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Synthesis of Type II β-Turn Surrogate Dipeptides Based on *syn*-α-Amino-α,β-dialkyl-β-lactams

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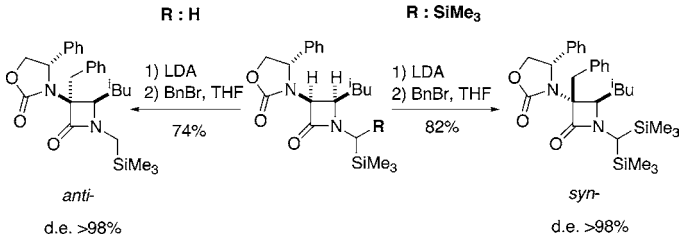
ABSTRACT



The achiral bis(trimethylsilyl)methyl group acts as an efficient stereochemical determinant of the α-alkylation reaction in β-branched α-phenyloxazolidinyl- or α-diphenyloxazolidinyl-β-lactams and provides the first stereocontrolled access to *syn*-α-amino-α,β-dialkyl(aryl)-β-lactams. These products are readily transformed into type II β-turn mimetic surrogates 2B.

During the last two decades, β-turn peptidomimetics[1] have been sought as promising candidates for drug discovery due to their ability to agonize or antagonize important biological processes. We recently have established a novel approach to the design of type II β-turn mimetics[2] based on the *separation of restriction and recognition elements* principle using the −(α-alkyl-α-amino-β-lactam)−(glycine)− segment as the betagenic (*i* + 1)−(*i* + 2)− central core (Figure 1). In the same report, we provided MD and NMR conformational evidence that only α-alkylated or syn-α,β-dialkylated β-lactam peptides **1A** and **1B** stabilize β-turned conformations in DMSO, whereas the α-unbranched or anti-α,β-dialkylated β-lactam peptides collapse to open conformations.

While the synthesis of dipeptide surrogates **2A** has been addressed for the first time in our laboratory[3] using the α-alkylation of *N*-[bis(trimethylsilyl)methyl]-β-lactams **4** as a key step (Figure 2), the extension of this methodology to

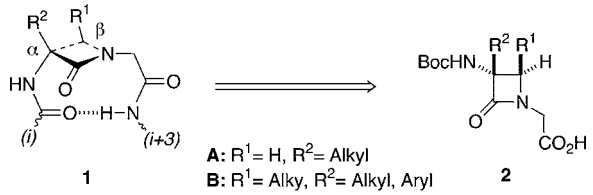


Figure 1. β-Lactam peptide approach to type II β-turn mimetics.

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(1) Kahn, M.; Eguchi, M. Synthesis of Peptides Incorporating β-Turn Inducers and Mimetics. In *Houben-Weyl, Methods of Organic Chemistry*; Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme: Stuttgart, 2003; Vol. E22c, pp 695−740 and references therein.

(2) Palomo, C.; Aizpurua, J. M.; Benito, A.; Miranda, J. I.; Fratila, R. M.; Matute, C.; Domercq, M.; Gago, F.; Martin-Santamaria, S.; Linden, A. *J. Am. Chem. Soc.* **2003**, *125*, 16243−16260.

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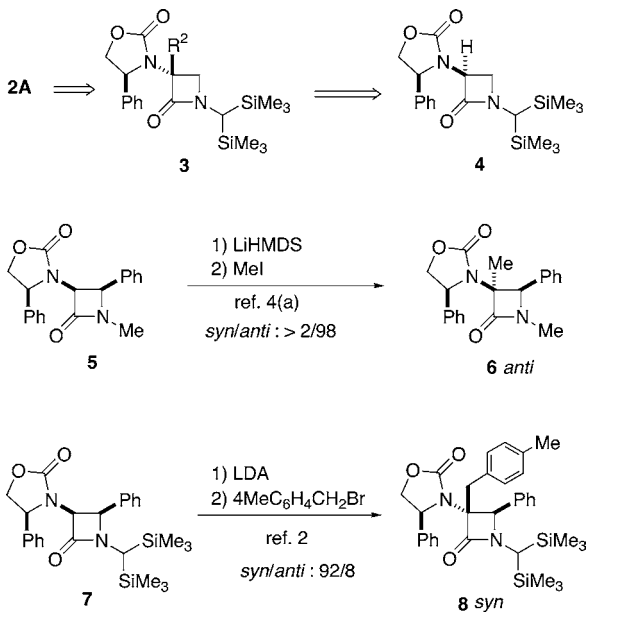


Figure 2. Stereochemical sense of the α-alkylation of α-(4-phenyl-1,3-oxazolidin-3-yl)-*β*-lactams.

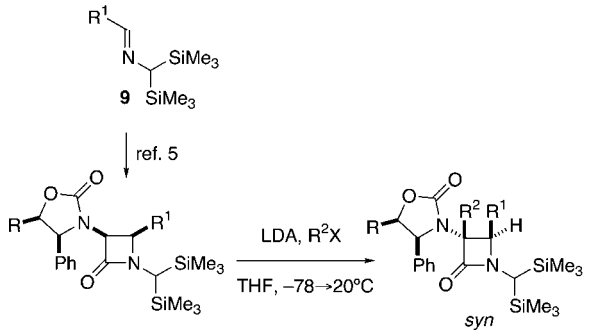
the preparation of *syn*-dialkyl dipeptides **2B** is not obvious. Indeed, Ojima and others[4] have established that the asymmetric alkylation of enolates generated by the deprotonation of *β*-substituted monocyclic *β*-lactams invariably leads to *anti*-α,*β*-dialkyl derivatives (e.g., **5**→**6**).

Nevertheless, contrary to these general observations, we have found[2] that several structurally very similar *β*-substituted *N*-[bis(trimethylsilyl)methyl]-*β*-lactams can afford mainly syn-α-alkylated products (e.g., **7**→**8**). Herein we report the first general synthesis of *syn*-α,*β*-dialkyl(aryl)-*β*-lactam dipeptides **2B** as well as a mechanistic model and experimental evidence that accounts for the stereochemistry observed as a function of the substituents borne by the nitrogen atom of the *β*-lactam.

To study the scope and stereochemical outcome of the α-alkylation reaction, a series of *β*-branched *N*-bis(trimethylsilyl)methyl-*β*-lactams were prepared from imines **9** and mono- or diphenyloxazolidinylacetic acid chlorides, according to the described methods (Scheme 1).[5]

As shown in Table 1, *β*-lactams **11**−**16** were completely deprotonated within a few minutes with LDA in THF at −78 °C, and the resulting enolates were cleanly alkylated in fair to good yields, either with activated benzyl and allyl bromides or with primary normal alkyl iodides.[6] Secondary alkyl iodides failed to facilitate the reaction.

Scheme 1



R= H	R= H
11 R^1= ^{i}Bu	**17** R^1= ^{i}Bu; R^2= $PhCH_2$
12 R^1= ^{i}Pr	**18** R^1= ^{i}Bu; R^2= CH_2=$CHCH_2$
13 R^1= Ph	**19** R^1= ^{i}Bu; R^2= Me
	20 R^1= ^{i}Pr; R^2= Me_2C=$CHCH_2$
	21 R^1= Ph; R^2= $PhCH_2$
	22 R^1= Ph; R^2= CH_2=$CMeCH_2$
	23 R^1= Ph; R^2= CH_2=$CHCH_2$
	24 R^1= Ph; R^2= Me

R= Ph	R= Ph
14 R^1= Me	**25** R^1= Me; R^2= $PhCH_2$
15 R^1= ^{i}Bu	**26** R^1= Me; R^2= CH_2=$CHCH_2$
16 R^1= Ph	**27** R^1= ^{i}Bu; R^2= $PhCH_2$
	28 R^1= ^{i}Bu; R^2= 2NaphthCH_2
	29 R^1= ^{i}Bu; R^2= CH_2=$CHCH_2$
	30 R^1= ^{i}Bu; R^2= nBu
	31 R^1= ^{i}Bu; R^2= Me
	32 R^1= Ph; R^2= $PhCH_2$
	33 R^1= Ph; R^2= Me

Inspection of the alkylation reaction of α-phenyloxazolidinyl-*β*-lactams (**11**−**13**; R = H; entries 1−9) led to the identification of the structural factors governing the syn/anti stereoselectivity. For instance, increasing the bulkiness of the R^2 group in the alkylating agent was found to improve the syn ratio. This effect was apparent from the good stereoselection observed for benzyl bromide (entries 1 and 5) or α-branched allyl bromides (entry 6), compared with the almost equimolar diastereomeric mixtures obtained from simple or *β*-substituted allyl bromides (entries 2, 4, and 7). Small reactive electrophiles like methyl iodide or methyl triflate (entries 3, 8, and 9) gave the poorer syn stereoselectivities. On the other hand, the aliphatic or aromatic nature of the *β*-substituent (R^1) seemed to exert a limited but appreciable effect on the diastereoselection, with the aliphatic groups giving uniformly higher ratios of syn isomers

(3) (a) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Benito, A.; Khamrai, U.K.; Eikeseth, U.; Linden, A. *Tetrahedron* **2000**, *56*, 5563−5570. (b) Palomo, C.; Aizpurua, J. M.; Benito, A.; Galarza, R.; Khamrai, U.K.; Vazquez, J.; DePascual-Teresa, B.; Nieto, P. M.; Linden, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3056−3058.

(4) (a) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307−5318. (b) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389. (c) Ojima, I. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; p 197. (d) Högberg, H.-E., Jr. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J.; Schaumann, E.; Thieme: Stuttgart, 1996; E21 Vol. 2, p 791.

(5) In contrast to conventional imines that only afford *β*-aryl-*β*-lactams upon Staudinger [2 + 2] cycloaddition with aminoketenes, imines **9** give either *β*-aryl-, *β*-alkyl-, or *β*-unsubstituted *β*-lactams in good yields and excellent stereoselectivities; see: (a) Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R.; Deya, P. M.; Dunogues, J.; Picard, J. P.; Ricci, A.; Seconi, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1239−1241. (b) Palomo, C.; Aizpurua, J. M.; Legido, M.; Mielgo, A.; Galarza, R. *Chem. Eur. J.* **1997**, *3*, 1432−1441.

(6) Although partial isomerization and decomposition was detected in some instances for the lithium enolates of α-diphenyloxazolidinyl-*β*-lactams (**14**−**16**; R = Ph), this problem was solved by warming immediately the mixtures of the enolates and alkyl halides from −78 to −30 °C. See Supporting Information for details.

Table 1. α-Alkylation of β-Substituted β-Lactams **11**−**16**

entry	R	product	R^2−X	yield (%)[a]	syn:anti[b]
1	H	17	$PhCH_2Br$	82	>98:2
2	H	18	CH_2=$CHCH_2Br$	91	67:33
3	H	19	MeI	90	53:47
4	H	20	CMe_2=$CHCH_2Br$	80	60:40
5	H	21	$PhCH_2Br$	84	90:10
6	H	22	CH_2=$CMeCH_2Br$	67	93:7
7	H	23	CH_2=$CHCH_2Br$	85	50:50
8	H	24	MeI	75	10:90
9	H	24	MeOTf	*c*	30:70
10	Ph	25	$PhCH_2Br$	67	>98:2
11	Ph	26	CH_2=$CHCH_2Br$	72[d]	95:5
12	Ph	27	$PhCH_2Br$	92	>98:2
13	Ph	28	$2NaphthCH_2Br$	78	>98:2
14	Ph	29	CH_2=$CHCH_2Br$	85	>98:2
15	Ph	30	^{n}BuI	58	>98:2
16	Ph	31	MeI	70[e]	71:29
17	Ph	31	MeI	82[d]	95:5
18	Ph	32	$PhCH_2Br$	81	>98:2
19	Ph	33	MeI	84[d]	73:27

[a] Yield of the pure mixture of syn and anti products. [b] Determined by ^{1}H NMR (500 MHz) analysis of the reaction crude. Configurations were assessed by NOE experiments and X-ray crystallography (compounds **28** and **30**; see Supporting Information). [c] Yield not determined. [d] Enolate trapping carried out at −30 °C for 16 h. [d] Enolate trapping carried out at −78 °C for 16 h.

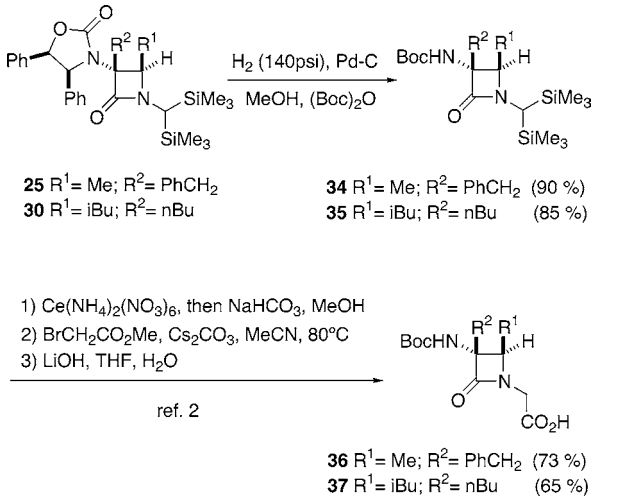
than their aromatic counterparts (compare entries 1, 2, and 3 with entries 5, 7, and 8, respectively). Our finding was that incorporation of a second phenyl group in the oxazolidinone ring (α-diphenyloxazolidinyl-β-lactams **14**−**16**; R = Ph) significantly enhanced the syn stereoselectivity in all instances, including those involving simple allyl and normal alkyl groups, and provided a convenient preparative entry to the desired α-amino *syn*-α,β-dialkyl(aryl)-β-lactams.

Transformation of α-diphenyloxazolidinyl-β-lactams into the dipeptide surrogates of type **2B** was carried out uneventfully, Scheme 2, by hydrogenolytic removal of the diphenyloxazolidinone ring and simultaneous Boc protection of the α-amino-β-lactam group, followed by the elaboration of the *N*-bis(trimethylsilyl)methyl moiety to the *N*-carboxymethyl group. For example, Boc-(β-lactam)-(Gly)-H fragments **36** and **37** were obtained in overall yields of 73 and 65%, respectively.

To gain insight into the *specific* syn stereodirecting effect exerted by the bis(trimethylsilyl) methyl and diphenyloxazolidinyl groups on the alkylation reactions disclosed above, we (a) explored the behavior of *N*-trimethylsilylmethyl-β-lactams bearing less hindered groups at the nitrogen atom and (b) conducted computational modeling of the respective intermediate β-lactam lithium enolates.

We found (Scheme 3) that reaction of *N*-bis-silyl-β-lactams **11** and **13** with cesium fluoride or tetra-*n*-butylammonium fluoride, respectively, resulted in clean mono- or didesilylation of the bis(trimethylsilyl)methyl moiety to provide the β-lactams **38**−**41** in high yields. α-Benzylation of *N*-trimethylsilylmethyl-β-lactams **38** and **39** under conditions identical to those used above afforded exclusively the anti

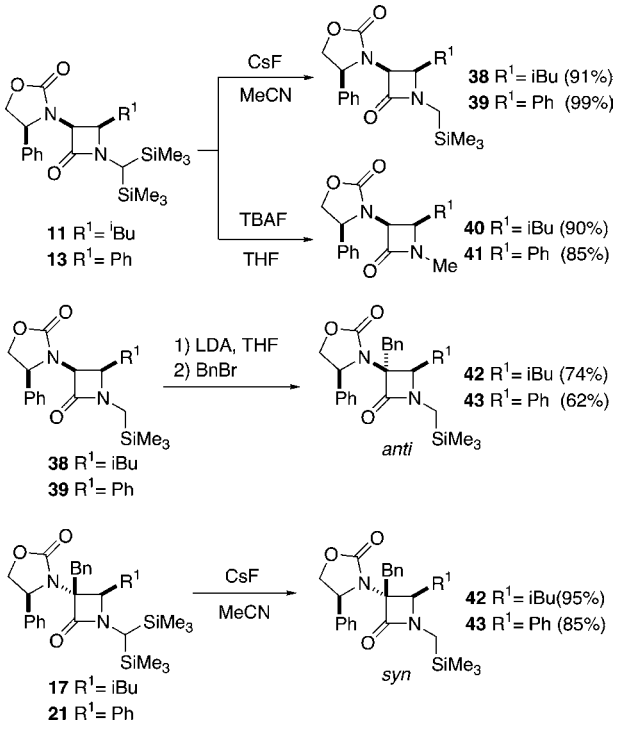
Scheme 2



isomers **42** and **43**, whereas desilylation of bis-silyl-α,β-dialkyl-β-lactams **17** or **21** gave the corresponding syn isomers. These results were meaningful, not only because they clearly stated the necessity of a *second* trimethylsilyl group to reach any syn selectivity but also because they anticipated the obtention of either syn or anti isomers from the *same* starting *N*-bis(trimethylsilyl)methyl-β-lactam by simply desilylating the N-substituent before the alkylation step.

A preliminary RHF/PM3[7] conformational analysis of the putative lithium enolates (Figure 3) arising from the deprotonation of two β-methyl-β-lactam models (R = H and R =

Scheme 3



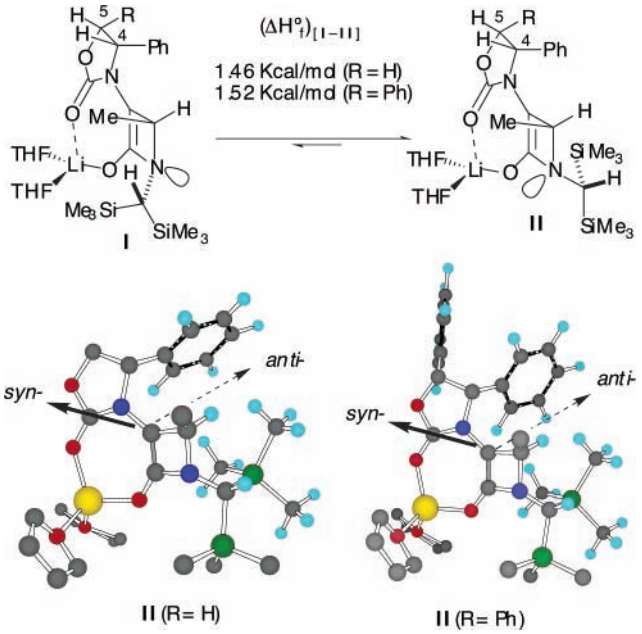


Figure 3. Comparison of the calculated RHF/PM3 structures of the lithium enolates of β-methyl β-lactam models (R = H) and (R = Ph). Some hydrogen atoms are omitted for clarity.

Ph) was conducted, assuming a lithium cation chelated by the oxazolidinone carbonyl oxygen atom and solvated by the THF solvent. In each case, two significant energy minima were characterized with the β-lactam nitrogen pyramidalized.[8] As expected, for the more stable conformations (**II**), the bis(trimethylsilyl)methyl group and the β-substituent (Me) were located at opposite faces of the β-lactam ring. Moreover, in these conformers, one of the $SiMe_3$ groups shielded the back face of the enolate, thereby inhibiting the formation of anti-α,β-dialkylated products. Finally, the second 5-phenyl group borne by the oxazolidinone ring in enolate **II** (R = Ph) caused a partial rotation of the 4-phenyl group with respect to **II** (R = H), which is consistent with the greater syn stereoselectivity observed for α-diphenyloxazolidinyl-β-lactams with respect to the monophenyl counterparts.

In summary, the α-alkylation of β-substituted α-phenyloxazolidinyl-*N*-bis(trimethylsilyl)methyl-β-lactams represents the first method for preparing enantiopure *syn*-α-amino-α,β-dialkyl(aryl)-β-lactams, which are suitable intermediates for the synthesis of type II β-turn dipeptide surrogates.

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Supporting Information Available: Preparation procedures and physical and spectroscopic data for compounds **17**−**43** and crystallographic data in CIF format and ORTEP diagrams of **28** and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) *MacSpartan Plus*, version 1.2.2; Wavefunction, Inc: Irvine, CA. The actual origin of the discrimination between the syn and anti alkylation paths is given by the energy differences of the respective transition states and not necessarily by the relative stability of the enolate intermediates.

(8) For crystallographic evidence concerning the tetrahedral character of the nitrogen atom in lactams and amides, see: (a) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373−1393. (b) Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764−773.