot synthesis of the known octahydroindolizidin-8-ol **7**.[15] Treatment of **6** with H_2 and Pd/C in MeOH for 24 h afforded indolizidine **7** in 97% yield after Cbz deprotection and lactamization (Scheme 3).

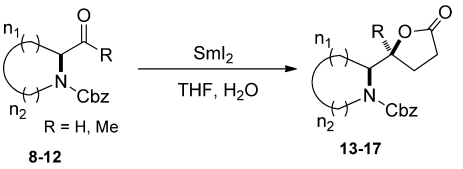
Scheme 3. Construction of an Indolizidine System from Lactone **6**

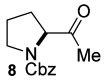
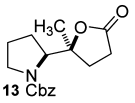
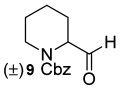
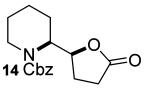
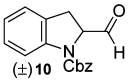
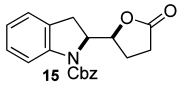
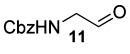
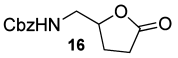
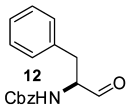
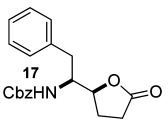


Employing the optimized conditions described in entry 11 (Table 1), we then turned our attention to the Sm(II)-mediated coupling reaction of other amino acid derivatives, in order to access different indolizidine, quinolizidine, and piperidine systems. Targeting the formal syntheses of pumiliotoxin 251D and (±)-epiquinamide, we first elected (*S*)-proline-derived methyl ketone **8** and *N*-Cbz-(±)-pipecolinal **9**, respectively, to study the Sm(II) reaction (Table 2). Moreover, considering the importance of indole moieties in natural products and medicinal chemistry[16] we also employed indoline-2-carboxylic acid derived aldehyde **10** as a substrate. Acyclic aldehydes **11**–**12** were also studied in the Sm(II)-mediated coupling. After the coupling of carbonyl compounds **8**–**12** with methyl acrylate, lactones **13**–**17** were obtained in 42–65% yields. Identical to what was observed in the case of lactone **6**, all these reactions furnished the *threo* isomer with good to complete diastereoselectivity. The stereochemistry of the coupling products was assigned by comparison of the NMR data of the lactones, and the stereochemistry of the corresponding cyclized products, with those of known compounds, and by crystallographic analysis of lactam **18**, derived from lactone **15** (Scheme 4).

To show the utility of the present method for the expedited preparation of indolizidine and quinolizidine systems, the formal syntheses of pumiliotoxin 251D and epiquinamide were accomplished from lactones **13** and **14**,

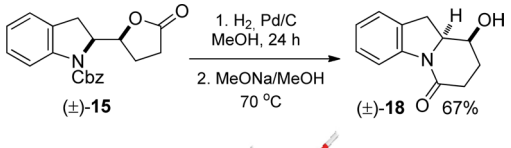
Table 2. Extension of the Sm(II)-Mediated Coupling to Other Amino Acids Derivatives

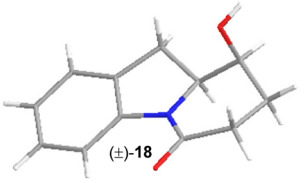


entry	aldehyde[a]	coupling product	yield	dr
1			60%[b]	1:0
2			65%	3:1
3			56%	2:1
4			42%	-
6			47%	1:0

[a] 0.25 mmol scale. [b] Yield based on two experiments each, with 0.25 and 4.0 mmol scale of starting material.

Scheme 4. X-ray Study of Lactam **20**

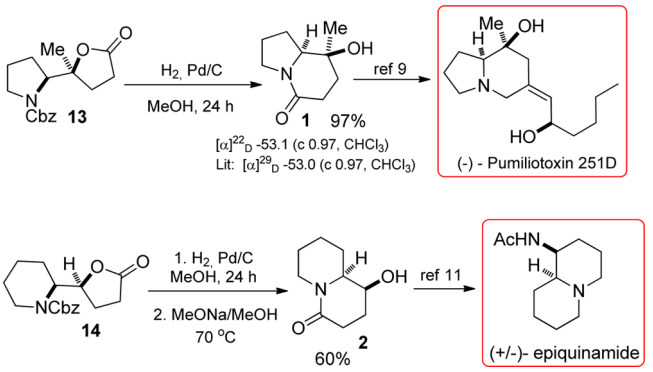




respectively, after Cbz removal and lactamization (Scheme 5).[17] *Threo* isomer **13**, obtained as a single isomer after the Sm(II)-mediated coupling, was converted to lactam **1** in a quantitative yield. Compound **1** not only is the key intermediate in the total synthesis of pumiliotoxin 251D described by Gallagher[9] but also constitutes the principal bicyclic core of the pumiliotoxins. Many additional routes to this intermediate have been published to date,[10,17b,18] but just a few of them provide compound **1** in a straighforward fashion. For the formal synthesis

(15) Lee, H. K.; Chun, J. S.; Pak, C. S. *J. Org. Chem.* **2003**, *68*, 2471.
(16) (a) De Sa Alves, F. R.; Barreiro, E. J.; Manssour Fraga, C. A. *Mini-Rev. Med. Chem.* **2009**, *9*, 782. (b) Joule, J. A. *Science of Synthesis (Houben-Weyl, Methods of Molecular Transformations)*; Georg Thieme Verlag: Stuttgart, 2000; Vol.10, pp 361–652. (c) Bonjoch, J.; Bosch, J. *Alkaloids* **1996**, *48*, 75. (d) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (e) Saxton, J. E. *The Chemistry of Heterocyclic Compounds*; Academic Press: New York, 1994; Vol. 25, Part IV. (f) Chadwick, D. J.; Jones, R. A.; Sundberg, R. J. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984; Vol. 4, pp 155–376.
(17) For a straightforward preparation of lactones similar to **13** and **14**, employing the addition of silyloxyfurans to iminion ions, see: (a) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, *1*, 55. (b) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905. (c) Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999. (d) de Oliveira, M. C.; Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6995.

Scheme 5. Formal Syntheses of Pumiliotoxin (−)-251D and (±)-Epiquinamide



of epiquinamide, racemic piperidine **14** was employed, in an analogous sequence. The spectroscopic data of **1** and **2** (Scheme 5) were in complete accordance with those described in the literature.[9−11]

In summary, we have demonstrated a straightforward approach for the construction of hydroxylated indolizidine, quinolizidine, and piperidine systems from cyclic and acyclic α-amino acid derivatives. Key to the approach is a highly diastereoselective SmI_2-mediated coupling of α-amino acid derivatives with methyl acrylate, followed by protecting group removal and lactamization. The approach has been used in the short formal syntheses of pumiliotoxin 251D and epiquinamide. To our knowledge, the new syntheses are among the shortest reported to date.

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Supporting Information Available. NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) (a) Cossy, J.; Cases, M.; Gomez Pardo, D. *Synlett* **1996**, 909. (b) Cossy, J.; Cases, M.; Gomez Pardo, D. *Bull. Soc. Chim. Fr.* **1997**, *134*, 141. (c) Barrett, A. G. M.; Damiani, F. *J. Org. Chem.* **1999**, *64*, 1410. (d) Ni, Y.; Zhao, G.; Ding, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3264. (e) Wang, B.; Fang, F.; Lin, G. *Tetrahedron Lett.* **2003**, *44*, 7981–7984. (f) O'Mahony, G.; Nieuwenhuyzen, M.; Armstrong, P.; Stevenson, P. J. *J. Org. Chem.* **2004**, *69*, 3968. (g) Wu, H.; Yu, M.; Zhang, Y.; Zhao, G. *Chin. J. Chem.* **2009**, *27*, 183.