Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1957–1960
Tetrahedron Letters

Synthesis of alexine-like compounds from chiral five-membered endocyclic enecarbamates

Marcelo Siqueira Valle [a], Pascal Retailleau [b], Carlos Roque Duarte Correia [a,*]

[a] *Institute of Chemistry, State University of Campinas—UNICAMP, PO Box 6154, CEP 13084-971, Campinas-SP, Brazil*
[b] *Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France*

Received 20 December 2007; revised 19 January 2008; accepted 21 January 2008
Available online 30 January 2008

Abstract

Stereoselective syntheses of enantiomerically enriched trihydroxy pyrrolizidine and indolizidines were accomplished from a common chiral endocyclic enecarbamate. The synthetic strategy features an efficient [2+2] cycloaddition of ketenes to the endocyclic enecarbamate and a highly regioselective Baeyer–Villiger oxidation of the intermediate azabicyclic-cyclobutanones. These new heterocycles are compounds structurally related to the alexines.

Polyhydroxylated indolizidines and pyrrolizidines form an important and diversified class of alkaloids. The structural complexity and the wide range of biological activity displayed by these natural compounds constitute one of the major impetus for their chemical synthesis. Alexine **1**,[1a] australine **2**[1b] and casuarine **3**[1c] are polyhydroxylated pyrrolizidine alkaloids exhibiting potent glucosidase inhibitory action and anti-HIV activity (Fig. 1).[1d,e] In a similar manner, polyhydroxylated indolizidines alkaloids, such as swainsonine **4**[2a] and castanospermine **5**,[2b] act as effective inhibitors of several glycosidases,[2c,d] also possessing antiviral activity.[1e]

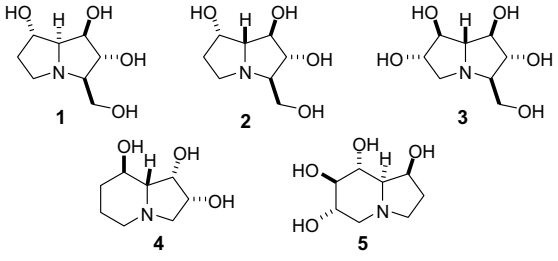


Fig. 1. Polyhydroxylated pyrrolizidine and indolizidine alkaloids.

Endocyclic enecarbamates are versatile and useful building blocks, which have been extensively used in the synthesis of N-heterocycles and alkaloids.[3,4] In particular, the five-membered endocyclic enecarbamates, bearing an electron-rich enamine functionality can undergo efficient [2+2] cycloaddition to ketenes to produce azabicyclic cyclobutanones. These compounds are key intermediates in the synthesis of a number of biologically active natural products.[3a–c,e,g]

In view of the great interest in the pharmacological properties of polyhydroxylated alkaloids, we decided to apply the [2+2] cycloaddition reaction of 5-membered endocyclic enecarbamates to ketenes as a direct access to novel polyhydroxylated N-heterocycles. Our synthetic strategy is illustrated in Figure 2 in which we demonstrate the synthesis of the new alexine-like compounds **6** and **7**, structurally related to alkaloids **1**–**5**. One of the key steps in this strategy involves a stereocontrolled [2+2] cycloaddition of haloalkylketenes to chiral endocyclic enecarbamate to form alkyl substituted azabicyclic cyclobutanones.

The required starting endocyclic enecarbamate **10** was synthesized in multigram scale following a protocol previously developed by us.[3i] The choice for a *tert*-butyl ester

* Corresponding author. Tel.: +55 19 3521 3086; fax: +55 19 3521 3023.
E-mail address: roque@iqm.unicamp.br (C. R. D. Correia).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.098

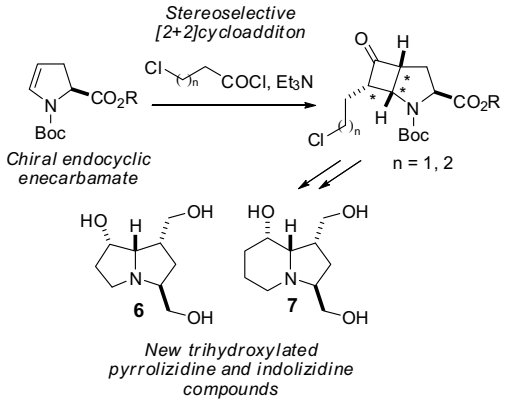
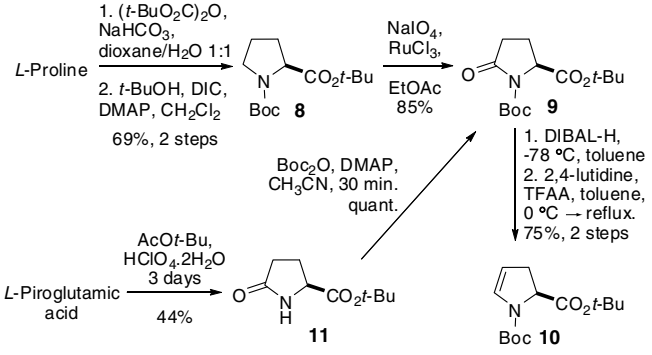


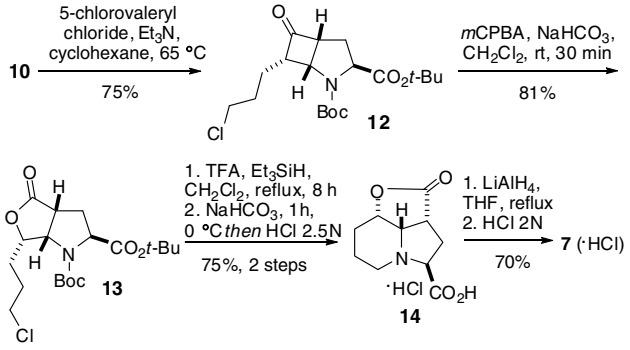
Fig. 2. Synthetic strategy to alexine-like compounds.

in the enecarbamate **10** was made to guarantee high facial stereoselectivity during the [2+2] cycloaddition to alkylketenes.[3i] The proline derivative **8** was readily prepared from L-proline (69% over two steps) as depicted in Scheme 1. Compound **8** was then oxidized with sodium periodate in the presence of a catalytic amounts of ruthenium to furnish pyroglutamic derivative **9** in 70–96% yields.[5] The lactam moiety of **9** was next reduced to the corresponding lactamol using diisopropylaluminum hydride (DIBAL-H) in THF at −78 °C. The resulting mixture of hemiacetals was then submitted to dehydration using trifluoroacetic anhydride (TFAA) and 2,4-lutidine in toluene to provide endocyclic enecarbamate **10** in 75% yield (over two steps; 44% overall yield over five steps). Alternatively, endocyclic enecarbamate **10** can be prepared with the same overall yield of 44% by esterification and Boc protection of L-pyroglutamic acid as depicted in Scheme 1.

With the endocyclic enecarbamate **10** in hand, we started the synthesis aiming at the construction of the trihydroxy indolizidine **7**. [2+2] Cycloaddition of enecarbamate **10** to chloroalkylketene (generate in situ from 5-chlorovaleryl chloride in presence of Et_3N) in cyclohexane as a solvent provided the *endo*-cycloadduct **12**, as the exclusive diastereoisomer in 75% yield (Scheme 2). Gratifyingly, the bulk *t*-butoxycarbonyl group at C-2 provided excellent stereocontrol during cycloaddition with the endo preference for the alkyl group arising from the minimum energy approach of the olefin and the ketene (Fig. 3).[6]



Scheme 1. Synthesis of endocyclic enecarbamate **10**.



Scheme 2. Synthesis of trihydroxylated indolizidine **7**.

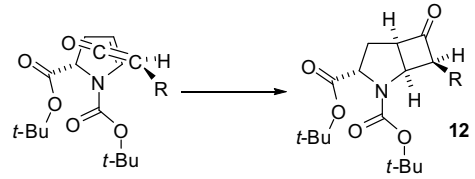
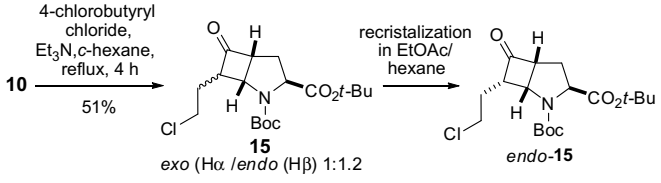


Fig. 3. Approach of the olefin and the ketene during cycloaddition (R = $CH_2CH_2CH_2Cl$).

Baeyer–Villiger oxidation of **12**, using *m*CPBA led to lactone **13** in 81% yield. As described in the previous work from our laboratory, ring expansion is exceptionally regioselective in such systems, producing a single isomeric lactone.[3a,b,e,g–i] Therefore, we hypothesize that the steric strain built into the Criegee's intermediate is the regio controlling element during oxidation, overriding stereoelectronic bias for the ring expansion.[3g] Conversion of lactone **13** to the tricyclic intermediate **14** was performed using a two-step procedure encompassing: (i) removal of the Boc group and cleavage of *tert*-butyl ester to the corresponding carboxylic acid with trifluoroacetic acid, and (ii) neutralization with sodium bicarbonate to promote intramolecular cyclization, followed by acidification with 2.5 mol/L HCl to form the rather stable hydrochloride **14** (we observe decomposition of this compound as free-base). Finally, the reduction of tricyclic lactone **14** with $LiAlH_4$ in THF under reflux resulted in the desired trihydroxy indolizidine **7** in 70% yield after purification using DOWEX-50W-X8. The synthesis of trihydroxy indolizidine 7 was accomplished in an overall yield of 32% after five steps from endocyclic enecarbamate **10**.

A similar strategy was employed for the synthesis of the trihydroxylated pyrrolizidine **6** (Scheme 3). However,

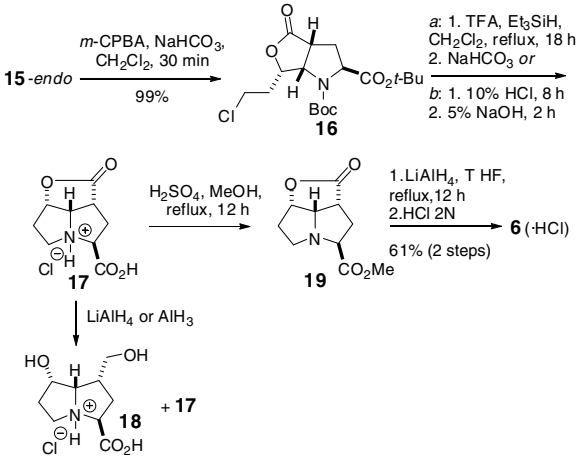


Scheme 3. Preparation of cyclobutanones **15**-*endo*/*exo*.

somewhat surprisingly, [2+2] the cycloaddition of enecarbamate **10** to the alkylketene derived from 4-chlorobutyryl chloride (Et_3N, cyclohexane as solvent at reflux) resulted in a mixture of *endo* and *exo* cycloadducts **15** (1.2:1 ratio) in a moderate yield of 51%. The reasons for this drastic reduction in yields and stereoselectivity are not clear at present. Previous results from our laboratory using simpler endocyclic enecarbamates provided higher yields and higher stereoselectivity for *endo* cycloadduct on similar [2+2] cycloadditions.[3b,g–i] Separation of the diastereomers turned out to be straightforward. The desired cycloadduct *endo*-**15** could be easily separated from the cycloadduct *exo*-**15** by recrystallization in a solvent mixture of EtOAc/hexane (1:1). The structure of the key cycloadduct *endo*-**15** was then confirmed by the X-ray analysis (Fig. 4).[7]

As expected cycloadduct *endo*-**15** underwent a clean Baeyer–Villiger oxidation (*m*CPBA, $NaHCO_3$ in CH_2Cl_2) to provide lactone **16** in almost quantitative yield (99%) as a single regioisomer. Simultaneous cleavage of the *tert*-butyl ester and Boc protecting groups of lactone **16** was carried out using excess of TFA, in the presence of Et_3SiH in dichloromethane to furnish the corresponding tricyclic amino acid **17** (trifluoroacetate salt) in only 22% yield (condition a, Scheme 4). Much higher yields of amino acid 17 were obtained when using stronger acid/neutralization conditions (HCl 10% then NaOH 5%) to provide hydrochloride **17** in 71% yield (condition b, Scheme 4). Reduction of lactone moiety of **17** with $LiAlH_4$ or AlH_3 (generated in situ) gave an inseparable mixture of the starting lactone **17** and the dihydroxy amino acid **18** instead of the expected triol **6**. To obtain the desired triol **6** the amino acid hydrochloride **17** was first reacted with $MeOH/H_2SO_4$ to generate amino ester **19**, which was then reduced with $LiAlH_4$ to yield the corresponding trihydroxy pyrrolizidine **6** in 61% yield from hydrochloride **17**, after purification by DOWEX-50W-X8.

In conclusion, trihydroxy pyrrolizidine **6**[8] and trihydroxy indolizidine **7**[9] were synthesized as alexine-like compounds from the common endocyclic enecarbamate **10** in a concise manner. Synthesis of indolizidine **7** was accomplished in an overall yield of 32% after six steps, whereas pyrrolizidine **6** was prepared in 22% overall yield after 5 steps. These total syntheses feature a selective [2+2] cycloaddition of alkylketenes generated in situ to endocyclic enecarbamate **10**, which can be efficiently synthesized from L-proline or pyroglutamic acid with an overall yield of 44%. The capacity of these new alexine-like compounds to inhibit glucosidases is being evaluated and the results of these assays will be reported in due course.



Scheme 4. Synthesis of trihydroxylated deoxyalexine **6**.

Acknowledgments

We thank the Research Support Foundation of the State of São Paulo (FAPESP) for financial support of this work (Grants 02/03431-8 and 05/00721-3) and for a doctoral fellowship to M.S.V. We also thank the Brazilian National Research Council (CNPq) for a research fellowship to C.R.D.C. and the ICSN-CNRS, France for complementary analyses.

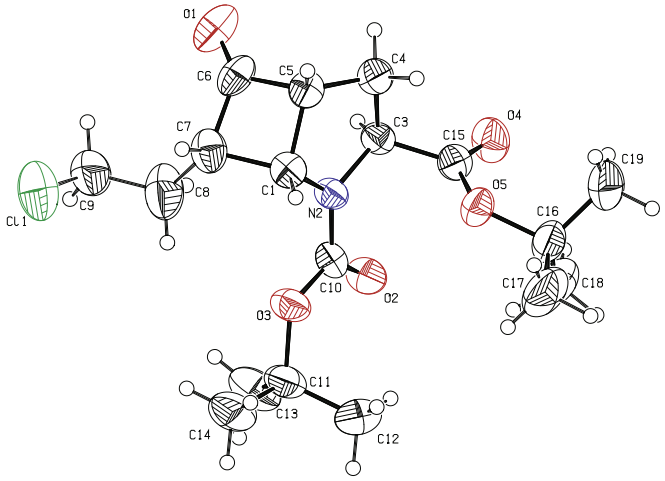


Fig. 4. Ortep drawing of cycloadduct *endo*-**15**.

References and notes

1. (a) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M. *Tetrahedron Lett.* **1988**, *29*, 2487–2490; (b) Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198–1206; (c) Nash, R. J.; Thomas, P. I.; Waigh, R. D.; Fleet, G. W. J.; Wormald, M. R.; Lilley, P. M. D.; Watkin, D. J. *Tetrahedron Lett.* **1994**, *35*, 7849–7852; (d) Tropea, J. E.; Molyneux, R. J.; Kaushal, G. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1989**, *28*, 2027–2034; (e) Taylor, D. L.; Nash, R. J.; Fellows, L. E.; Kang, M. S.; Tyms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273–277.
2. (a) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257–2264; (b) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811–814; (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199–210; (d) Winchester, B. *Biochem. Soc. Trans.* **1992**, *20*, 699–705.
3. (a) de Faria, A. R.; Matos, C. R. R.; Correia, C. R. D. *Tetrahedron Lett.* **1993**, *34*, 27–30; (b) de Faria, A. R.; Carvalho, E. S.; Correia, C. R. D. *Tetrahedron Lett.* **1995**, *36*, 5109–5112; (c) Carpes, M. J. S.; Miranda, P. C. M. L.; Correia, C. D. R. *Tetrahedron Lett.* **1997**, *38*, 1869–1872; (d) Sugisaki, C. H.; Carroll, P. J. *Tetrahedron Lett.* **1998**,

39, 3413–3416; (e) Miranda, P. C. M. L.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 7735–7738; (f) Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646–6652; (g) de Faria, A. R.; Salvador, E. L.; Correia, C. R. D. *J. Org. Chem.* **2002**, *67*, 3651–3661; (h) de Oca, A. C. B. M.; Correia, C. R. D. *Arkivoc* **2003**, *10*, 390–403; (i) Ambrósio, J. C. L.; Santos, R. H. de A.; Correia, C. R. D. *J. Braz. Chem. Soc.* **2003**, *14*, 27–38.

4. (a) Garcia, A. L. L.; Correia, C. R. D. *Tetrahedron Lett.* **2003**, *44*, 1553–1557; (b) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039–3042; (c) Plehiers, M.; Hootele, C. *Can. J. Chem.* **1996**, *74*, 2444–2453; (d) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966–3976; (e) Driessens, F.; Hootele, C. *Can. J. Chem.* **1991**, *69*, 211–217.
5. Yoshifuji, S.; Tanaka, K.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873.
6. For a comprehensive review on [2+2] cycloadditions, see: Tidwell, T. T. *Ketenes*; John Wiley and Sons: Toronto, 1995. For other reviews, see: (a) Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159–646; (b) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219; (c) Ghosez, L.; Brynaert, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5, pp 85–122; (d) Snider, B. B. *ChemTracts-Org. Chem.* **1991**, *4*, 403; (e) Tidwell, T. T. *Acc. Chem. Res.* **1990**, *23*, 273; (f) Ghosez, L.; O'Donnell, M. J. In *Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; pp 79–140.
7. CCDC 670768 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
8. Characterization data for **6** (HCl): R_f 0.10 (CH_2Cl_2/MeOH/NH_4OH 14:5:1); $[\alpha]_D^{20}$ +9.20 (*c* 0.5, H_2O); IR (film, cm^{-1}): 3304, 2947 2284, 1469, 1383, 1335, 1176, 1116, 1028, 903; ^1H NMR (500 MHz, D_2O): δ 1.95 (m, *J* 3.8 Hz, *J* 6.9 Hz, *J* 7.9 Hz, 1H), 2.24 (*m*, 2H), 2.34 (br dd, *J* 11.0 Hz, 2H), 2.83 (m, 1H), 3.52 (br dd, *J* 11.0 Hz, 1H), 3.74 (m, *J* 4.1 Hz, *J* 2.5 Hz, 1H), 3.87 (m, 1H), 3.90 (m, 1H), 3.94 (m, 2H), 3.97 (m, 2H), 4.09 (dd, *J* 3.5 Hz, *J* 8.5 Hz, 1H), 4.65 (br dd, *J* 2.5 Hz, *J* 2.8 Hz, 1H); ^{13}C NMR (125 MHz, D_2O): δ 30.2, 35.4, 40.4, 54.2, 59.8, 61.1, 69.8, 73.8, 76.4; TOF MS ES+ calcd for $C_9H_{18}NO_3^+$: 188.1, found 188.1; HRMS *m*/*z* calcd for $C_9H_{18}NO_3^+$: 188.1287, found 188.1264.
9. Characterization data for **7** (HCl): R_f 0.20 ($CHCl_3$/MeOH 1:1); $[\alpha]_D^{20}$ −8.75 (*c* 0.1, H_2O); IR (film, cm^{-1}): 3310, 2952, 2889, 1597, 1455, 1368, 1339, 1115, 1083, 1049; ^1H NMR (300 MHz, $CDCl_3$): δ 1.62–1.77 (m, 2H), 1.85–2.20 (m, *J* 3.66 Hz, *J* 5.13 Hz, 4H), 2.61 (m, *J* 7.32 Hz, 1H), 3.17 (td, *J* 3.66 Hz, 13.18, 1H), 3.51 (br td, 1H), 3.58 (br dd, *J* 1.41 Hz, 1H), 3.72–4.00 (m, *J* 2.93 Hz, 3H), 3.80 (t, *J* 2.20 Hz, 1H), 4.30 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH), 28, 2 (CH_2), 28.6 (CH_2), 40.8 (CH), 46.4 (CH_2), 58.8 (CH_2), 59.8 (CH_2), 62.6 (CH), 63.1 (CH), 65.8 (CH); ESI-MS calcd for $[M+H]^+$: 202.2, found 202.2.