Pergamon

Tetrahedron Letters, Vol. 36, No. 4, pp. 625-628, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02319-0

Conformationally Constrained Dipeptides: Synthesis of 7,5- and 6,5-Fused Bicyclic Lactams by Stereoselective Radical Cyclizations

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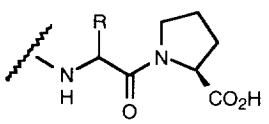
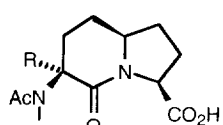
Abstract: A study of radical cyclizations of β-substituted α–N-acetyl acrylamide have been performed: high level of regio- and stereoselectivity was obtained.

Conformationally restricted peptides are the subjet of increasing interest as potential new bioactive molecules.[1] Peptide mimics with amide bonds and amino acid side chains disposed in a more rigid arrangement could give valuable information on the bioactive conformation of the mimicked peptide in the complex with its receptor. Moreover, peptidomimetics of potentially therapeutic value may display beneficial features such as enhanced oral bioavailability and metabolic stability.

As a part of a project directed to the design and synthesis of novel serino protease inhibitors,[2] we became interested in the development of a general method for the synthesis of 7,5- and 6,5-fused lactams of type **2** which can be viewed as conformationally restricted substitutes for Ala-Pro and Phe-Pro dipeptides **1**.



1 R = CH_3, CH_2Ph



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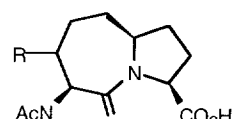
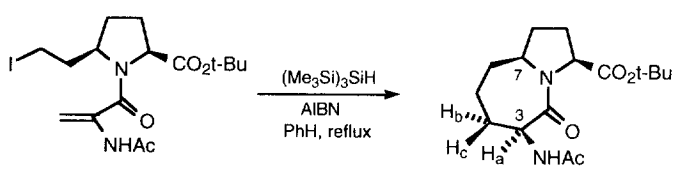


2a

In a previous paper we reported a stereoselective synthesis of compound **2a** (R = H) through the radical cyclization of iodide **3** (Scheme 1).[3] Only the *7-endo-trig* regioisomer was produced and excellent 1,4-asymmetric induction achieved in the formation of the newly created stereocentre.



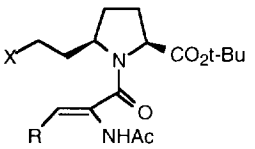
3

4 Y = 42%, d.e. > 95%

Scheme 1

We decided to study the effects of a β-substituent in the α-N-acetyl acrylamide moiety of **3** on the regio- and stereochemical outcome of the radical cyclization in order to ascertain the extension of this

radical-based methodology to the preparation of compounds **2**. Before embarking on this study, yield improvement of the reaction in Scheme 1 was in order. Extensive investigation on experimental conditions affecting this radical cylization resulted in a maximum 42% yield and the amount of recovered identifiable products accounted for only the half of the mass balance. We imputed this fact to the low thermal stability of iodide **3** which actually was shown to partially decompose upon treatment with refluxing benzene for several hours. This also explain the net drop in chemical yield (8-15%) caused by the use of a higher boiling solvent such as toluene. Replacement of the iodide group by a phenylselenyl function gave a thermally more stable derivative whose treatment with excess n-Bu_3SnH and catalytic AIBN in refluxing benzene led to the cyclized product **4** in a respectable 61% yield and 99% diastereomeric excess. The reduction product was also formed and isolated in 8% yield.



5; X = OH, R=H
6; X = SePh, R = H
7; X = SePh, R = Me
8; X = SePh, R = Ph

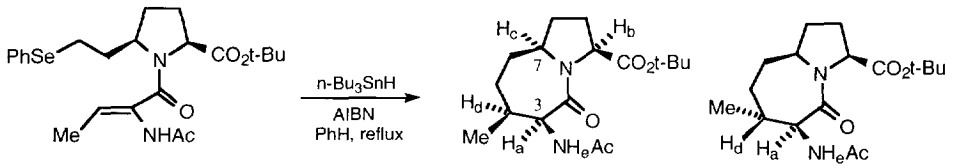
The selenide **6** was readily obtained in good yield from the alcohol **5**, which is a common intermediate for the preaparation of iodide **3**, by reaction with N-(phenylseleno)phtalimide in the presence of tributylphosphine at 0°C.[4]

Interestingly, molecular mechanics calculations using different force fields showed in any case that the major cyclized product was more stable than the corresponding epimeric compound at C-3. The energy differences between global minima were 0.4 (MM2*), 2.7 (MM3*) and 4.6 Kcal/mol (AMBER*).[5] The demonstration that molecular mechanics calculations are a reliable tool for the conformational analysis of these types of molecules came from the comparison between experimental and calculated vicinal coupling constants.[6] In the case of compound **4** the agreement between experimental and theoretical J_{a-b} and J_{a-c} was excellent indepedently of the force field used, as evidenced by data reported in Table 1

Table 1

	MM2	MM3	AMBER	Exp.
J_{a-b}	1.4	1.3	1.6	1.8
J_{a-c}	11.0	10.7	11.1	11.0

The next issue we addressed was the influence of alkyl and aryl substituents of the acrylamide moiety on the regio- and stereoselectivity of the radical cyclization. To this end compounds **7** and **8** were prepared following the same procedure as in the unsubstituted case. Slow addition (13 hours) of excess n-Bu_3SnH and catalytic AIBN to a refluxing solution of **7** in benzene gave rise to the formation of only two out of six possible cyclized products in 52% isolated yield in a 1:1 ratio. The reduction product was also formed in 28% yield. Extensive n.m.r. analysis showed that the cyclic products were both 7,5-fused bicyclic lactams, confirming the high preference of these systems toward *7-endo* regiocontrol.



7 **9** **10**

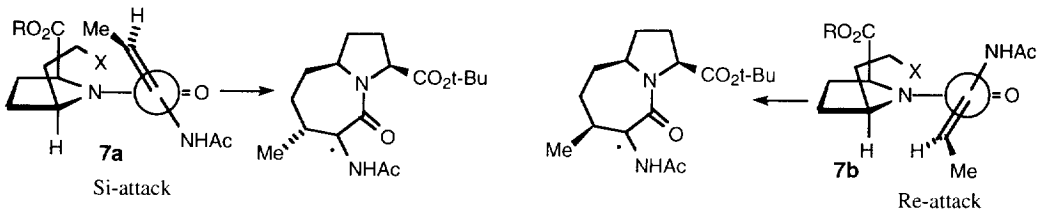
Scheme 2

Configurational assignments were deduced by a combination of experimental and theoretical results. The S configuration of the C-3 in **9** was secured by the presence of a n.O.e. between H_a and H_c. Comparison of the experimental $H_{e\text{-}a}$ and $H_{a\text{-}d}$ coupling constants with calculated values (Table 2) allowed us to determine the configuration of the remaining stereogenic centers of **9** and **10**, as depicted in Scheme 2.

Table 2

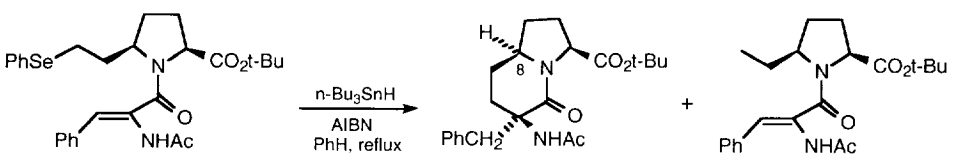
Compound		MM2	MM3	AMBER	Exp.
9	$J_{e\text{-}a}$	8.9	6.0	5.4	6.0
9	$J_{a\text{-}d}$	1.2	1.1	1.5	1.6
10	$J_{e\text{-}a}$	9.7	7.9	6.9	7.9
10	$J_{a\text{-}d}$	10.4	9.6	10.3	9.9

Therefore we can conclude that the attack of the alkyl radical on the β position of the acrylate double bond is not a stereoselective process (β-stereocontrol) while the subsequent radical hydrogen abstraction by the intermediate amide α-radical (ρ-stereocontrol) occurs with very high diastereofacial selectivity.[7] The lack of selectivity in the first step can be explained assuming as reactive conformations of the starting acrylamide two rotamers **7a** and **7b** in which the α,β-unsaturated system is twisted out of the carbonyl plane.



Similar preference for non-planar conformations has been demonstrated by Giese[8] through X-ray diffraction studies on chiral methacrylamides related to our systems. The high degree of selectivity of the hydrogen atom transfer reaction (1,4-induction) is controlled by the disubstituted pyrrolidine nucleus functioning as a chiral auxiliary; [3] the adjacent stereocentre produced in the intramolecular addition does not seem to have any effect (1,2-induction).

By contrast, phenyl-substituted acrylamide **8**, when reacted with n-Bu_3SnH and AIBN in refluxing benzene, afforded only one bicyclic compound in 34% yield along with a surprisingly high percentage (44%) of reduction product **12**. N.m.r. analysis clearly showed it to be the 6,5-fused bicyclic lactam **11** (Scheme 3). No 7,5-fused lactam sideproducts were detected.[9] The configuration of the newly formed stereocentre was tentatively assigned as indicated in **11** by the observation of a n.O.e. between the benzylic and C-8 protons.



8 **11** **12**

Scheme 3

Acknowledgements: This work was supported by M.U.R.S.T. (40%). We thank Molecular Design Ltd. for the use of the program REACCS. An EC grant (HCM Program-A2, contract No. ERBCHRXCT920027) is gratefully acknowledged as well as the Istituto Luso Farmaco d'Italia for the scholarship granted to Dr. L. Belvisi.

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(*Received in UK* 4 *November* 1994; *accepted* 25 *November* 1994)