Pergamon

Tetrahedron Letters, Vol. 35, No. 23, pp. 4031-4034, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0692-Q

Synthesis of 7,5-Fused Bicyclic Lactams by Stereoselective Radical Cyclization[1]

Lino Colombo,* Marcello Di Giacomo, Gianluca Papeo, Oliviero Carugo[a,2]

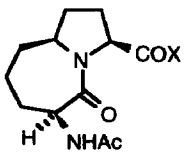
Dipartimento di Chimica Farmaceutica and a. Dipartimento di Chimica Generale, Università di Pavia,via Taramelli 12, I-27100 Pavia

Carlo Scolastico, Leonardo Manzoni

Dipartimento di Chimica Organica e Industriale, Università di Milano, via Venezian 21, I-20133 Milano

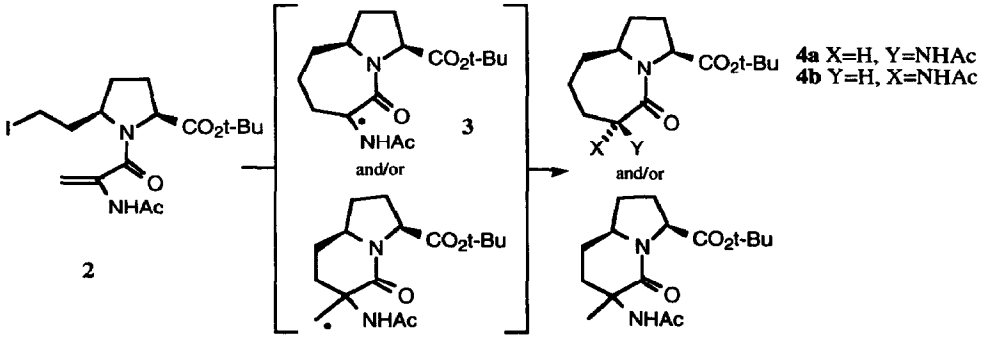
Abstract: 7,5-Fused bicyclic lactams of type **1** were synthesised by a route involving the radical cyclization of the intermediate **2**. High level of stereoselection was obtained in this reaction.

The development of new therapeutic agents against neurodegenerative processes is an area of increasing interest for the research community and pharmaceutical companies.[3] In fact, the dramatic increase of life expectancy is likely to increase the incidence of cognitive disfunctions in the population. As a part of our efforts to design and prepare new compounds showing cognition-activating properties (nootropics), we focused our attention on conformationally restricted proline-containing dipeptide. Fused bicyclic lactams **1a-d** have been identified as lead compounds in a recent QSAR study of ten amnesia reversal compounds.[4] The disclosure of our results on the synthesis of **1a-d** was prompted also by the appearance of a very recent report centered on the generation of the same 7,5-fused bicyclic lactams by a route involving an N-acyliminium ion cyclization.[5]



1a X = Ot-Bu
1b X = OH
1c X = OMe
1d X = H

We devised a completely different synthetic approach based on the radical cyclization of a preformed pyrrolidinyl nucleus in which the nitrogen atom is engaged in an amide bond with the carboxyl function of the 2-acetoamidoacrylic acid as depicted in the following scheme.



In principle, two regioisomeric products could be produced in the cyclization according to Baldwin rules, as 7-*Endo-Trig* and 6-*Exo-Trig* paths are both favored processes.[6] Although simple 6-heptenyl radicals have been reported to cyclize preferentially in 6-*Exo* mode,[7] we were confident that the stabilization exerted through the capto-dative effect [8] by the amide carbonyl and the N-acetyl groups on the radical **3** might force the reaction to follow a 7-*Endo* pathway. In fact, the only presence of an N-formyl group in a 5-aza-6-heptenyl radical has been shown to enable complete 7-*Endo* regiocontrol to be achieved in the assembly of the azepine ring by attack of aryl radicals onto enamide functions.[9]

The real concern was about the stereochemical outcome of the cyclization, as the new stereocentre is generated in the step involving hydrogen transfer from *n*-Bu_3SnH to the likely planar radical intermediate **3**. However, it has been reported that good 1,4-asymmetric induction could be achieved in the radical hydrogen abstraction by C_2-symmetrical acrylamide-derived radicals.[10] The stereochemical control of this process has been explained by a reaction of the preferred conformation **5**, *anti* to the shielding 5-membered ring. MM2* calculations[11] on radical **3** showed that two main conformational arrangements **3a** and **3b** can be accessible in a 3 Kcal/mol range, differing from the magnitude and sign of the torsion angle which defines the relative orientation of the -NAc and carbonyl groups (Figure 1). Hydrogen attack *anti* to the pyrrolidine moiety onto either conformer should lead to diastereomeric products. Conformer **3a** should enjoy more stabilization by electronic factors as the singly occupied radical orbital is twisted with a smaller out of plane angle. This will result in a better orbital overlap and consequently in an enhanced resonance stabilization. Our hypothesis was eventually confirmed by experiments which demonstrated that the radical cyclization of **3** led stereoselectively to isomer **4a**.

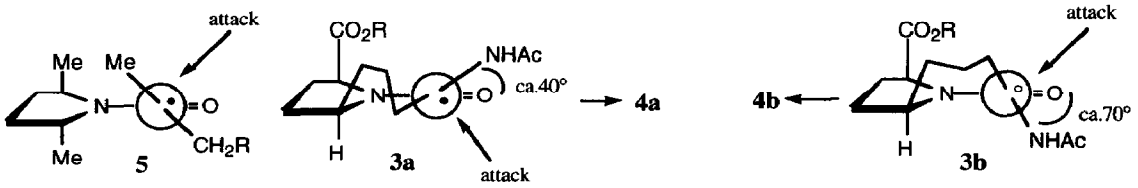
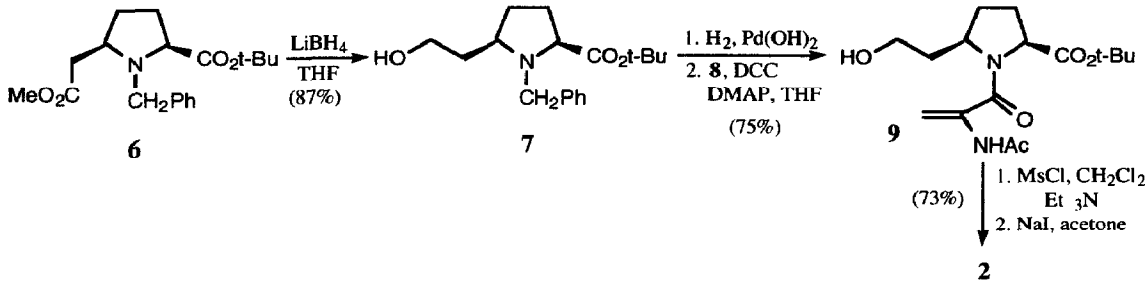


Figure 1

The synthesis of the radical precursor **2** started from the known proline derivative **6**, [12] easily obtainable in a highly stereoselective way from the inexpensive L-glutamic acid in five steps. Minor modifications of the published procedure allowed the rapid preparation of 65 grams of diester **6** in a single run with only one chromatographic purification.



Chemoselective reduction[13] of the methyl ester with $LiBH_4$ at room temperature cleanly afforded the corresponding alcohol **7**. Hydrogenolysis of the amine protecting group was particularly efficient in terms of yield and reaction rate when carried out in the presence of palladium hydroxide (Pearlman's catalyst). Condensation of the resulting secondary amine with 2-acetoamido acrylic acid **8** was mediated by the use of 1,3-dicyclohexylcarbodiimide (DCC) and catalytic 4-dimethylaminopyridine. The outcome of this reaction proved to be dramatically dependent on the addition order of the reagents. Good yields could be obtained only when a tetrahydrofuran solution of the acid was added dropwise to a solution mixture of the pyrrolidine and DCC. Treatment of the 2-acetoamidoacrylic acid with DCC followed by addition of the amine led to the formation of an intractable mixture. Conversion of the hydroxy compound **9** into the primary iodide **2** was best accomplished by a standard procedure involving the intermediate preparation of a mesylate followed by displacement with sodium iodide in refluxing acetone. The mesylation reaction afforded variable amounts of the corresponding chloride, but the two component mixture was altogether converted into the same final product **2**. Thus the precursor of the radical cyclization **2** was obtained from **6** in 49% overall yield and > 90% purity with no need of any chromatographic purification.

The final radical cyclization was performed using the tin method by slow addition (syringe pump, 6-8 hrs) of 0.01-0.02M benzene solutions of *n*-Bu_3SnH and catalytic AIBN (10-20%) to a 0.1M solution of iodide **2** in the same solvent. Careful analysis of the reaction mixture showed the exclusive presence of the 7-*Endo* isomer along with only trace amounts (2-3%) of the product deriving from iodide reduction. Adjustments of the experimental conditions resulted in an optimized 41% yield and 88% diastereomeric excess. Substantial increase in stereoselection up to 99% was counterbalanced by a net drop of the chemical yield (25-30%).

The use of $(Me_3Si)_3SiH$[14] as a radical initiator had a detrimental effect on yields under slow addition conditions. However, acceptable yield (42%) and very high diastereoselection (>95% d.e.) were achieved when $(Me_3Si)_3SiH$ and AIBN were added in one portion. On the other hand, addition of 1 equivalent of Bu_3SnH and 10% AIBN in one portion produced an almost equimolar mixture of the cyclized and reduced products. This finding could suggest that the rate constant of the cyclization reaction is similar to the rate coefficient of the hydrogen transfer from Bu_3SnH to the primary alkyl radical derived from iodide **2** (typically 10^5-10^6 $M^{-1}s^{-1}$).[15] Taking into account that the rate constant measured for 7-*Endo* closure in the simple heptenyl radical is *ca.* 7 x 10^2 s^{-1},[7] it is safe to conclude that the capto-dative substituent effect is likely to be responsible for the great acceleration of the *endo* pathway.

The stereochemistry of the newly formed stereocentre was determined by single X-ray analysis of the methyl ester **1c**, obtained by esterification with diazomethane of the acid **1b** resulting from the acidic hydrolysis (trifluoroacetic acid) of **1a**. As anticipated, the absolute configuration was shown to be S.

Finally, DIBAH reduction of **1a** in toluene at -78°C afforded in acceptable yield (50-60%, not optimized) the aldehyde **1d**.

Compounds **1a-d** will be tested to evaluate their pharmacological activity. We are currently studying by *ab initio* methods the conformational behaviour of the radical **3** and the transition state of the hydrogen abstraction reaction,[16] in order to gain deeper insights into the factors responsible for such a high selectivity.

Acknowledgements: This work was supported by Magis Farmaceutici and M.U.R.S.T. (40%). We thank Dr. M. Mella (Pavia) for recording n.m.r. spectra and Dr. L. Belvisi (Milano) for calculations. We thank also Ms. V. Molteni for helpful assistance.

References and Notes

1. Dedicated to Professor Giorgio Traverso on occasion of his retirement.
2. To whom correspondence concerning the X-ray structure should be addressed. X-ray crystallographic data will be deposited at the Cambridge Crystallographic Data Centre.
3. Mattson, R. J.; Moon, S. L. *Annu. Rep. Med. Chem.* **1988**, *23*, 29-38; Pavia, M. R.; Davis, R. D.; Schwarz, R. D. *Annu. Rep. Med. Chem.* **1989**, *25*, 21-29; Williams, M.*Annu. Rep. Med. Chem.* **1992**, *27*, 1-10.
4. Cosentino, U.; Moro, G.; Pitea, D.; Todeschini, R.; Brossa, S.; Gualandi, F.; Scolastico, C.; Giannessi, F. *Quant. Struct.-Act. Rlat.* **1990**, *9*, 195-201.
5. Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393-396.
6. Baldwin, E. J. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.
7. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959-974; Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472-473.
8. For a review on capto-dative effect: Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 917-932.
9. Rigby, J. H.; Qabar, M. N. *J. Org. Chem.* **1993**, *58*, 4473-4475; Fidalgo, J.; Castedo, L.; Domìnguez, D. *Tetrahedron Lett.* **1993**, *34*, 7317-7318. Other 7-*Endo* radical cyclizations: Ghosh, A. K.; Ghosh, K.; Pal, S.; Chatak, U. R. *J. Chem. Soc., Chem. Commun.* **1993**, 809-811; Nwecomb, M.; Marquardt, D. J.; Deeb, T. M. *Tetrahedron* **1990**, 2329-2344; Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140-3147; Merritt, J. E.; Sasson, M.; Kates, S. A.; Snider, B. B. *Tetrahedron Lett.* **1988**, *29*, 5209-5212; Beckwith, A. L. J.; Boate, D. R. *Tetrahedron Lett.* **1985**, *26*, 1761-1764; Bachi, M. D.; Frolow, F.; Hoornaert, C. J. *J. Org. Chem.* **1983**, *48*, 1841-1849.
10. Giese, B.; Hoffman, U.; Roth, M.; Velt, A.; Wyss, C.; Zehnder, M.; Zipse, H. *Tetrahedron Lett.* **1993**, *34*, 2445-2448.
11. MacroModel V3.5X: Mohamadi, F.; Richards, N.G.J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still; W. C. *J. Comput. Chem.*. **1990**, *11*, 440. Caution must be exercised when evaluating quantitative results from molecular mechanics calculations on radical containing structures. Radicals are best treated by *ab initio* methods (see ref. 16).
12. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539-4547.
13. Hamada, Y.; Kohda, K.; Shioiri, T. *Tetrahedron Lett.* **1984**, *24*, 5303-5306.
14. Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641-3642; Giese, B; Kopping, B. *Tetrahedron Lett.* **1989**, *30*, 681-684; Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678-683.
15. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986; p.9.
16. Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375-8384.

(*Received in UK* 21 *March* 1994; *accepted* 8 *April* 1994)