Pergamon

Tetrahedron Letters, Vol. 38, No. 33, pp. 5809-5810, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01291-4

Stereoselective Synthesis of 1,3-Disubstituted Hexahydro-1,4-diazepin-2-ones.

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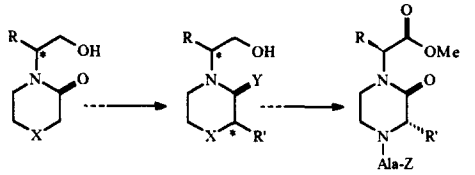
Abstract : Diastereoselective alkylation of hydroxylactam **6** allowed the preparation of 1,3-disubstituted hexahydro-1,4-diazepin-2-one derivatives in optically pure form. © 1997 Published by Elsevier Science Ltd.

During our on-going program dealing with the asymmetric synthesis of biologically active compounds, we previously reported the efficient and enantiomerically selective synthesis of 3-substituted piperidines (**2a**),[3] and 3-substituted piperazines (**2b**)[4] by diastereoselective alkylation of chiral non-racemic 6-membered lactams (**1**).[5]

This strategy is highly versatile and, very recently, we have demonstrated that enantiomerically pure 3-substituted-2-oxopiperazines **2c**, obtained as intermediates during the synthesis of **2b**, could also easily afford conformationally constrained peptidomimetics (**3**)[6] in which nitrogen atoms *i* and *i*+1 are linked by an ethylene bridge.



1a X= CH_2 **2a** X= CH_2, Y= H_2 **3**
1b X= N-Boc **2b** X= NH, Y= H_2
2c X= N-Boc, Y= O

Continuing our study in the asymmetric synthesis field, we are currently attempting to widen our methodology and we particularly wondered whether our approach was suitable with the use of more flexible lactams. We herein report the successful asymmetric synthesis of the title compounds, by diastereoselective alkylation of a chiral non-racemic 7-membered lactam.

The synthesis of a 7-membered ring generally proceeds in moderate to low yield. Indeed reaction of propanediyl *bis*-triflate[7] with the known diprotected dipeptide **4**[6] afforded lactam **5**[8] in 23% yield only. Selective reduction of the ester function of **5**[9] furnished the key optically pure hydroxylactam **6** in 76% yield.

Alkylation of **6** was investigated under the conditions previously determined in our laboratory.[3-6] Reaction of **6** with *t*-BuLi (2.0 equiv.), at -78°C, in THF in the presence of HMPA, then addition of the electrophile afforded compounds **7**[10] observed, by ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR, as single diastereomers[11] (Table).

X-ray analysis of the benzylated derivative **7b**[12] evidenced the expected relative configuration of the C-3 and C-1' side chains[5]. In order to confirm that no racemization occurred during transformations **4** to **7**, we also prepared **7a** in two steps from Boc-L-Ala-L-LeuOMe (**8**) using the *N-N'* dialkylation strategy depicted for the preparation of **5** and previously shown to be non-racemizing in oxopiperazine synthesis.[6] The 7-membered ring **9** was obtained in 20% yield. Reduction of its ester function furnished, in 60% yield, a compound indistinguishable from **7a** (^1H, ^{13}C NMR and optical rotation) attesting the *S* configuration of both asymmetric centers.

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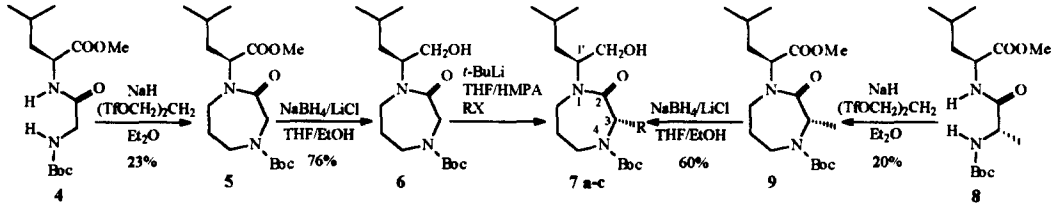

Table

RX	Compound	Yield (%)	de* (%)
CH_3I	**7a**	47	>95
$PhCH_2Br$	**7b**	52	>95
CH_2=CH-CH_2Br	**7c**	53	>95

*) Determined from ^1H and ^{13}C NMR.

In conclusion, the preparation of enantiomerically 7-membered lactams by stereoselective alkylation can be accomplished similarly to the 6-membered series. Since the required amido alcohol **6** can be obtain in only two steps from multigram-scale available dipeptide **4**, despite the low yield of the cyclization step, this method provides a fast access to the title compounds. It is also noteworthy that in contrast to independent observations made on 7-membered *N*-benzyllactams,[13] any product resulting from an alkylation at the α-leucinol position could be detected (NMR) probably due to a reduced acidity of the corresponding proton in our case. Whereas only theoretical studies have been made on hexahydro-1,4-diazepin-2-one,[14] this method provides a new entry for this kind of constrained peptides. Indeed, a recent example of hexahydro-1,4-diazepin-3-one has been reported as dipeptidomimetic.[15] Finally, there is also no doubt that replacement of the *iso*-butyl side-chain by any other aminoacid side-chain and subsequent chemistry on this side chain should afford all kinds of substituted products at the N-1 position. The use of phenylglycine methyl ester should afford, after hydrogenolysis, N1-unsubstituted derivatives as depicted in the piperidine[3] and piperazine[4] series.

Acknowledgment : We thank CAPES/COFECUB for a research grant to AP.

References and notes

1. On leave of absence from Instituto de Química, Universidade Federal do Rio Grande do Sul, Porto Alegre - Brazil
2. Laboratoire d'Hétérochimie Organique. IRCOF - INSA de Rouen - France.
3. Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2529-2532.
4. Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2533-2536.
5. Micouin, L.; Jullian, V.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron : Asymmetry* **1996**, *7*, 2839-2846.
6. Pohlmann, A.; Schanen, V.; Guillaume, D.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1997**, *62*, 1016-1022.
7. Lindler, E.; von Au, G.; Eberle, H.-J. *Chem. Ber.* **1981**, *114*, 810-813.
8. All new compounds were fully characterized by IR, MS, ^1H and ^{13}C NMR spectroscopy and exhibit satisfactory combustion analyses for C, H, N. **5**: $[\alpha]_D^{20}$ -43 (c=0.1; $CHCl_3$); IR (film) 1737, 1695, 1654, 1166 cm^{-1}; MS (CI): 360 $[MNH_4]^+$, 343 $[MH]^+$, 304, 287, 243; ^1H NMR (δ ppm) 5.15 (dd, H-2, J= 9.9, 5.2), 4.16 (d, H-3', J= 16.4), 3.89 (d, H-3', J= 16.4), 3.69 (m, H-5'), 3.60 (s, OCH_3), 3.30 (m, H-5'), 1.76 (m, 2 H-6'), 1.57 (m, CH_2 *i*-Bu), 1.42 (m, CH *i*-Bu), 1.37 (s, Boc), 0.84 (d, 2 CH_3 *i*-Bu, J= 6.5). ^{13}C NMR (δ ppm) 172.1, 171.5 ($COOCH_3$, CO), 154.5 (CO Boc), 80.3 (C Boc), 55.4 (C-2), 52.3 (C-3'), 51.9 (CH_3OCO), 46.6 (C-5'), 44.2 (C-7'), 37.4 (CH_2 *i*-Bu), 28.0 (CH_3 Boc), 27.9 (CH *i*-Bu), 23.0, 21.3 (CH_3 *i*-Bu).
9. Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252-1255.
10. **7a**: $[\alpha]_D^{20}$ +18 (c=0.3; $CHCl_3$); IR (CH_2Cl_2) 3444, 1693, 1644 cm^{-1}; MS (CI): 329 $[MH]^+$, 273, 241, 180; ^1H NMR (55°C, δ ppm) 4.42 (m, H-3), 4.54 (m, H-1'), 3.72 (dt, H-5, J= 14.0, 4.7), 3.64 (dd, H-2', J= 11.5, 4.6), 3.57 (dd, H-2', J= 11.5, 8.3), 3.38 (ddd, H-7, J= 15.1, 11.8, 3.4), 3.22 (ddd, H-7, J= 15.1, 4.2, 3.5), 3.17 (m, H-5), 2.40 (s, OH), 1.91 (m, H-6), 1.67 (m, H-6), 1.49 (m, CH_{2a} *i*-Bu), 1.46 (m, Boc, CH_3-3), 1.26 (m, CH_{2b} *i*-Bu, CH *i*-Bu), 0.94 (d, CH_3 *i*-Bu, J= 6.4), 0.92 (d, CH_3 *i*-Bu, J= 6.4). ^{13}C NMR (55°C, δ ppm) 173.3 (CO), 154.5 (CO Boc), 80.2 (C Boc), 64.0 (C-2'), 57.2 (C-3), 56.1 (C-1'), 42.5, 41.4 (C-5, C-7), 37.6 (CH_2 *i*-Bu), 28.2 (CH_3 Boc), 27.4 (C-6), 25.2 (CH *i*-Bu), 22.9, 22.4 (CH_3 *i*-Bu), 16.9 CH_3-3).
11. A NMR Spectrum of **7** is recorded in $CDCl_3$ at 55°C to avoid signal broadening of the signals due to multiple slowly interconvertible 7-membered ring conformations.
12. Chiaroni, A.; Riche, C.; Pohlmann, A.; Guillaume, D.; Quirion, J.-C.; Husson, H.-P. *Acta Crystallogr.*, to be published.
13. Meyers, A. I.; Kunnen, K. B.; Still, W.C. *J. Am. Chem. Soc.* **1987**, *109*, 4405-4407.
14. Czaplewski, C.; Lamnek, B.; Ciarkowski, J. *Polish J. Chem.* **1994**, *68*, 2589-2598.
15. Pellegrini, M.; Weitz, I.S.; Chorev, M.; Mierke, D.F. *J. Am. Chem. Soc.* **1997**, *119*, 2430-2436.

(*Received in France* 5 *May* 1997; *accepted* 24 *June* 1997)