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Tetrahedron Letters 45 (2004) 6311–6315
Tetrahedron Letters

Stereoselective synthesis of C^{α}-tetrasubstituted azabicyclo[X.3.0]alkane amino acids

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Received 26 April 2004; revised 17 June 2004; accepted 18 June 2004
Available online 10 July 2004

Abstract—By a stereoselective alkylation approach a synthesis of eight enantiopure, sterically constrained C^{α}-tetrasubstituted azabicycloalkane amino acids was carried out.

Biologically active peptides are involved in a great number of physiological processes through their interaction with receptors and enzymes. Amino acids possessing alkyl substituents have emerged as important tools for controlling peptide conformation because their steric interactions can restrict the motion between backbone and side-chain within a peptide and may promote particular peptide secondary structures. Furthermore, the hydrophobic nature of the alkyl substituent may enhance the affinity between ligand and receptor. Peptides themselves are not ideal drug candidates due to their low metabolic stability, rapid excretion and lack of selectivity towards a specific receptor. An attractive alternative lies in peptide analogues or de novo designed molecules that mimic the action of the native peptides at the receptor level (peptidomimetics).[1]

In the course of our studies on peptide secondary structure mimics, we synthesized several 5,5- 6,5-, 7,5- and 8,5-fused 1-aza-2-oxobicyclo[X.3.0]alkane amino acids[2] (Fig. 1, general formula I), that can be regarded as conformationally constrained substitutes for Ala-Pro dipeptide units. Functionalizing these molecules with lipophilic appendages is a very attractive possibility because peptide–receptor affinity could be improved by interaction of the substituent with hydrophobic pockets in the receptor.

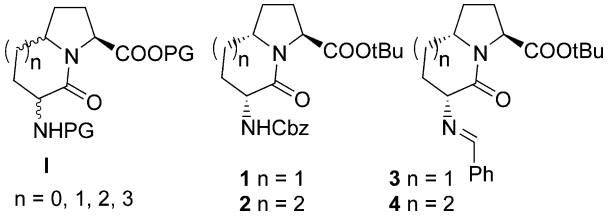

Figure 1. Bicyclic lactams.

In this paper, we report on a convenient method for the synthesis of *trans*-fused bicyclic lactams substituted with a benzyl or allyl group at the C3 position (Scheme 1).

In previous works we have synthesized benzyl substituted lactams both via radical[3] or nonradical approaches.[4] However, the lack of versatility of these two synthetic pathways and the difficulty encountered extending these procedures to large scale synthesis persuaded us to investigate a new approach for the synthesis of benzyl or allyl bicyclic lactams.

Keywords: Peptidomimetics; Alkylation; Lactams; Bicyclic aliphatic compounds; Enolates.
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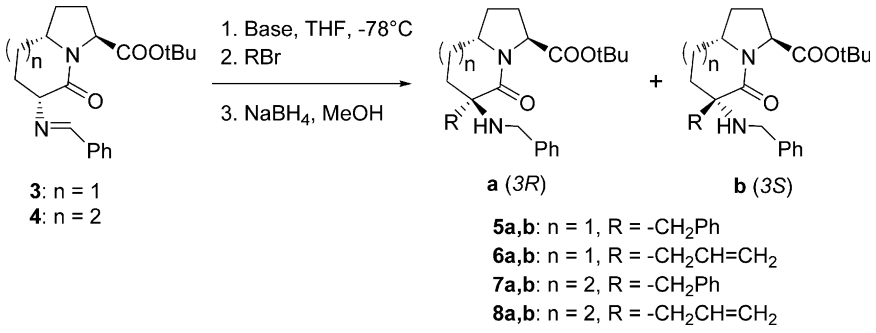
doi:10.1016/j.tetlet.2004.06.077



Scheme 1. Synthesis of C^{α}-tetrasubstituted azabicycloalkane amino acids.

The method here described is based on the stereoselective alkylation of a Shiff base amide enolate. Thus, starting from the known lactams **1** and **2**[2a] (Fig. 1), N-deprotection and treatment with benzaldehyde gave the imines **3** and **4** (Fig. 1). Reaction of **3** and **4** with a base and benzyl bromide or allyl bromide yielded the alkyl derivatives **5**–**8** (Scheme 1).

It is well documented that the outcome of alkylation reactions depends on a series of factors such as solvent,[5] base counterion[6] and temperature. These can dramatically affect both the yield and the stereoselectivity of the process.

The purpose of this work was to explore how the reaction conditions can affect yields and steric course of the alkylation reaction performed at the position C3 of bicyclic lactams.

We anticipated that due to the steric and electronic factors in compounds **3** and **4** the reaction with the base was regioselective, only the proton at C3 was removed, and no epimerization at C9 or C10, respectively, has been observed.

As it can be seen from the results collected in Table 1, formation of the enolate from **3** with LiHMDS followed by alkylation with benzyl bromide proceeded with moderate yields to afford the (3*R*) isomer **5a** as the major product (Table 1, entry 1).

The reactivity of an alkali metal enolate is very sensitive to its state of aggregation and the maximum reactivity would be expected in a medium where the cation is strongly solvatated. So, with the aim of decreasing the steric demand of enolate, the reaction was conducted in presence of a polar aprotic solvent such as DMPU;

Table 1. Reaction conditions for alkylation of compounds **3** and **4**

Entry	Imine	Base	*T* (°C)[a]	R	Prod.	Yield (%)	Ratio (3*R*)**a**/(3*S*)**b**
1	**3**	LiHMDS	−78→rt	–CH_2Ph	**5a,b**	56	92:8[b]
2	**3**	LiHMDS+DMPU	−78→rt	–CH_2Ph	**5a,b**	86	82:18[b]
3	**3**	LiHMDS	−50	–CH_2Ph	**5a,b**	89	90:10[b]
4	**3**	NaHMDS	−78→rt	–CH_2Ph	**5a,b**	55	75:25[b]
5	**3**	NaHMDS+DMPU	−78→rt	–CH_2Ph	**5a,b**	81	81:19[b]
6	**3**	KHMDS	−78→rt	–CH_2Ph	**5a,b**	24	31:69[b]
7	**3**	LiHMDS+Mg^{++}	−78→rt	–CH_2Ph	**5a,b**	43	5:95[b]
8	**3**	LiHMDS+Mg^{++}	−50→−20	–CH_2Ph	**5a,b**	43	>2:98[b]
9	**3**	LiHMDS+Sn^{++}	−78→rt	–CH_2Ph	**5a,b**	33	21:79[b]
10	**3**	LiHMDS	−78→rt	–$CH_2CH{=}CH_2$	**6a,b**	75	89:11[c]
11	**3**	LiHMDS	−50	–$CH_2CH{=}CH_2$	**6a,b**	90	84:16[c]
12	**3**	LiHMDS+DMPU	−78→rt	–$CH_2CH{=}CH_2$	**6a,b**	78	84:16[c]
13	**3**	LiHMDS+Mg^{++}	−78→rt	–$CH_2CH{=}CH_2$	**6a,b**	55	7:93[c]
14	**3**	LiHMDS+Mg^{++}	−50→−20	–$CH_2CH{=}CH_2$	**6a,b**	45	<2:>98[c]
15	**4**	LiHMDS	−78→rt	–CH_2Ph	**7a,b**	53	21:79[c]
16	**4**	LiHMDS	−50	–CH_2Ph	**7a,b**	82	40:60[c]
18	**4**	NaHMDS	−78→rt	–CH_2Ph	**7a,b**	81	10:90[c]
19	**4**	NaHMDS	−50→−20	–CH_2Ph	**7a,b**	73	20:80[c]
20	**4**	NaHMDS+DMPU	−78→rt	–CH_2Ph	**7a,b**	59	9:91[c]
17	**4**	LiHMDS+Mg^{++}	−78→rt	–CH_2Ph	**7a,b**	68	<2:>98[c]
21	**4**	LiHMDS	−78→rt	–$CH_2CH{=}CH_2$	**8a,b**	67	54:46[c]
22	**4**	LiHMDS	−50	–$CH_2CH{=}CH_2$	**8a,b**	67	55:45[c]
23	**4**	LiHMDS+Mg^{++}	−78→rt	–$CH_2CH{=}CH_2$	**8a,b**	20	6:94[c]

[a] Base was added at −78 °C, then bromide was added at reported temperature.
[b] Ratio determined by ^1H NMR.
[c] Ratio determined by HPLC.

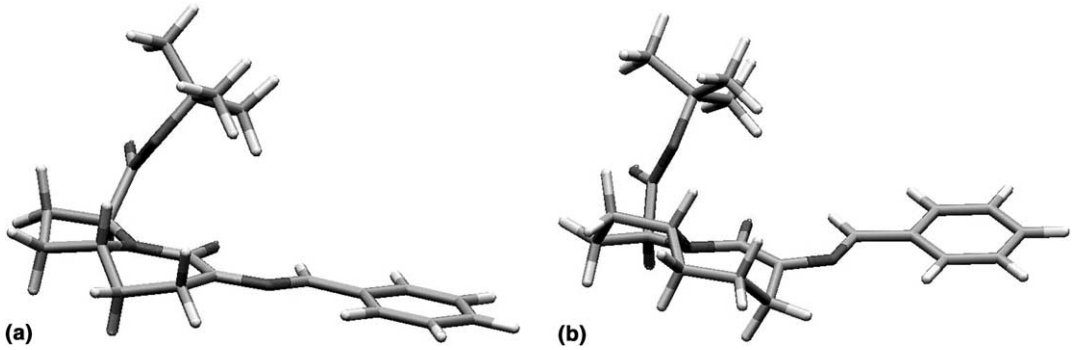


Figure 2. (a) RHF/3-21+G minimum energy conformation of the enolate derived from 6,5-fused bicyclic lactam **3**. (b) RHF/3-21+G minimum energy conformation of the enolate derived from the 7,5-fused bicyclic lactam **4**.

a dramatic effect was observed on the yield, which increased until 86% (entry 2) while only a slight effect can be observed on the diastereisomeric ratio. The same result has been reached performing the reaction at −50 °C instead of −78 °C (entry 3).

The change from lithium to sodium counterion showed little effect on the yield while the diastereoselectivity was considerably decreased (entry 4). Again the presence of DMPU enhanced the yield of the alkylation (entry 5). On the contrary switching to KHMDS had a dramatic effect and the preferred product obtained, even if with moderate yield, was the (3*S*) isomer **5b** (Table 1, entry 6). The data suggest that there could be different possible conformations and aggregations of the enolate in solution, and the equilibrium between chelated and nonchelated system can favour one or the other diastereoisomer. This was investigated using metal additives in the alkylation reaction.

As known in the literature, the conformation of the reactive enolate could drastically change if coordinative effects are present. A totally reversed stereochemically outcome can be obtained if the enolate is generated with LiHMDS and a bicoordinating Lewis acid such as $MgBr_2{\cdot}Et_2O$ is added (entries 7 and 8). The same result can be obtained also using $SnCl_2$ as LA even if with low yield (entry 9).

The allylation of **3** gave the same results, the temperature or the presence of DMPU showed influence on the yield leaving almost unchanged the diastereoisomeric ratio (entries 10–12). The presence of $MgBr_2{\cdot}Et_2O$ reverses completely the stereochemistry outcome of the reaction (entries 13 and 14).

By contrast, the benzylation of **4** turned out to afford selectively the (3*S*) isomer **7b**, independently of the reaction conditions. In this case the preferred reactive

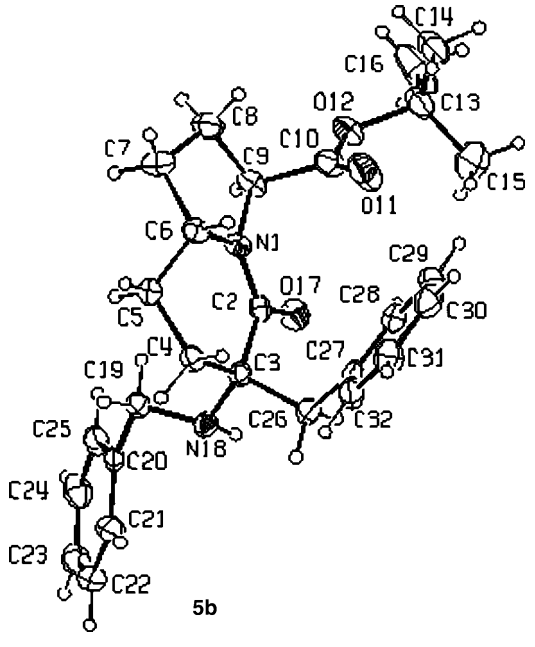


Figure 3. ORTEP plot of isomer **5b** with atom numbering scheme. Displacement ellipsoids at 30% probability level.

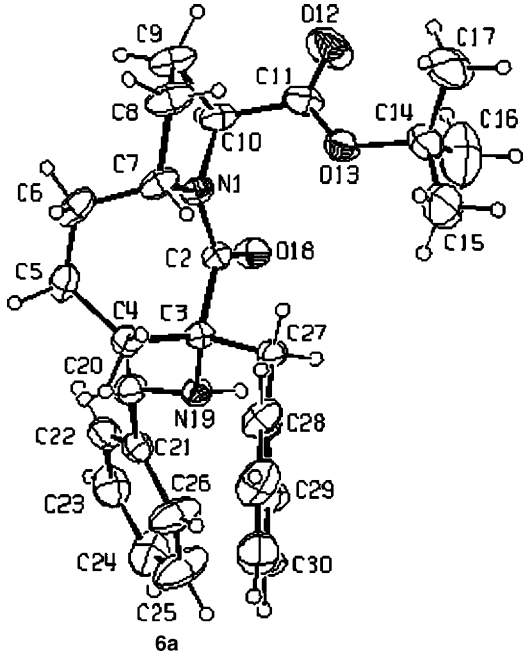


Figure 4. ORTEP plot of isomer **6a** with atom numbering scheme. Displacement ellipsoids at 30% probability level.

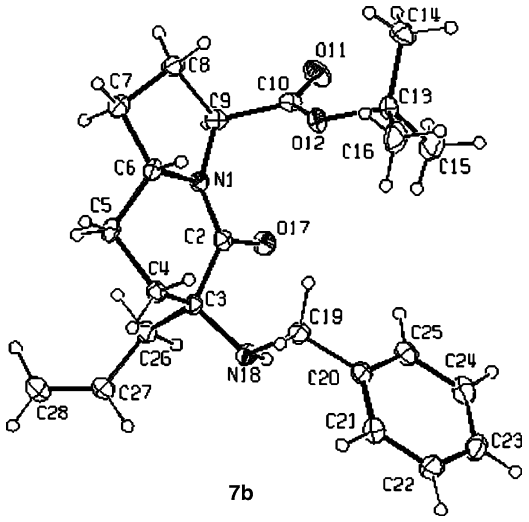


Figure 5. ORTEP plot of isomer **7b** with atom numbering scheme. Displacement ellipsoids at 30% probability level.

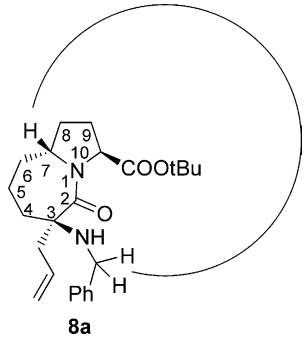


Figure 6. NOE in compound **8a**.

conformation was not affected by the presence of Lewis acid or at least was the same with or without coordinating metals; the enhancing of the diastereoselectivity was the only effect observed.

The allylation on compound **4** afforded **8b** as the major product (entry 23), even if with a very low yield, only when a LA was present, otherwise low diastereoselectivity can be reached.

The stereochemical outcome of the alkylation reaction could be rationalized by invoking a pseudo-axial attack[7] onto the lowest energy conformers obtained from ab initio calculations[8] for the bicyclic intermediate enolates (Fig. 2). The preferred geometry of the 6,5-fused enolate derived from **3** features a pseudo-chair conformation of the lactam ring (Fig. 2a), that should lead to the 3*R* **5a** or **6a** diastereoisomer if the pseudo-axial attack of the alkylating reagent is hypothesized. On the contrary, the same attack to the preferred lactam ring geometry of the 7,5-fused enolate derived from **4** (Fig. 2b) should favour the 3*S* **7b** or **8b** diastereoisomer. Some other factors as coordination phenomena, become important when the alkylation of the bicyclic lactam **3** is conducted in the presence of bicoordinating metals (Mg, Zn) or KHMDS; in this case a switching of the favoured face of attack of the incoming alkylating reagent is observed.

The pure isomers **5b** and **6a** were obtained by recrystallization from ethylic ether and their absolute configuration was assigned by X-ray structure analysis.[9] On the basis of the known stereogenic centres of the molecules, as shown in Figure 3, the X-ray structure of **5b** clearly indicated that the 3-benzyl group is *cis* to the *tert*-butoxycarbonyl group, which implied a 3*S* configuration. By contrast, the X-ray structure of **6a** (Fig. 4) indicated that the 3-allyl group was *trans* to the *tert*-butoxycarbonyl group, which implied a 3*R* configuration. Compound **7b** (Fig. 5) was also recrystallized from ethylic ether and X-ray analysis showed a *cis* relation between 3-benzyl group and the *tert*-butoxycarbonyl group unequivocally assigning the *S* configuration at C3 for lactam **7b**.

For allyl substituted compounds **8a**,**b** the stereochemistry of the newly formed stereocentre was unequivocally determined by NOE experiments (Fig. 6). In compound **8a** a NOE between the protons of benzylamine and H7 assigns the relative configuration at C3 as 3*R*.

In conclusion we have developed a new and versatile method for the preparation of C^{α}-substituted peptidomimetics based on stereoselective alkylation of a Shiff base amide enolate. The use of these scaffolds in the synthesis of biologically active molecules, as well as the application of this methodology to the preparation of other C3-substituted lactams are in progress and will be reported in due course.

Acknowledgements

The authors thank CNR and MIUR (COFIN and FIRB research programs) for financial support.

Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.06.077.

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8. Ab initio geometry optimizations were performed at the RHF/3-21+G level using Gaussian 98 (Frisch, M. J. et al., Gaussian, Inc.: Pittsburgh, PA, **1998**). Starting conformation for the 6,5-*trans* and 7,5-*trans* fused enolates deriving from **3** and **4** were generated by molecular mechanics calculations using the Macromodel version 5.5 program and the Macromodel (Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467) implementation of the AMBER force field (Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem*. **1986**, *7*, 230–252).
9. Tables of atomic coordinates, anisotropic thermal parameters, bond lengths and angles of isomers **5b**, **6a** and **7b** may be obtained free of charge from The Director CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK, on quoting the deposition numbers CCDC 229008–229010, the names of the authors and the journal citation (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk; web site: http://www.ccdc.cam.ac.uk). X-ray data were collected on a Bruker Smart Apex CCD area detector using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data reductions were made using SAINT programs. The structures were solved by SIR-92 and refined on F^2 by full-matrix least-squares using SHELXL-97. *Crystal data* for **5b**: $C_{27}H_{34}N_2O_3$, $M_r = 434.56$, colourless plate $0.33\times0.20\times0.08$ mm, orthorhombic, $P2_12_12_1$, $a = 6.2365(10)$, $b = 18.367(2)$, $c = 21.042(2)$ Å, $V = 2410.2(5)$ Å^3, $Z = 4$, $T = 293(2)$ K, $\mu = 0.078$ mm^{-1}. 41452 measured reflections, 2459 independent reflections, 2413 reflections with $I > 2\sigma(I)$, $2.94 < 2\theta < 50.00°$, $R_{int} = 0.066$. Refinement on 2459 reflections, 292 parameters. Final $R = 0.0591$, wR = 0.1309 for data with $F^2 > 2\sigma(F^2)$, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.16$, $\Delta\rho_{min} = -0.17$ eÅ^{-3}. *Crystal data* for **6a**: $C_{28}H_{36}N_2O_3$, $M_r = 448.59$, colourless prism $0.40\times0.34\times0.20$ mm, monoclinic, $P2_1$, $a = 6.5233(5)$, $b = 11.5837(8)$, $c = 17.0095(10)$ Å, $\beta = 95.96(1)°$, $V = 1278.36(15)$ Å^3, $Z = 2$, $T = 293(2)$ K, $\mu = 0.075$ mm^{-1}. 35023 measured reflections, 3091 independent reflections, 2556 reflections with $I > 2\sigma(I)$, $2.40 < 2\theta < 55.00°$, $R_{int} = 0.058$. Refinement on 3091 reflections, 301 parameters. Final $R = 0.0461$, wR = 0.1240 for data with $F^2 > 2\sigma(F^2)$, $(\Delta/\sigma)_{max} = 0.000$, $\Delta\rho_{max} = 0.20$, $\Delta\rho_{min} = -0.23$ eÅ^{-3}. *Crystal data* for **7b**: $C_{23}H_{32}N_2O_3{\cdot}H_2O$, $M_r = 402.52$, colourless prism $0.46\times0.18\times0.08$ mm, monoclinic, $P2_1$, $a = 6.6256(6)$, $b = 16.9585(15)$, $c = 19.8997(17)$ Å, $\beta = 92.43(2)°$, $V = 2233.9(3)$ Å^3, $Z = 4$, $T = 150(2)$ K, $\mu = 0.081$ mm^{-1}. 27304 measured reflections, 6724 independent reflections, 4007 reflections with $I > 2\sigma(I)$, $4.74 < 2\theta < 60.00°$, $R_{int} = 0.094$. Refinement on 6724 reflections, 727 parameters. Final $R = 0.0415$, wR = 0.0649 for data with $F^2 > 2\sigma(F^2)$, $(\Delta/\sigma)_{max} = 0.002$, $\Delta\rho_{max} = 0.21$, $\Delta\rho_{min} = -0.17$ eÅ^{-3}.