ORGANIC LETTERS

2008
Vol. 10, No. 3
369−372

Structural Characterization of an Enantiomerically Pure Amino Acid Imidazolide and Direct Formation of the β-Lactam Nucleus from an α-Amino Acid

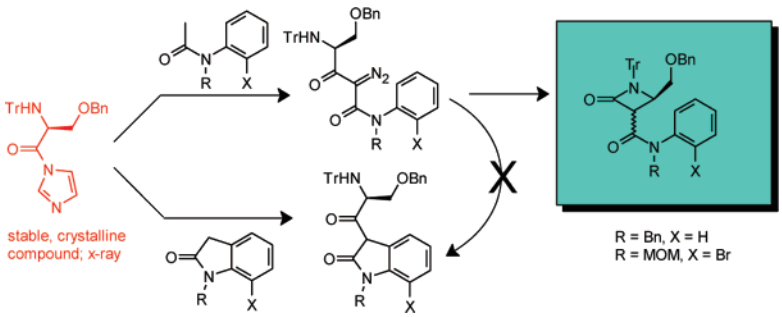
Brian S. Gerstenberger, Jinzhen Lin, Yvette S. Mimieux, Lauren E. Brown, Allen G. Oliver, and Joseph P. Konopelski*

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

joek@chemistry.ucsc.edu

Received October 25, 2007

ABSTRACT



Decomposition of a diazo β-ketoamide derived from *N*-trityl serine imidazolide and *N*-protected acetanilides provides, instead of the expected 3-acyloxindole product, an enantiomerically pure (EP) β-lactam. The amino acid stereocenter is incorporated, the second chiral center is induced, and trityl protection of the β-lactam ring is realized for the first time. The desired 3-acyloxindole is obtained from oxindole and Tr-Ser(OBn)-imidazole, the X-ray of which provides the first structural determination of an EP amino acid imidazolide.

Nitrogen heterocycles occupy a premier position in both natural product chemistry and pharmaceutical science, and both azetidin-2-ones (β-lactams) and indoles are among the most investigated of such ring systems due to their well-documented impact on small molecule drug discovery. In addition, enantiomerically pure (EP) β-lactams act as multifunctional organic motifs for the elaboration of more complex targets[1] and as rigid β-turn scaffolds.[2,3] Furthermore, the facile synthetic relationship between β-amino acids[4] and β-lactams[5] and the vibrant interest in polymers of EP β-amino acids ("β-foldamers")[6,7] ensures that research into this strained four-membered ring system will continue unabated.

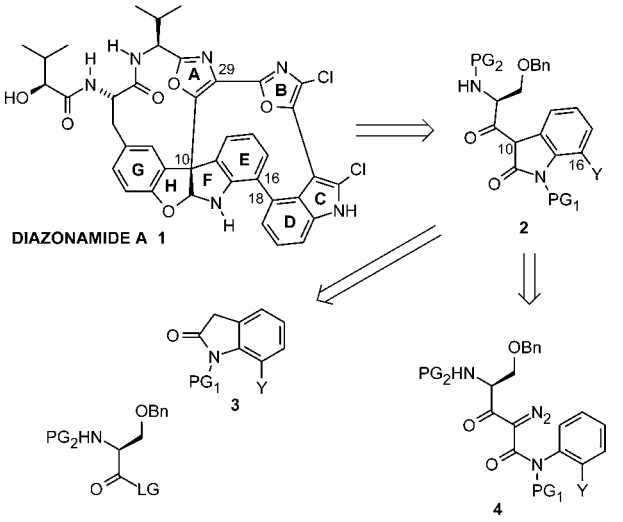
For our synthesis[8] of the marine natural product diazonamide A (**1**)[9] we required the construction of highly functionalized 3-acyloxindole **2**. Two approaches were conceived

(1) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226−240.
(2) Maier, T. C.; Frey, W. U.; Podlech, J. *Eur. J. Org. Chem.* **2002**, 2686−2689.
(3) Palomo, C.; Aizpurua, J. M.; Balentová, E.; Jimenez, A.; Oyarbide, J.; Fratila, R. M.; Miranda, J. I. *Org. Lett.* **2007**, *9*, 101−104.
(4) (a) Juaristi, E. *Enantioselective Synthesis of β-Amino Acids*; Wiley-VCH: New York, 1997. (b) Juaristi, E.; Soloshonok, V. *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Wiley: New York, 2005.
(5) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I. The Synthesis of β-Amino Acids and Their Derivatives from β-Lactams. In *Enantioselective Synthesis of β-Amino Acids*; Wiley-VCH: New York, 1997; Chapter 14. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. The Synthesis of β-Amino Acids and Their Derivatives from β-Lactams: Update. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Wiley: New York, 2005; Chapter 20.

10.1021/ol7025922 CCC: $40.75 © 2008 American Chemical Society
Published on Web 01/09/2008

(Scheme 1). One sought direct acylation of the corresponding C3-unsubstituted oxindole (**3**, PG = protection group, Y = H or halogen) with a serine derivative (LG = leaving group). The second route relied on diazo compound **4**, which would

Scheme 1. Diazonamide A Retrosynthesis

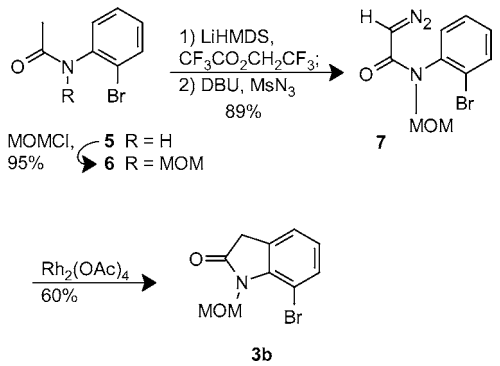


be subjected to Rh^{II}-catalyzed decomposition to promote C−H insertion and oxindole formation as described by Doyle.[10] Herein we report that each of these synthetic routes led to unexpected discoveries. The direct acylation route led to the first isolation and structural characterization of an EP amino acid imidazolide and culminated with the synthesis of **2**. The Rh^{II}-catalyzed C−H insertion route did not lead to **2**, but rather to the first reported direct transformation of an EP α-amino acid derivative to the *β*-lactam nucleus with complete retention of absolute stereochemistry and induction of the second ring chiral center.

The literature describes very few examples of oxindole acylation at C3 and no examples employing amino acids or their derivatives, some of which are prone to racemization. We were guided to trityl (Tr) protection of the serine amine functionality (PG_2) for both routes to **2** by the body of work in this area from the Rapoport group and the documented chiral stability of such derivatives.[11] It was also hoped (for the sequence of **4** to **2**) that this protection scheme would prevent not only N−H insertion[12] of the reactive carbenoid to the amino acid nitrogen but also C−H insertion into the serine side chain. The acid imidazolide was chosen for ease of preparation[13] and compatibility with the acid-labile trityl group.

Oxindoles **3** were prepared from two different routes. *N*-Benzyloxindole (**3a**) was prepared from isatin by a recently published procedure.[14] Unfortunately, the corresponding MOM-protected 7-bromoisatin did not produce the desired material from this procedure nor was the *N*-protection of 7-bromooxindole successful. Therefore, a more general and higher-yielding route to **3b** was developed that employed acetanilide **5**, prepared in quantitative yield from 2-bromoaniline (Scheme 2). Protection of **5** afforded **6** in excellent

Scheme 2. Oxindole Preparation



yield. The anion of **6** (LiHMDS) was reacted with 2,2,2-trifluoroethyl trifluoroacetate yielding the trifluoro-*β*-ketoamide, which could be converted without purification into **7** in 89% yield through diazo transfer (MsN_3/DBU) and in situ ketone cleavage during workup (10% NaOH).[15] This diazo compound underwent clean C−H insertion yielding **3b** in 60% (50% overall yield from **5**).

Standard in situ[13] reaction of Tr-Ser(OBn)-OH with 1,1′-carbonyldiimidazole (CDI, 1.05 equiv) afforded the expected solution of acid imidazolide **8** and imidazole, which was added directly to the anion of oxindoles **3a,b**. Reaction yields were variable and were ascribed to such factors as incomplete imidazolide formation,[16] the presence of imidazole in the solution of acid imidazolide, and difficulties in managing the reactive oxindole anion content in the presence of growing amounts of more acidic *β*-ketolactam product.

(6) (a) Gelman, M. A.; Gellman, S. H. Using Constrained *β*-Amino Acid Residues to Control *β*-Peptide Shape and Function. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Wiley: New York, 2005; Chapter 22. (b) Campo, M. A.; Escalante, J.; Šebesta, R. *β*-Amino Acids with Proteinogenic Side Chains and Corresponding Peptides: Synthesis, Secondary Structure, and Biological Activity. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Wiley: New York, 2005; Chapter 23.

(7) Seebach, D.; Kimmerlin, T.; Šebesta, R.; Campo, M. A.; Beck, A. K. *Tetrahedron* **2004**, *60*, 7455−7506.

(8) Konopelski, J. P.; Hottenroth, J. M.; Mónzo-Oltra, H.; Véliz, E. A.; Yang, Z.-C. *Synlett* **1996**, 609−11.

(9) (a) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2103−2304. (b) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765−4769; *Angew. Chem.* **2001**, *113*, 4901−4904. (c) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770−4773; *Angew. Chem.* **2001**, *113*, 4905−4909.

(10) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017−1022.

(11) Sim, T. B.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2532−2536.

(12) (a) Ferris, L.; Haigh, D.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2885−2888. (b) Aller, E.; Buck, R. T.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2879−2884.

(13) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72−74.

(14) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505−11515.

(15) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663−1666.

(16) Morton, R. C.; Mangroo, D.; Gerber, G. E. *Can. J. Chem.* **1988**, *66*, 1701−1705.

We postulated that isolation and purification of imidazolide **8**, if possible, could be used to improve the yield. To this end, Tr-Ser(OBn)-OH was reacted with excess CDI (1.5 equiv) to ensure complete conversion, followed by aqueous workup to remove the excess CDI. We were both pleased and surprised to find that this acid imidazolide, obtained in 97% yield, was a stable crystalline solid that was easily purified by column chromatography on silica gel.[17] Although a number of simple acid imidazolides have been shown to be isolable compounds,[18] the literature, to our knowledge, makes no mention of EP amino acid imidazolide stability, although these reactive amides are used extensively in synthesis.[19] Indeed, just the opposite appeared to be the case, as acid imidazolides are routinely prepared and immediately used without isolation because of their high reactivity.[13] We have also prepared stable crystalline acid imidazolides from Tr-Phe-OH and Tr-Val-OH.

A review of the Cambridge Crystal Structure Database reveals that there are very few examples of structurally characterized activated amino acid amide compounds. Compound **8** crystallizes in the chiral space group $C222_1$ (Figure 1). The position of the amine hydrogen, H3, was located

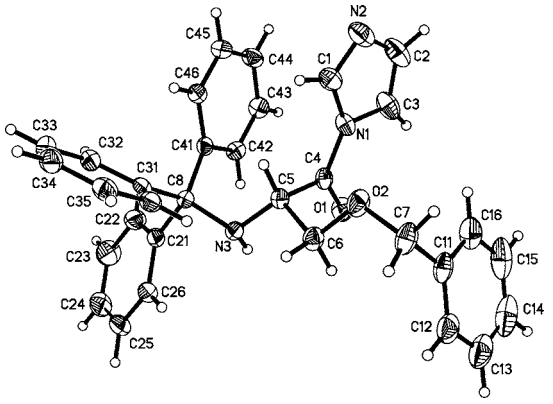
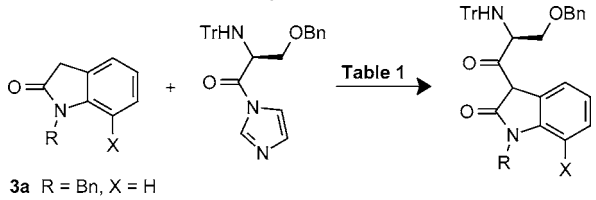


Figure 1. Solid-state structure of acid imidazolide **8**.

from a difference Fourier map. It is oriented toward the imidazole nitrogen, N2, of an adjacent, symmetry-related molecule giving rise to one-dimensional chains of H-bonded molecules running through the lattice parallel to the *a*-axis (N3···N2′ distance = 3.3243(19) Å, see table of hydrogen bonds).[20] The structure in Figure 1 confirms that chirality is retained throughout the synthesis. The bond distances and angles within the molecule are comparable to other, similar compounds.[21,22] For one of these studies[21b] it was speculated that the electron-donating properties of the trityl group stabilized the carbonyl to reaction by nucleophiles, whereas the more common carbamate protection groups for nitrogen are electron-withdrawing and activate the carbonyl.

With clean acid imidazolide **8** in hand, *C*-acylation under the previous conditions using the sodium anion of **3** provided a 10% increase in yield (Table 1, entry 5). The problem of

Table 1. Formation of 3-Acyloxindoles



entry	oxindole	base (equiv)	**8**	yield (%)
1	**3a**	NaH (1.0)	in situ	42
2	**3a**	NaH (4.0)	in situ	50
3	**3b**	NaH (2.0)	in situ	50
4	**3b**	LDA (2.0)	in situ	40
5	**3b**	NaH (2.0)	isolated	60
6	**3b**	Li-imidazolide (2.0)	isolated	70
7	**3b**	Li-imidazolide (5.0)	isolated	72

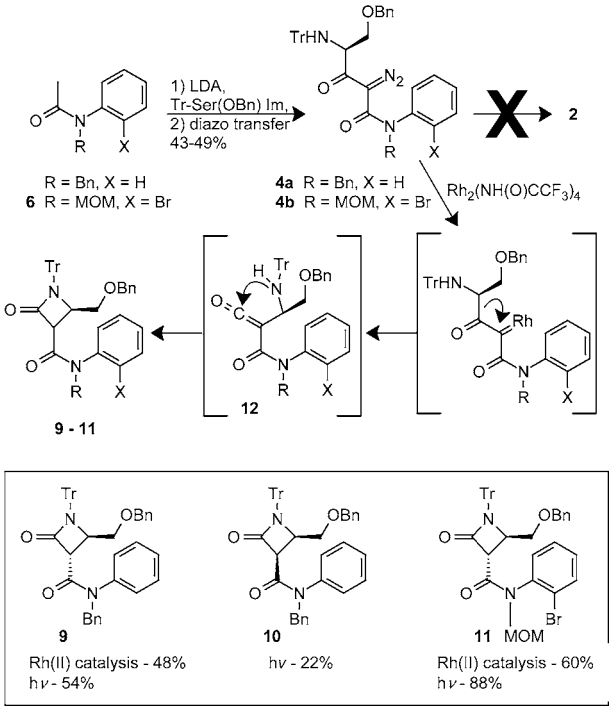
reactive anion management was solved by employing lithium imidazolide as base rather than the preformed anion of **3**. This final optimization led to a reproducible 72% yield of desired product **2**.

Success in the transformation of **7** to **3b** via the Rh^{II}-catalyzed C−H insertion reaction offered us excellent precedent for our second route to **2**, namely, diazo decomposition of **4**. Compounds **4a**,**b** were synthesized by acylation of the anions derived from *N*-benzylacetanilide and **6** (LDA) using in situ generated imidazolide **8**, which gave the β-ketoamides in 45−55% yield (Scheme 3). Treatment with mesyl azide (MsN_3)[23] or 4-acetamidobenzenesulfonyl azide with DBU gave the desired diazo compounds **4a**,**b** in 89% and 96% yield, respectively. However, no oxindole was observed upon rhodium-catalyzed diazo decomposition. Unexpectedly, we obtained the *trans*-trityl-protected β-lactam. The structure of *trans* isomer **9** was confirmed by X-ray crystallography. The *trans* isomer **11** was isolated in 60% yield by treatment with the rhodium catalyst.

This unexpected and unprecedented route to the β-lactam nucleus directly from an α-amino acid, to our knowledge the first documented transformation of its kind, is best explained mechanistically by invoking a stereospecific Wolff

(17) For a previous synthesis of **8**, without isolation, see Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, *64*, 126−132.
(18) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351−367.
(19) Staab, H. A.; Bauer, H.; Schneider, K. M. *Azolides in Organic Synthesis and Biochemistry*; Wiley-VCH: New York, 1998.
(20) The crystal structure for **8** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. 655083.
(21) (a) Barlos, K.; Papaioannou, D.; Voliotis, S.; Prewo, R.; Bieri, J. H. *J. Org. Chem.* **1985**, *50*, 696−697. (b) Sliedregt, K. M.; Schouten, A.; Kroon, J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1996**, *37*, 4237−4240. (c) Mamos, P.; Papaioannou, D.; Kavounis, C.; Nastopoulos, V. *Acta. Crystallogr.* **1997**, *C53*, 1973−1975.
(22) The crystal structure of achiral Tos-MeAib-Im has been reported. See (a) Toniolo, C.; Crisma, M.; Formaggio, F. *Biopolymers* **1996** *40*, 627−651. (b) Crisma, M.; Moretto, V.; Formaggio, F.; Toniolo, C. *Z. Kristallogr.* **1999**, *214*, 766−770.
(23) Taber, D. F.; Ruckle, R. E.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077−4078.

Scheme 3. Wolff Rearrangement to β-Lactam



rearrangement[24] to form ketene intermediate **12**, which undergoes intramolecular attack by the trityl-protected amine. Intramolecular ring closures of *N*-trityl groups have been observed previously.[25] Wolff rearrangements catalyzed by Rh(II) species are rare, but have been documented.[26] Furthermore, this appears to be the first known synthesis of a trityl protected β-lactam amide, as a recent effort to add a trityl group to the 4-membered lactam afforded poor yield.[27]

To support this mechanism, diazoketones **4** were decomposed with silver benzoate,[28] a well-known reagent for the Arndt−Eistert elongation of α- to β-amino acids, and with UV radiation.[29] Desired lactams **9**−**11** were isolated from each reaction, which supports the Wolff rearrangement pathway (through **12**) in the metal-catalyzed transformation. The cleanest and highest-yielding reactions were photochemical. Upon irradiation, compound **4a** gave a 2.5:1 separable mixture of *trans* and *cis* β-lactam isomers, respectively, in 76% yield. Comparison with the rhodium-catalyzed reaction (*vide supra*) revealed the presence of the *cis* isomer in the former reaction. However, only the *trans* isomer (88% yield) was isolated from irradiation of **4b** (Scheme 3, box). Wolff rearrangements generally proceed with retention of configuration;[30] this was verified for **9** by refinement of the X-ray data[31] (Flack parameter = 0.04 (11)). In addition, we have shown that the reaction is completely stereospecific; i.e., D-Tr-Ser(OBn)-imidazole (*ent*-**8**) affords the enantiomeric material *ent*-**9** as shown by chiral column HPLC; there is no indication of enantiomer formation in either reaction.

Questions concerning the origin and scope of this unexpected Wolff rearrangement, in contrast to N−H or C−H insertion, the utility of trityl protection of the β-lactam amide functionality and the facile access to stable crystalline amino acid imidazolides in high yield are currently under study in our laboratory and will be reported in due course.

Acknowledgment. We thank the NIH (CA98878) for generous support of this work. In addition, we thank the ACS-PRF Summer School, "Crystallography for Organic Chemists" for the opportunity for one of us (L.E.B.) to particpate and collect the data for **9**. Purchase of the 600 MHz NMR used in these studies was supported by funds from the National Institutes of Health (S10RR019918) and National Science Foundation (CHE-0342912). The single crystal X-ray diffraction data for **8** were recorded on an instrument supported by the National Science Foundation, Major Research Instrumentation (MRI) Program under Grant No. CHE-0521569.

Supporting Information Available: Synthetic procedures, complete spectroscopic data, ^{1}H and ^{13}C NMR spectra for all new compounds and CIF files for **8** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7025922

(24) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193−2256.
(25) May, J. P.; Fournier, P.; Pellicelli, J.; Patrick, B. O.; Perrini, D. M. *J. Org. Chem.* **2005**, *70*, 8424−8430.
(26) Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem.* **2005**, *70*, 5840−5851 and references therein.
(27) Reddy, D. R.; Iqbal, M. A.; Hudkins, R. L.; Messina-McLaughlin, P. A.; Mallamo, J. P. *Tetrahedron Lett.* **2002**, *43*, 8063−8066.
(28) Sudrik, S. G.; Maddanimath, T.; Chaki, N. K.; Chavan, S. P.; Chavan, S. P.; Sonawane, H. R.; Vijayamohanan, K. *Org. Lett.* **2003**, *5*, 2355−2358 and references therein.
(29) Podlech, J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 471−472.
(30) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: 1998; pp 498ff.
(31) The crystal structure for **9** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. 655084.