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Stereoselective Iodocyclization of 3-Acylamino-2-methylene Alkanoates: Synthesis of Analogues of *N*-Benzoyl-*syn*-phenylisoserine

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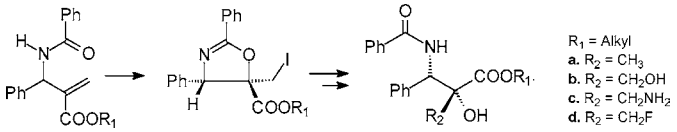
ABSTRACT



A convenient approach to racemic analogues of *N*-benzoyl-*syn*-phenylisoserine was realized via the stereoselective iodocyclization of amides obtained from Baylis–Hillman adducts.

β-Amino-α-hydroxy acids show important biological activities.[1] In particular, *N*-benzoyl-*syn*-phenylisoserine **1**, the C-13 side chain of paclitaxel (Taxol, **2a**), has been the target of numerous synthetic efforts, and many paclitaxel derivatives have been prepared in the quest for new products with broader activity and lower toxicity than the parent drug (Figure 1).[2] Thus, biological assays carried out with the C-2′-

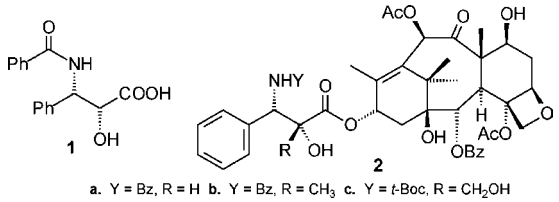


Figure 1.

methylated derivative **2b** revealed a significant enhancement of potency in comparison with **2a**.[3] The increased inhibition activity against microtubule depolymerization and cytotoxycity toward KB-V1 was ascribed to a higher energy barrier between the conformations around the 2′−3′ bond.[3b] In addition, the hydroxymethyl derivative **2c** demonstrates inhibitory activity in microtubule depolymerization but was devoid of significant cytotoxicity against KB or KB-V1 (Figure 1).[4]

(1) For reviews, see: (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117−128. (b) *Enantioselective Synthesis of β-Amino Acids*: Juaristi, E., Ed.; Wiley-VCH: New York, 1996. (c) Seebach, D.; Mattews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015−2022. (d) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180.

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Within an ongoing project aimed at inducing conformational changes and then activity changes in bioactive oligopeptides[5] by introduction of conformationally restricted β-amino acids,[6] we disclose here an efficient method leading to derivatives of racemic syn-2-substituted 2-hydroxy-3-amino acids **3a**−**d**, analogues of *N*-benzoyl-*syn*-phenylisoserine **1** (Figure 2), starting from the Baylis−Hillman adducts **4**.

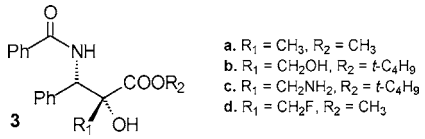
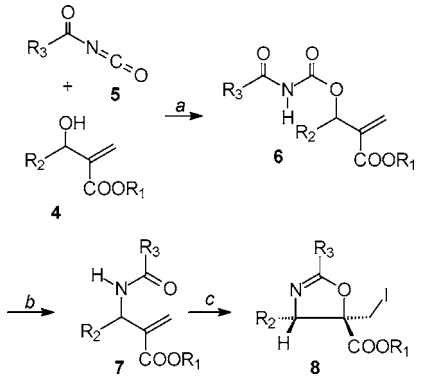


Figure 2.

At first, 3-acylamino-2-methylene-3-arylpropanoates **7** were prepared by treatment of *N*-acylcarbamates **6** with DABCO in DCM at room temperature (Table 1)[7] and one

Table 1. Preparation of 3-Acylamino Esters **7** and 4,5-Disubstituted 4,5-Dihydro-1,3-oxazoles **8**[a]



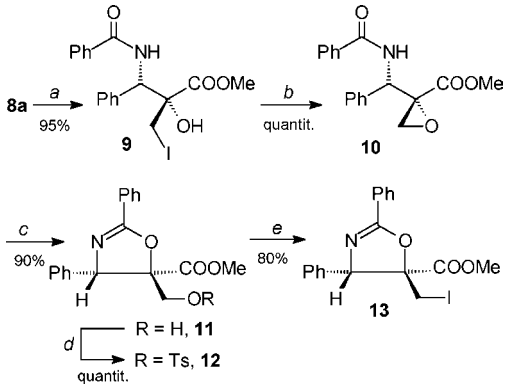
entry	R_1	R_2	R_3	yield **7** %[b]	yield **8** %[b]
a	Me	Ph	Ph	79	92
b	Me	4-O_2N−C_6H_4	Ph	93	85
c	Et	Ph	Ph	78	88
d	*t*-Bu	Ph	Ph	94	91
e	Et	Ph	*t*-Bu	75	86
f	*t*-Bu	Ph	Bn	83	87
g	*t*-Bu	Ph	CH_2Cl	79	78
h	*t*-Bu	Ph	CCl_3	84	87
i	Et	4-CH_3O−C_6H_4	Ph	71	75
j	Et	4-Cl−C_6H_4	Ph	78	84

[a] Reagents and conditions: (a) DCM, rt, quantitative yield. (b) DABCO, DCM, rt. (c) NIS, $CHCl_3$, rt. [b] Yield of pure product after isolation.

or two heteroatoms were subsequently introduced on the carbon backbone of these compounds by means of an iodocyclization reaction.[8−11] In fact, use of NIS in chloroform at room temperature in the cyclization of 3-acylamino derivatives **7** gave the corresponding dihydro-1,3-oxazoles **8** in high yield. The reaction proceeded with total diastereoselection, leading to a single product, as shown from GC analysis and ^{1}H and ^{13}C NMR spectra of the crude reaction mixtures.

This behavior, which could be ascribed to structural features of the starting amide, was different from the previously reported cyclizations of acyclic amides, which invariably led to diastereomeric mixtures of cis- and trans-4,5-disubstituted dihydro-1,3-oxazoles.[12] At first, the geometry of products **8** was assigned as cis by means of NOE experiments. Then the configuration at C-5 in **8a** was inverted by simple steps to give the corresponding isomer **13** (Scheme 1). The comparison of the ^{1}H NMR spectra

Scheme 1 [a]



[a] Reagents and conditions: (a) 3 M H_2SO_4 in MeOH, rt. (b) Dry Na_2CO_3, MeOH, rt. (c) CsF, DMF, 90 °C. (d) TsCl, Et_3N, DMAP, 0 °C. (e). NaI, DMSO, 100 °C.

evidenced a shielded ABq for CH_2I in **8a** at δ 3.00, whereas the analogous signal was unshielded in compound **13** (3.84

(5) (a) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069−1084. (b) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 79−88. (c) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 3573−3584. (d) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1997**, *8*, 133−137. (e) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 261−270. (f) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 4029−4042. (g) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3353−3358. (h) Fava, C.; Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3697−3703.

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(8) (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321−3408. (b) Orena, M. Amination Reactions Promoted by Electrophiles. In *Houben-Weyl, Methods of Organic Chemistry, Stereoselective Synthesis*; Helmchen, G., Hofmann, R. W., Mulzer, J., Schauman, E., Eds., Thieme: Stuttgart, 1995; Vol. E 2le, pp 5291−5355.

(9) For recent work on iodocyclization, see: (a) Jordá-Gregori, J. M.; González-Rosende, M. E.; Sepùlveda-Arques, J.; Galeazzi, R.; Orena, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1135−1143. (b) Jordà-Gregori, J. M.; Gonzalez-Rosende, M. E.; Cava-Montesinos, P.; Sepùlveda-Arques, J.; Galeazzi, R.; Orena, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3769−3777.

(10) All reactions were performed starting from racemic amides, but β-amino acids can be obtained in the enantiomerically pure form by kinetic resolution of their phenylacetamides with penicillin G acylase. So, by using enantiomerically pure starting materials, our approach leads to enantiomerically pure compounds. See: Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1998**, *63*, 2351−2353, and references therein.

δ), where the effect of the phenyl group is missing. The opposite trend was observed for the COO*Me* signal (**8a**, 3.93 δ; **13**, 3.19 δ), thus allowing definite assignment of the cis configuration to **8a** and trans configuration to **13**.

To explain the observed stereoselection, a full conformational analysis was carried out for the amide **7a**, by using molecular mechanics methods.[13] Calculations showed that a conformational equilibrium takes place for this compound, and rotamer **A**, leading to cis isomer **8a**, lies at lower energy by 2.2 kcal/mol with respect to rotamer **B**, which would lead to the trans isomer, **13** (Figure 3).[14−16] Due to this difference

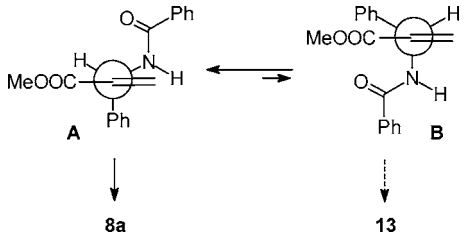


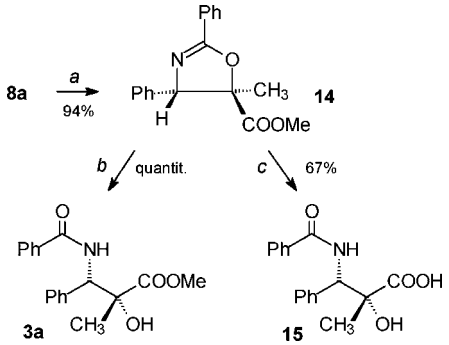
Figure 3. Conformational equilibrium for **7a** leading to **8a**.

in energy, it appears that only rotamer **A** is significantly populated, and this causes the reaction outcome. Thus, conformational stability seems to be the driving force leading to the cis isomers **8**, although synergic effects at the transition state could not be discarded.[17]

With compounds **8** in hand, at first the synthesis of **3a** began with cleavage of the C−I bond of **8a**, performed with 1-ethylpiperidinium hypophosphite,[18,19] to give the 5-methyl derivative **14** in high yield.

Subsequent cleavage of the heterocyclic ring, carried out with 3 M HCl in methanol, afforded the corresponding methyl ester **3a**, whose spectral data were in total agreement with that of the reported compound.[3h] Conversely, treatment of **14** with 6 M HCl/methanol 1:1 led to the corresponding acid **15** (Scheme 2).

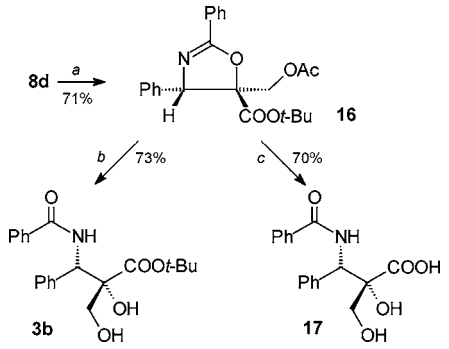
Scheme 2 [a]



[a] Reagents and conditions: (a) 1-Ethylpiperidinium hypophosphite, AIBN, refluxing toluene. (b) 3 M HCl in MeOH, rt. (c) 6 M HCl in refluxing MeOH.

Furthermore, the nucleophilic substitution at the iodomethyl group of **8d**, directed toward preparation of the hydroxymethyl derivative **3b**, was not trivial, and the introduction of the acetoxy group proved to be troublesome, due to the low reactivity of the iodine, probably due to steric hindrance.[20] In fact, reaction of **8d** with either acetate anion on IRA 120 in refluxing toluene, and potassium acetate in DMF at 80 °C, failed and starting material was recovered along with some decomposition. However, when cesium acetate was employed as a source of acetate anion in DMF at 110 °C, the substitution proceeded in moderate yield, leading to the 5-acetoxymethyl derivative **16**, which was subsequently cleaved on treatment with 1 M HCl in refluxing MeOH to give the ester **3b**. In analogy with **14**, treatment of **16** with 6 M HCl in refluxing MeOH led to the acid **17** in good yield (Scheme 3).

Scheme 3 [a]



[a] Reagents and conditions: (a) CsOAc, dry DMF, 110 °C. (b) 1 M HCl, MeOH, 60 °C. (c) 6 M HCl in refluxing MeOH.

On the other hand, substitution of the iodine atom of **8d**, with the aim of preparing the analogue **3c**, proceeded

(11) A single example of iodocyclization of Baylis−Hillman adducts was found in the literature: Drewes, S. E.; Njamela, O. L.; Roos, G. H. P. *Chem. Ber*. **1990**, *123*, 2455−2456.

(12) (a) Cardillo, G.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1489−1490. (b) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1985**, *41*, 163−167. (c) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1345−1349.

(13) Molecular mechanics calculations were performed using the implementation of Amber all-atom force field (AMBER*) within the framework of Macromodel version 5.5. The solvent effect was included by using the implicit chloroform GB/SA solvation method of Still et al. The torsional space of each molecule was randomly varied with the usage-directed Monte Carlo conformational search of Chang−Guida−Still. For each search, at least 1000 starting structures for each variable torsion angle were generated and minimized until the gradient was less than 0.01 kcal $Å^{-1}$ mol^{-1}. Duplicate conformations and conformations with an energy excess of 5 kcal/mol above the global minimum were discarded.

(14) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case D. A. *J. Comput. Chem*. **1986**, *4*, 230−252.

(15) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem*. **1990**, *11*, 440−452.

(16) (a) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc*. **1990**, *112*, 6127. (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc*. **1989**, *111*, 4379−4386.

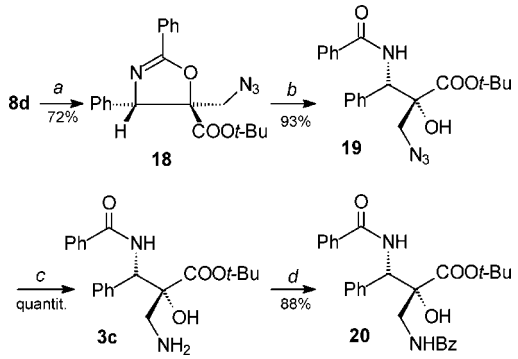
(17) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. E.; Hehre, W. J. *J. Am. Chem. Soc*. **1987**, *109*, 672−677.

(18) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett*. **1999**, *40*, 2415−2416.

(19) When Bu_3SnH was employed, tin derivatives unseparable from **3a** were produced in the reduction reaction.

straightforwardly by using sodium azide in DMSO *(CAUTION!)* (Scheme 4).

Scheme 4 [a]



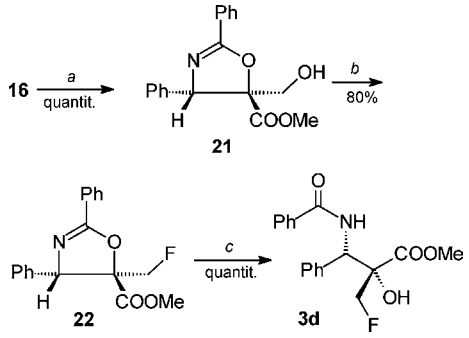
[a] Reagents and conditions: (a) NaN_3, DMSO, 80 °C. (b) 3 M HCl in MeOH, rt. (c) Zn, NH_4Cl, MeOH, rt. (d) BzCl, Et_3N, DMAP, 0 °C.

Thus, the azidomethyl derivative **18** was obtained in good yield, and cleavage of the heterocyclic ring led to the azido ester **19**.

After conversion into the amino ester **3c**, performed by using Zn−NH_4Cl, subsequent benzoylation gave **20**.[21]

The reaction of the acetoxymethyl derivative **16** with Na_2CO_3 in MeOH provided the hydroxymethyl derivative **21**. Treatment with DAST in DCM gave **22** in good yield, which was then converted into the ester **3d** (Scheme 5).

Scheme 5 [a]



[a] Reagents and conditions: (a) Anhydrous Na_2CO_3, MeOH, rt. (b) DAST, dry DCM, rt. (c) 3 M HCl in MeOH, rt.

In summary, starting from the Baylis−Hillman adducts **4**, we developed a practical, stereoselective synthesis of racemic analogues of *syn*-phenylisoserine **1**. The preparation of derivatives **3a**−**d** in the enantiomerically pure form and evaluation of biological activity data for new compounds **3c**−**d** are currently underway and will be reported in due course.

Acknowledgment. We thank M.I.U.R. (Rome, Italy) for financial support within PRIN 2002 framework.

Supporting Information Available: Experimental procedures and spectral data are given for all compounds, together with ^{1}H NMR and ^{13}C NMR spectra of **3a**−**d**, **8a**, **13**, **14**, **16**, **18**, and **22** and charts of optimized geometries and NACs for compound **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Compound **8d** was employed, in place of **8a**, since cleavage of the ester function of **8a** was observed under nucleophilic substitution reaction conditions.

(21) Hydroxyamination of Baylis−Hillman adducts was already reported: Pringle, W.; Sharpless, K. B. *Tetrahedron Lett*. **1999**, *40*, 5151−5154.