ORGANIC LETTERS

2001
Vol. 3, No. 13
1985−1987

Photoinduced Formation of β-Oxy-α,α-disubstituted-α-amino Acid Derivatives from Ketoximes

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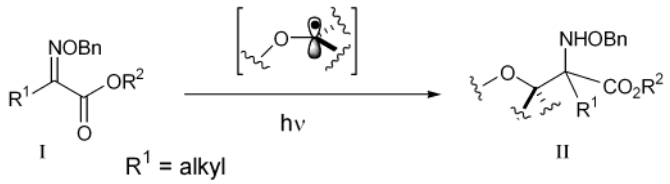
Received April 3, 2001

ABSTRACT



The first intermolecular radical addition onto ketoxime ethers is described. β-Oxygenated quaternary α-amino acid derivatives II were obtained upon irradiation of α-alkoxycarbonyl ketoxime ethers I in the presence of suitable α-alkoxy carbon radical precursors and a sensitizer.

Compounds with nitrogenated quaternary carbons display a wide variety of interesting properties. In addition to such synthetically challenging structures as the sodium channel blocker (−)-tetrodotoxin (**1**,[1] Figure 1),[2] they include quaternary α-amino acids, which are capturing the interest of a growing number of research groups in a variety of disciplines. Some quaternary α-amino acids have antibiotic or inhibitory activities;[3] others have a metabolic stability and conformational constraint that propitiate their use as peptidomimetics;[4] others, such as (+)-myriocin (**2**, Figure 1),[5] are immunosuppressants; and others have other biologically relevant properties.[6] The development of efficient synthetic protocols for the construction of quaternary nitrogen-bearing centers, and in particular of quaternary α-amino acids,[7] is therefore an important synthetic goal.

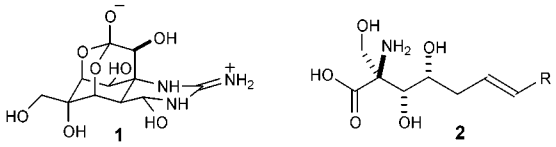


Figure 1. Two important examples of molecules with nitrogenated quaternary centers: (−)-tetrodotoxin (**1**) and (+)-myriocin (**2**; R = $(CH_2)_6C(O)(CH_2)_5CH_3$).

In principle, an attractive and versatile solution would be provided by the process outlined in eq 1, because it would give straightforward access to a variety of nitrogenated

(1) See: (a) Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745−2748. (b) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960−5968, and references therein.

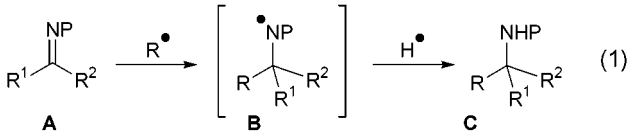
(2) Other examples include the following. (a) Huperzine A: Kozikowski, A. P.; Tückmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641−650. Qian, L.; Ji, R. *Tetrahedron Lett.* **1989**, *30*, 2089−2090. (b) Cephalotaxine: Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264−10269. Nagasaka, T.; Sato, H.; Saeki, S.-I. *Tetrahedron: Asymmetry* **1997**, *8*, 191−194. Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115−119. (c) The immunosuppressant FR901483: Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778−7786. Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593−4596. Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765−767. (d) Halichlorine: Trauner, D.; Schwarz, J. B. Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542−3545. Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *13*, 1847−1850.

(3) For antibiotics, see, for example: (a) Hanessian, S.; Haskell, T. H. *Tetrahedron Lett.* **1964**, *36*, 2451−2460. (b) Konishi, M.; Naruishi, M.; Tsuno, T.; Tsukiura, H.; Kawaguchi, H. *J. Antibiot.* **1973**, *26*, 757−764. For inhibitors, see, for example: (c) Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *64*, 120.

(4) (a) Veber, D. F.; Freidinger, R. M. *Trends Neurosci.* **1985**, *8*, 392. (b) Goodman, M.; Zhang, J. *Chemtracts* **1997**, *10*, 629−645. (c) Mossel, E.; Formaggio, F.; Crisma, M.; Toniolo, C.; Broxterman, Q. B.; Boesten, W. H. J.; Kamphuis, J.; Quaedflieg, P. J. L. M.; Temussi, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1305. (d) Bellier, B.; McCort-Tranchepain, I.; Ducos, B.; Danascimento, S.; Meudal, H.; Noble, F.; Garbay, C.; Roques, B. P. *J. Med. Chem.* **1997**, *40*, 3947.

10.1021/ol015930h CCC: $20.00
Published on Web 06/01/2001

quaternary derivatives **C** starting from common and easily available precursors **A**. Being a free radical reaction, this transformation should also enjoy mild reaction conditions and should be compatible with a wide range of functional groups. However, intermolecular radical addition onto C=N double bonds proved to be difficult. Even for aldoimine derivatives (other than formaldimines), efficiency has been achieved only recently;[8,9] for the more hindered ketoimines **A** there has hitherto been no success at all. We report here the first successful reaction of this type, which allows the preparation of quaternary α-amino acids from α-alkoxycarbonyl ketoxime ethers.

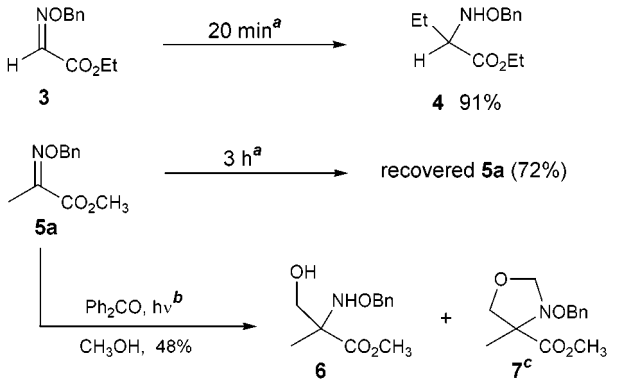


R^1 and R^2 = carbon substituents

In keeping with the above antecedents, our attempts to add primary, secondary, or tertiary alkyl radicals to methyl 2-(benzyloxyimino)propanoate (**5a**) under a variety of conditions all failed, including those that worked well for its aldoxime analogue **3** (Scheme 1). Addition did take place, however, when we used the comparatively more nucleophilic α-alkoxy carbon radicals. UV irradiation of a methanolic solution of **5a** in the presence of benzophenone afforded the desired quaternary derivative **6** by addition of hydroxymethyl radical.

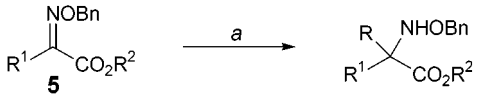
Addition of a 1-hydroxy-1-methylethyl radical derived from 2-propanol was also successful, giving the amino alcohol derivative **8** (Table 1, entry 1). The formation of **8**, which has two vicinal fully substituted carbon atoms, illustrates the ability of the radical process to introduce sterically demanding substituents at the quaternary center. With 1,3-dioxolane as solvent, the product was **9**, in which a formyl group masked as an ethylene glycol acetal has been efficiently introduced (74%).

Scheme 1



[a] Et_3B (500 mol %), toluene, Δ. [b] A 450 W Hanovia medium-pressure mercury lamp was employed. [c] Approximately one-third of adduct **6** was partially transformed into the protected methylene amino acetal **7** by reaction with formaldehyde generated in situ.

Table 1. Photoinduced Radical Addition onto Acyclic (**5a**) and Cyclic (**5b**) Ketoxime Ethers



entry	**5**: R^1, R^2	product: R	yield (%)
1[b]	**5a**: CH_3, CH_3	**8**: -C(OH)$(CH_3)_2$	58
2[c]	**5a**: CH_3, CH_3	**9**: -CH$(OCH_2)_2$	74, 80,[d] 85[e]
3[b]	**5b**: -CH_2CH_2-	**10**: -C(OH)$(CH_3)_2$	73
4[c]	**5b**: -CH_2CH_2-	**11**: -CH$(OCH_2)_2$	73

[a] **General Procedure**. A 0.02 M solution of the ketoxime ether in the appropriate solvent (see notes *b* and *c*), contained in a Pyrex vessel, was deoxygenated by bubbling Ar for 10 min. Benzophenone (100 mol %) was then added and the mixture was irradiated externally with a 450 W Hanovia medium-pressure mercury lamp. Once the substrate was consumed (TLC), the solvent was rotaevaporated and the adduct purified by flash chromatography (the table lists isolated yields). [b] 2-Propanol was used as solvent. [c] 1,3-Dioxolane was used as solvent. [d] $ZnCl_2$ (50 mol %) was added after deoxigenation. [e] *p*-TsOH (50 mol %) was added instead of $ZnCl_2$.

(5) For the biological significance of myriocin, see, for example: Chen, J. K.; Lane, W. S.; Schreiber, S. L. *Chem. Biol.* **1999**, *6*, 221−235 and references therein. For its total synthesis, see: (a) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1982**, 488−490. (b) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1613−1619. (c) Yosikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Chem Pharm. Bull.* **1994**, *42*, 994−996; *Tetrahedron* **1995**, *51*, 6209−6228. (d) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 2097−2100. (e) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887−7890. Formal synthesis: (f) Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R. *Tetrahedron Lett.* **1993**, *34*, 1653−1656. (g) Deloisy, S.; Thang, T. T.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1994**, *35*, 4783−4786. (h) Deloisy, S.; Thang, T. T.; Olesker, A.; Lukacs, G. *Bull. Chem. Soc.* **1996**, *133*, 581−585.

(6) Examples include the following. (a) (+)-Conagenin: Hatakeyama, S.; Fukuyama, H.; Mukugi, Y.; Irie, H. *Tetrahedron Lett.* **1996**, *37*, 4047−4050. Kovács-Kulyassa, A.; Herczegh, P.; Sztaricskai, F. *Tetrahedron* **1997**, *53*, 13883−13896. Enders, D.; Bartsch, M.; Runsink, J. *Synthesis* **1999**, 243−248. (b) (+)-Lactacystin. For a recent critical review, including synthetic contributions by E. J. Corey, J. E. Baldwin, H. Uno, N. Chida, S. Omura, A. B. Smith, III, J. Adams, and J. S. Panek, see: Masse, C. E.; Morgan, A. J.; Adams, J.; Panek, J. S. *Eur. J. Org. Chem.* **2000**, 2513−2528. For another recent review, see: Corey, E. J.; Li, W.-D. Z. *Chem Pharm. Bull.* **1999**, *47*, 1−10. See also: Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726−731. (c) Sphingofungines: Liu, D.-G.; Wang, B. Lin, G.-Q. *J. Org. Chem.* **2000**, *65*, 9114−9119. Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908−919. Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818−6819.

(7) For reviews, see: (a) Cativiella, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. (b) Cativiella, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645−732. (c) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem.* **1998**, 1337−1351. (d) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225−227. (e) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748. (f) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889−917.

(8) See: (a) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059−2060. (b) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951−3961, and references therein. For the use of sulfonyl-substituted oxime ethers as acylating agents, see: (c) Jeon, G.-H.; Yoon, J.-Y.; Kim, S.; Kim, S. S. *Synlett* **2000**, 128−130, and references therein.

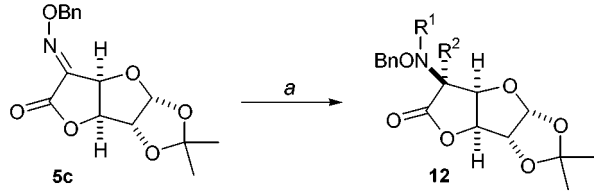
(9) Despite recent advances, and with the exception of ethyl radical, efficient intermolecular addition of unbranched carbon radicals to aldimine derivatives has yet to be achieved.

The reaction also worked with cyclic ketoximes. For example, **5b** afforded the quaternary derivatives **10** and **11** in good yields. Notably, **5b** was appreciably more reactive than its acyclic analogue **5a**: whereas 2 h were needed for near-total consumption of **5a** in 2-propanol, **5b** was completely consumed in only 20 min under identical reaction conditions.

A first survey on the influence of a protic or a Lewis acid on the efficiency of the process was investigated using the reaction of **5a** with 1,3-dioxolan-2-yl radical. Moderate improvements in the addition yield were observed when the reaction was performed in the presence of either $ZnCl_2$ or *p*-TsOH, which may be due to further activation of the C═N double bond by complexation or by protonation of the nitrogen (Table 1, entry 2).

Our synthetic interest in (+)-myriocin next led us to use the more complex ketoxime **5c** as substrate (Table 2).[10] To

Table 2. Photoinduced Radical Additions onto Ketoxime Ether **5c**



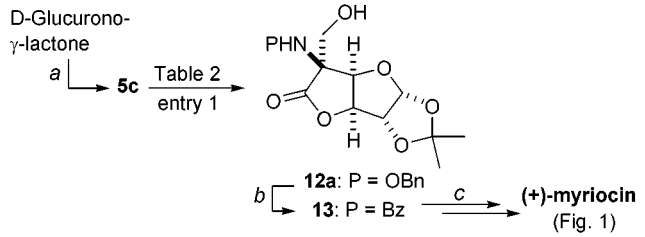
entry	solvent	product (yield, %)[b]	R^1, R^2
1	methanol	**12a** (42%)	H, -CH_2OH
		12b[c]	-CH_2OCH_3, -CH_2OH
		12c[c]	$R^1 + R^2$ = -CH_2OCH_2-
2	2-propanol	**12d** (70%)	H, -$C(OH)(CH_3)_2$
3	1,3-dioxolane	**12e** (74%)	H, -$CH(OCH_2)_2$
4	*t*-BuOMe	**12f** (47%)	H, -CH_2O*t*-Bu
5	CH_3CN[d]	**12g** (57%)	H, -$C(O)(CH_2)_4CH_3$

[a] As in Table 1. [b] Isolated yields. [c] Variable amounts (~10−15%) of **12b** and **12c** were obtained together with **12a**. [d] $CH_3(CH_2)_4CHO$ (10 equiv).

our delight, upon irradiation of **5c** in methanol addition of the hydroxymethyl radical took place with complete stereoselectivity, giving **12a** in a practical 42% yield at the 1 g scale (Table 2, entry 1). Subsequent N−O cleavage and selective N-benzoylation gave the amino alcohol **13**, which is known[5b,f] to be transformable into (+)-myriocin (Scheme 2). Even without optimization, the preparation of **13** from commercial glucuronolactone via adduct **12a**, as outlined in Scheme 2, compares favorably with previously reported procedures,[5f−h] in regard to both the number of steps and the overall yield.

With a view to the preparation of myriocin analogues, we also added other radicals to **5c**. Addition of 1-hydroxy-1-methylethyl and 1,3-dioxolan-2-yl radicals took place uneventfully as before to give **12d** and **12e** as single stereoisomers in good yields (Table 2, entries 2 and 3), and reaction

Scheme 2



[a] See ref 10. [b] 1. H_2, $Pd(OH)_2$, CH_3OH, 40 psi, rt, 86%. 2. BzCl, CH_3OH, 50%. [c] See refs 5b and 5f.

in *t*-BuOMe gave **12f** (Table 2, entry 4). Addition of acyl radicals derived from aldehydes was also possible using acetonitrile as solvent (Table 2, entry 5).

The success of the above reactions is in part ascribed to the stability of the starting α-alkoxycarbonyl ketoxime ethers **5a**−**c** under the reaction conditions.[11,12] Remarkably, they tolerate easily abstracted hydrogen atoms on the starting ketoximes **5**, in particular the benzylic hydrogens of the oxime ether group.

In summary, the procedures reported here allow easy access to α,α-disubstituted amino acids of type **II** starting from readily available ketoxime ethers **I**.[13] Thus, intermolecular radical addition onto C═N bonds involving fully substituted C has now been incorporated into the synthetic repertoire for the construction of nitrogen-bearing quaternary centers. The usefulness of this approach is illustrated by the quick preparation of the (+)-myriocin precursor **13** from cheap D-glucuronolactone and by the dioxolane derivatives **9**, **11**, and **12e**, which are versatile protected forms of α-formyl α,α-disubstituted α-amino acid derivatives that are susceptible to further transformation into a wide variety of nitrogenated quaternary compounds. Further exploration of the characteristics and scope of the new reaction is in progress.

Acknowledgment. This work was supported by the Xunta de Galicia under Grant PGIDT00PXI20901PR and by the Spanish Ministry of Education under Grant PB98-0606 and through a fellowship to S.T. We also thank Dr. P. B. Anzeveno for supplying experimental details on the preparation of **5c**.

Supporting Information Available: Experimental procedures, analytical data, and ^1H and ^{13}C NMR spectra of the addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Anzeveno, P. B.; Creemer, L. J. *Tetrahedron Lett.* **1990**, *31*, 2085−2088.

(11) Previous attempts at photochemical initiation of radical addition to aldimines failed: Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780−782.

(12) The behavior of **5a**−**c** contrasts strongly with that reported for the structurally related 5,6-dihydro-1,4-oxazin-2-ones, which upon Pyrex-filtered UV irradiation in 2-propanol undergo dimerization: Gaudiano, G.; Frank, E.; Wysor, M. S.; Averbuch, S. D.; Koch, T. H. *J. Org. Chem.* **1993**, *58*, 7355−7363, and references therein.

(13) Besides classical methods, new radical-mediated procedures allow the quick preparation of α-oximino lactones and acylated oxime ethers. See, respectively: Clive, D. L. J.; Subedi, R. *Chem. Commun.* **2000**, 237−238. Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190−12191.