

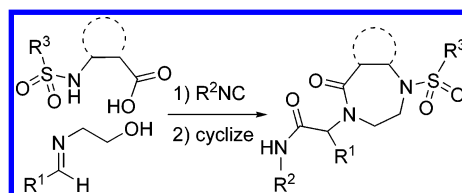
# Ugi Multicomponent Reaction Followed by an Intramolecular Nucleophilic Substitution: Convergent Multicomponent Synthesis of 1-Sulfonyl 1,4-Diazepan-5-ones and of Their Benzo-Fused Derivatives

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A short, two-step approach to the synthesis of diazepane or diazocane systems, based on a Ugi multicomponent reaction followed by a subsequent intramolecular  $S_N2$  reaction was studied. 1-Sulfonyl tetrahydrobenzo[*e*]-1,4-diazepin-1-ones **1** were obtained in very high yield through a Ugi multicomponent reaction followed by Mitsunobu cyclization. On the other hand, aliphatic 1-sulfonyl 1,4-diazepan-5-ones **2** could be obtained employing different cyclization conditions (sulfuryl diimidazole). A similar approach toward diazocane rings using hydroxamates as nucleophiles was less successful, affording only *O*-cyclized adducts or unexpected side products. A mechanistic explanation of the observed outcomes is proposed.

## Introduction

Multicomponent reactions (MCRs)<sup>1</sup> are, for their intimate nature, extremely convergent, producing a remarkably high increase of molecular complexity in just one step. Therefore, especially when the components may be varied at will, they are very well suited for the generation of libraries. Among MCRs, those based on the peculiar reactivity of isocyanides, such as the Ugi<sup>2</sup> and the Passerini<sup>3</sup> reactions, have been among the most widely used, also in an industrial context.<sup>4</sup> While the classical versions of these reactions lead to acyclic adducts, interesting heterocyclic structures may be accessed by intramolecular variants or by coupling the MCR with a subsequent secondary transformation, taking advantage of additional functionalities suitably placed on one or two of the components.<sup>5</sup> In the last years our group has reported new convergent syntheses of heterocycles through this latter approach.<sup>6–11</sup>

We are particularly interested in coupling the Ugi reaction with aliphatic substitutions.<sup>7,11,12</sup> While brilliant examples of Ugi reactions followed by  $S_NAr$  reactions have been recently reported,<sup>1,13–17</sup> less attention has been devoted to  $S_N2$  reactions.<sup>18–25</sup>

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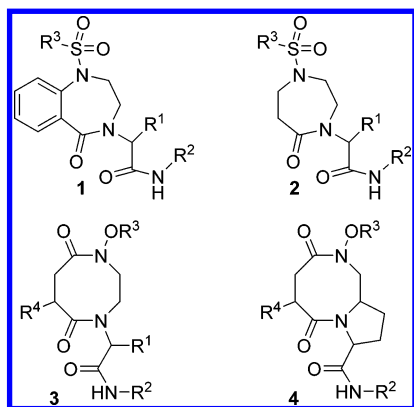
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## SCHEME 1



We reasoned that interesting heterocyclic scaffolds could be produced in a straightforward manner by already introducing a suitable nucleophile and an alcoholic moiety in two of the four components of the Ugi reaction and by performing a subsequent intramolecular Mitsunobu reaction.<sup>26</sup> We have recently described the straightforward synthesis of benzoxazepinones using phenols as nucleophiles. We now describe our approaches toward compounds of general formula **1–4** (Scheme 1), employing sulfonamides and hydroxamates as nucleophiles for the Mitsunobu reaction. In all cases our plan involved inclusion of the nucleophilic moiety into the carboxylic components of the Ugi MCR.

## Results and Discussion

As sulfonamide derivatives we employed the four carboxylic acids **7a,b**,<sup>27,28</sup> and **8a,b**,<sup>29,30</sup> easily synthesized from anthranilic acid or  $\beta$ -alanine (Scheme 2). Imines **5** were obtained by mixing equimolar quantities of the appropriate aldehyde and ethanolamine in Et<sub>2</sub>O in the presence of molecular sieves. The imines derived from aliphatic aldehydes were purified by distillation, whereas those derived from aromatic aldehydes were used as such, after evaporation of the solvent. Interestingly, <sup>1</sup>H NMR showed that the compounds derived from condensation of ethanolamine with aliphatic saturated aldehydes were actually equilibrium mixtures of the imine **5** and of the isomeric oxazolidines **6**, with the latter prevailing (the exact ratios are reported in the experimental section and in the Supporting Information).

The Ugi condensation of these two bifunctionalized components with a series of isocyanides proceeded smoothly to afford in moderate to good yields the desired adduct **9** or **10** (Table 1). It should be noted that, in this multicomponent condensation, 6 different functional groups are present simultaneously in the same pot and that protection of the hydroxy group was not necessary. The yield was lower than 60% only in the cases of entries 1, 4, 14, 17, and 21. In the case of entries 1 and 14, the reason was the relatively easy self-condensation of valeraldehyde, isovaleraldehyde, or of their imines under the reaction conditions. This side process was not completely avoided by the use of freshly distilled imine and by the presence of molecular sieves in the reaction media. The moderate yield obtained in entries 4, 17, and 21 is probably due to the great bulkiness of the isocyanide.

The NMR spectra of all the Ugi products **9** and **10** were complicated by the conformational equilibrium between the two rotamers around the tertiary amide bond. Only at temperatures > 110 °C did complete or nearly complete coalescence occur.

Having in hand the sulfonylamino alcohols **9** and **10**, we subjected them to normal Mitsunobu conditions (DEAD or TBAD, PPh<sub>3</sub> in THF) (methods A–C) (Scheme 3, Table 2). In the case of **9** the reaction turned out to be quite clean forming the expected 1-sulfonyl tetrahydrobenzo[e]-1,4-diazepin-1-ones **1** in good to excellent yields. We could therefore prepare a small collection of these compounds. In some cases we preferred the use of di-*tert*-butyl azodicarboxylate (DBAD, methods B and C) simply for an easier separation of the product from the hydrazo dicarboxylate byproduct. The yield was actually very similar using TBAD or DEAD. Although in the first tests we included also Et<sub>3</sub>N in the reaction mixture (methods A and B), according to what found in the analogous cyclization of phenols,<sup>11</sup> we later found that the presence of Et<sub>3</sub>N was not really necessary, and that the same yields were obtained also without it (method C). Apart from entries 1 and 2, the cyclization yields were always excellent (around 90%).

In the case of the  $\beta$ -alanine-derived compound **10a** (used as model for preliminary studies) the outcome was more complex. Under the usual Mitsunobu conditions the reaction was fast and reached completion in few minutes at 0 °C. However, to our surprise, the expected product **2a** was formed in only 32% yield and was accompanied as a major product (55%) by the bicyclic adduct **11a**. The latter was formed with a remarkable stereoselectivity (15:1 diastereomeric ratio). The structure of **11a** was assigned on the basis of NMR spectra (see the Supporting Information).

We tried to improve the yield of **2a** by changing various reaction parameters (phosphine, azodicarboxylate, solvent) but without success. Thus we turned to completely different conditions. However, on treating **10** with methanesulfonyl chloride and Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> at –30 → 0 °C, exclusively the bicyclic compound **11a** was formed, with no trace of **2a**. After various unsuccessful attempts, our attention was drawn by *N,N'*-sulfuryl diimidazole. This reagent was introduced as an alternative to the Mitsunobu reaction by Hanessian in the 80s,<sup>31,32</sup> but since then, to our knowledge, it has never been employed again in an intramolecular fashion.

To our satisfaction, treatment of **10a** with *N,N'*-sulfuryl diimidazole in the presence of a suitable base gave cleanly only the diazepanone **2a**, without any formation of **11a**. The reaction

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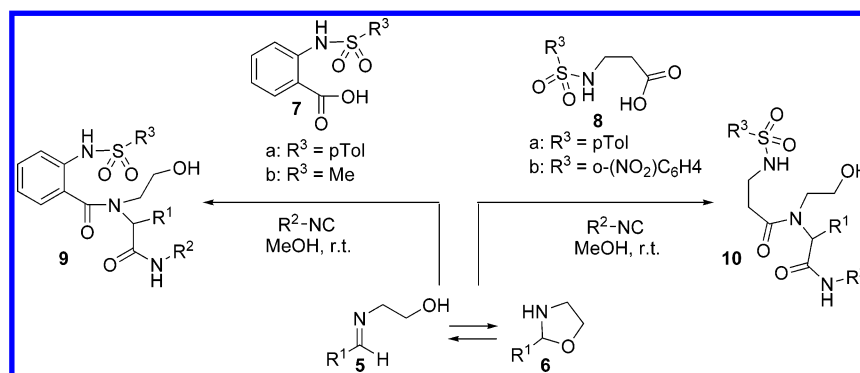
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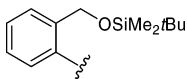
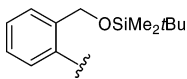
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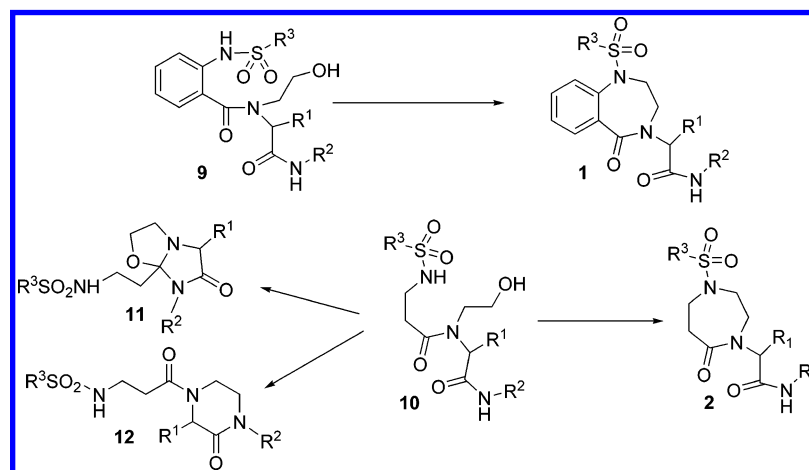
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SCHEME 2

TABLE 1. Results of Ugi Reaction of Imines 5, Isocyanides, and  $\beta$ -Sulfonylamino Acids 7 or 8

entry	product	carboxylic acid	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield
1	9a	7a	<i>t</i> Bu	<i>cy</i> Hex	<i>p</i> -Tol	48%
2	9b	7a	3-BrC <sub>6</sub> H <sub>4</sub>	<i>n</i> Bu	<i>p</i> -Tol	63%
3	9c	7a	<i>cy</i> Hex	Bn	<i>p</i> -Tol	88%
4	9d	7a	<i>cy</i> Hex	<i>t</i> BuCH <sub>2</sub> CMe <sub>2</sub> -	<i>p</i> -Tol	35%
5	9e	7b	3-BrC <sub>6</sub> H <sub>4</sub>	Bn	Me	70%
6	9f	7b	<i>i</i> Pr	<i>cy</i> Hex	Me	77%
7	9g	7b	Ph	<i>n</i> Bu	Me	57%
8	9h	7b	2-furyl	<i>cy</i> Hex	Me	67%
9	9i	7a	<i>i</i> Pr		<i>p</i> Tol	69%
10	9j	7b	<i>cy</i> Hex	<i>t</i> BuO <sub>2</sub> C-CH <sub>2</sub> -	Me	62%
11	10a	8a	<i>i</i> Pr	<i>cy</i> Hex	<i>p</i> -Tol	67%
12	10b	8a	<i>cy</i> Hex	Bn	<i>p</i> -Tol	69%
13	10c	8a	<i>i</i> Pr	<i>t</i> Bu	<i>p</i> -Tol	95%
14	10d	8a	<i>n</i> Bu	Bn	<i>p</i> -Tol	25%
15	10e	8a	4-ClC <sub>6</sub> H <sub>4</sub>	<i>cy</i> Hex	<i>p</i> -Tol	62%
16	10f	8a	3-MeOC <sub>6</sub> H <sub>4</sub>	<i>t</i> Bu	<i>p</i> -Tol	70%
17	10g	8a	3-MeOC <sub>6</sub> H <sub>4</sub>	<i>t</i> BuCH <sub>2</sub> CMe <sub>2</sub> -	<i>p</i> -Tol	52%
18	10h	8a	3-MeOC <sub>6</sub> H <sub>4</sub>	<i>n</i> Bu	<i>p</i> -Tol	62%
19	10i	8a	2-furyl	<i>cy</i> Hex	<i>p</i> -Tol	77%
20	10j	8a	3-MeOC <sub>6</sub> H <sub>4</sub>	<i>t</i> BuO <sub>2</sub> C-CH <sub>2</sub> -	<i>p</i> -Tol	90%
21	10k	8a	<i>i</i> Pr		<i>p</i> -Tol	45%
22	10l	8b	<i>i</i> Pr	Bn	2-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> -	80%
23	10m	8b	Ph	<i>cy</i> Hex	2-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> -	79%

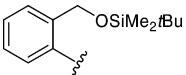
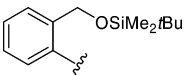
SCHEME 3



was optimized on changing the base and the solvent. With Et<sub>3</sub>N, DBU (1,8-diazabicyclo[5,4,0]undec-7-ene), or K<sub>2</sub>CO<sub>3</sub> no reaction occurred. With *n*Bu<sub>4</sub>NF the reaction took place but sluggishly. Best results were obtained with 1.2 equiv of NaH

or NaHMDS (NaN(SiMe<sub>3</sub>)<sub>2</sub>) in DMF. **2a** was isolated in 68% yield and easily purified by chromatography (whereas separation of **2a** from **11a** after classical Mitsunobu was rather difficult).

TABLE 2. Results of Cyclization of Hydroxysulfonamides 9–10<sup>a</sup>

entry	product	method	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield (1 or 2)	yield (11)	yield (12)
1	1a	A	<i>i</i> Bu	cyHex	<i>p</i> -Tol	51%		
2	1b	B	3-BrC <sub>6</sub> H <sub>4</sub>	<i>n</i> Bu	<i>p</i> -Tol	70%		
3	1c	C	cyHex	Bn	<i>p</i> -Tol	85%		
4	1d	A	cyHex	<i>t</i> BuCH <sub>2</sub> CMe <sub>2</sub> -	<i>p</i> -Tol	82%		
5	1e	B	3-BrC <sub>6</sub> H <sub>4</sub>	Bn	Me	98%		
6	1f	C	<i>i</i> Pr	cyHex	Me	95%		
7	1g	C	Ph	<i>n</i> Bu	Me	91%		
8	1h	C	2-furyl	cyHex	Me	92%		
9	1i	C	<i>i</i> Pr		<i>p</i> -Tol	91%		
10	1j	C	cyHex	<i>t</i> BuO <sub>2</sub> C-CH <sub>2</sub> -	Me	93%		
11	2a	A	<i>i</i> Pr	cyHex	<i>p</i> -Tol	32%	55%	
12	2a	D	<i>i</i> Pr	cyHex	<i>p</i> -Tol	68%		
13	2b	D	cyHex	Bn	<i>p</i> -Tol	55%		18%
14	2c	D	<i>i</i> Pr	<i>t</i> Bu	<i>p</i> -Tol	52%		
15	2d	D	<i>n</i> Bu	Bn	<i>p</i> -Tol	46%		10%
16	2e	D	4-ClC <sub>6</sub> H <sub>4</sub>	cyHex	<i>p</i> -Tol	52%		10%
17	2f	D	3-MeOC <sub>6</sub> H <sub>4</sub>	<i>t</i> Bu	<i>p</i> -Tol	60%		22%
18	2g	D	3-MeOC <sub>6</sub> H <sub>4</sub>	<i>t</i> BuCH <sub>2</sub> CMe <sub>2</sub> -	<i>p</i> -Tol	62%		14%
19	2h	D	3-MeOC <sub>6</sub> H <sub>4</sub>	<i>n</i> Bu	<i>p</i> -Tol	42%		18%
20	2i	D	2-furyl	cyHex	<i>p</i> -Tol	27%		
21	2j	D	3-MeOC <sub>6</sub> H <sub>4</sub>	<i>t</i> BuO <sub>2</sub> C-CH <sub>2</sub> -	<i>p</i> -Tol	30% <sup>b</sup>		30%
22	2k	D	<i>i</i> Pr		<i>p</i> -Tol			45%
23	2l	D	<i>i</i> Pr	Bn	2-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> -	36%		50%
24	2m	D	Ph	cyHex	2-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> -	41%		28%

<sup>a</sup> Yields are of isolated products after chromatography and do not take into account the recovered starting materials. **Method A:** DEAD, PPh<sub>3</sub>, Et<sub>3</sub>N, THF, 0 °C. **Method B:** TBAD, PPh<sub>3</sub>, Et<sub>3</sub>N, THF, 0 °C. **Method C:** TBAD, PPh<sub>3</sub>, THF, 0 °C. **Method D:** sulfonyl diimidazole, NaHMDS or NaH, DMF, room temperature, 4–18 h. <sup>b</sup> In this case separation of **2j** from **12j** proved difficult and was not performed.

Also in this case, in order to assess the scope of the protocol, we varied the aldehyde, the isocyanide, and the sulfonyl group (see Table 2). The methodology proved to be reasonably general. However, in several cases, the cyclization reaction furnished a byproduct, whose structure did not correspond to the bicyclic compound **11** but instead to the ketopiperazine **12**. The assignment of this structure was made on the basis of NMR spectra (see the Supporting Information). With sulfonamido alcohols derived from aliphatic aldehydes, usually this byproduct was formed in little amount, but when an aromatic isocyanide, namely, the “convertible” Linderman isocyanide,<sup>33</sup> was employed (entry 22) the ketopiperazine **12** was formed exclusively. Substantial amount of this side product were also observed in entries 21, 23, and 24. It seems that the formation of ketopiperazine is favored by a higher acidity of the amide derived from the isocyanide, by an increased steric bulk of the sulfonamide, and in part when sulfonamido alcohols are derived from aromatic aldehydes.

The short preparation of **1** and **2** (just two steps) opens the way to the synthesis of collections of compounds arising from decoration of the 1-sulfonyl-1,4-diazepan-5-one and of the 1-sulfonyl tetrahydrobenzo[*e*]-1,4-diazepin-1-one scaffolds. These heterocycles, despite their close resemblance to important drugs, have been very little explored so far in medicinal chemistry.<sup>27,34,35</sup> Although in the case of **2** the overall yields are in some cases only moderate, the possibility to obtain in just two

simple steps relatively complex structures, with the introduction of three diversity points, makes this protocol well suited for the preparation of collections of potentially bioactive substances.

Another nucleophile that can be employed in Mitsunobu reactions is the hydroxamate. So we decided to explore its use in this strategy, including it once again into the carboxylic component of an Ugi reaction. We reasoned that monohydroxamates of malonic acids would have been problematic due to the presence of further relatively acidic protons at the α-position. Therefore we chose monohydroxamates of succinic acid instead, with the goal to obtain the unprecedented mesocyclic scaffolds **3** or **4** (substituted diazocanediones).

The acid **13** was easily obtained by reaction of succinic anhydride with *O*-benzyl hydroxylamine (Scheme 4).<sup>36</sup> The Ugi condensation with imine **5b** and benzyl isocyanide afforded in moderate yield the adduct **14**. Also in this case protection of the alcoholic moiety was not necessary.

When **14** was treated under the standard Mitsunobu conditions (DEAD, PPh<sub>3</sub>, 0 °C) two new products were rapidly formed. However, the main one was not the expected 1,4-diazocane-5,8-dione **3a** nor the isomeric compound **15a**. Identification of this new unexpected product was not easy, because it tended to decompose in part upon chromatography or in the presence of traces of acids (even upon simple dissolution in CDCl<sub>3</sub>, due to the likely presence of traces of DCl) giving the imide **17**. On the other hand, in the presence of Et<sub>3</sub>N, it was converted back into starting material **14**. Eventually, after fast chromatography and quick NMR analysis in DMSO-*d*<sub>6</sub>, we could obtain a clean spectrum of **16a**, which was consistent with the isomerized ester. This structure is also in agreement with the observed conversion

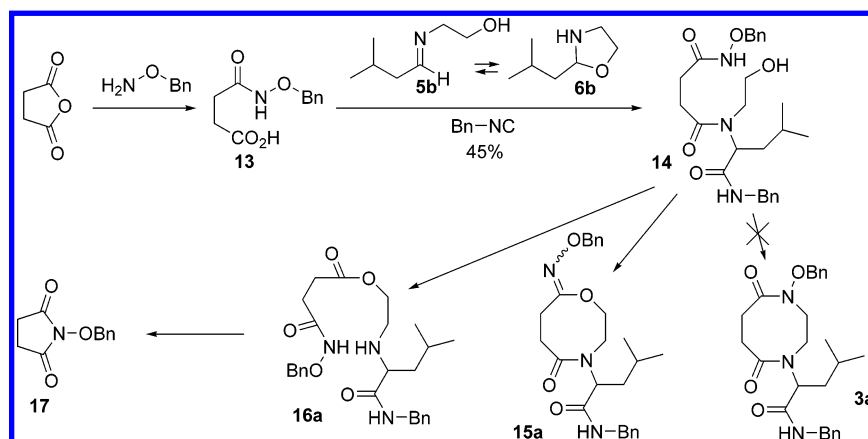
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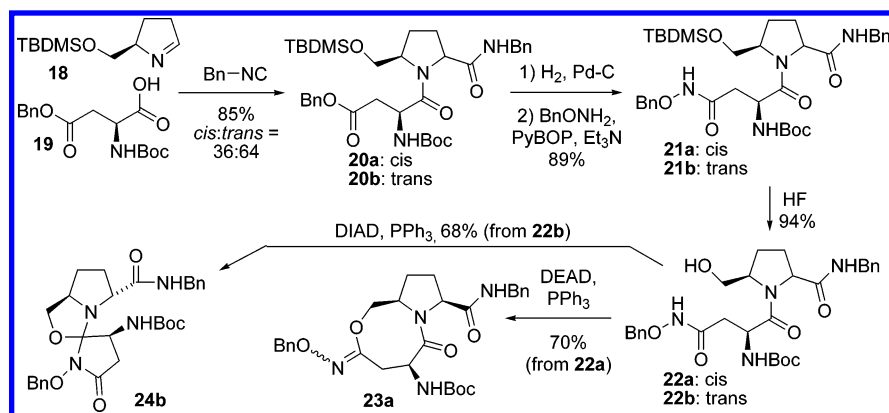
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SCHEME 4



SCHEME 5



into **17** under acid conditions and **14** under basic conditions. The yield of this compound could not be established precisely, but it was clearly the main product. A minor product (this time completely stable) was isolated in 25% yield from the reaction mixture. It was recognized as the *O*-cyclized adduct **15a**. It is well known that hydroxamates are ambident nucleophiles and that they can cyclize under Mitsunobu conditions either to cyclic hydroxamates or to iminolactones.<sup>37–40</sup> In our case, the <sup>1</sup>H and <sup>13</sup>C NMR spectra are definitely more consistent with the iminolactone structure **15** than with the expected cyclic hydroxamate **3**. In particular the <sup>13</sup>C spectrum shows three quaternary carbons at 175.1, 171.0, and 156.2 ppm. The last value fits better with an iminolactone than with a cyclic hydroxamate. There is a CH<sub>2</sub> at 68.5 ppm, suggesting a CH<sub>2</sub>O group. Finally, at <sup>1</sup>H NMR, the same CH<sub>2</sub> gives signals at 4.39 and 4.07 ppm, values that seem too high for a CH<sub>2</sub>N group. In the spectra of **15a**, there is only one set of signals, indicating that it is probably just one of the possible diastereoisomers around the C=N double bond. We think that the other one is formed in little amount and therefore we were not able to isolate it. We tried to improve the yield of **15a**, but without success: using di-*iso*-propyl azodicarboxylate (DIAD) or di-*tert*-butyl azodicarboxylate (DBAD) the situation was even worse and nearly no adduct **15a** was formed.

We explored the same reaction also on the more complex substrates **22a,b**, hoping that the pyrrolidine ring could furnish a steric bias favoring the desired cyclization (Scheme 5). These compounds were obtained starting from the chiral, enantiomerically pure, pyrroline **18**, whose preparation and use in Ugi reactions were recently reported by us.<sup>9</sup> The reaction of **18** with the aspartic derivative **19** and benzyl isocyanide proceeded in high yield to give a 2:1 trans:cis diastereoisomeric mixture.<sup>9</sup> Conversion of the benzyl ester into the corresponding hydroxamate and removal of the silyl protecting group gave the alcohols **22a,b**, which could be conveniently separated and fully characterized at this stage.

They were independently submitted to Mitsunobu conditions and were found to give a completely different outcome. The cis compound gave only one significant product **23a**, in good yields. This adduct was recognized as the *O*-cyclized product by its NMR spectra. On the contrary, cyclization of the *trans* compound **22b** gave a mixture of two isomeric products in a 68:32 ratio. This reaction was best carried out with DIAD, since the diethyl hydrazo dicarboxylate coeluted with the product. However the same mixture was formed also with DEAD. Although these two isomers did not separate on thin-layer chromatography (TLC) or with high-performance liquid chromatography (HPLC), they gave distinct NMR signals that did not merge even at 120 °C. The most important feature of these isomers at NMR is the presence of only three carbonyl signals at 171.3/172.6, 165.2/166.0, and 154.8, instead of the expected four. Moreover, there is a quaternary signal at 108.4/109.7. The <sup>1</sup>H NMR shows clearly the presence of the NHBn hydrogen and the absence of OH groups or of other amidic NHs (apart

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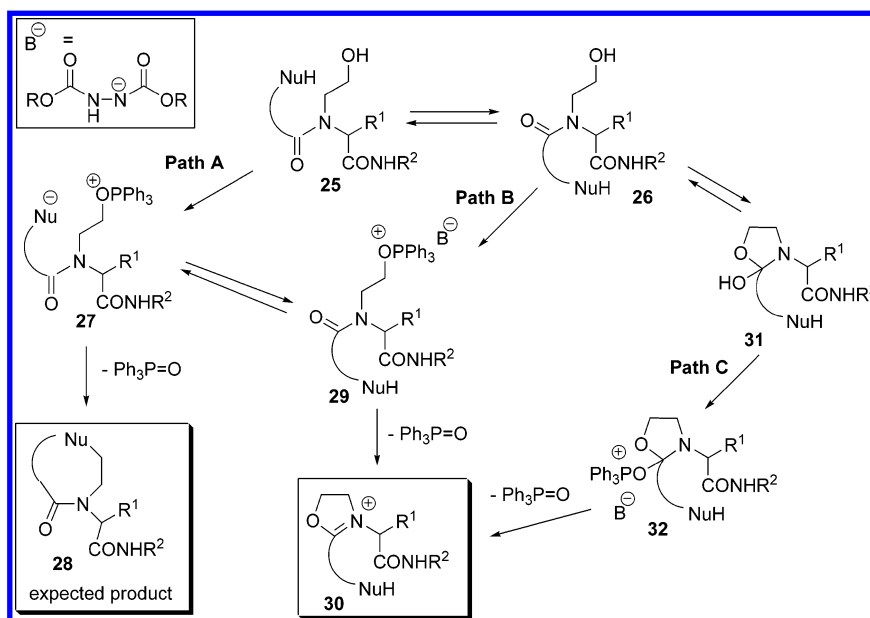
(38) Panday, S. K.; Langlois, N. *Tetrahedron Lett.* **1995**, *36*, 8205–8208.

(39) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995–3000.

(40) Langlois, N.; Calvez, O. *Tetrahedron Lett.* **2000**, *41*, 8285–8288.



SCHEME 6



from the *NHBoc*). On standing in solution, especially in the presence of water, **24b** tended to decompose, indicating a relatively facile hydrolysis. These and other data indicate the structure **24b** depicted in Scheme 5 as the most likely one. The presence of a new stereogenic center explains the formation of two isomers, while the 108.4/109.7 signal is in agreement with the orthoester-type carbon.

Although interesting, the results obtained with the hydroxy hydroxamates **14** and **22** are not very promising from the synthetic point of view. The yield of the cyclized product is heavily dependent from subtle structural or stereochemical variations, and moreover, the *O*-cyclized products are favored. The resulting iminolactones are not very attractive from the point of view of medicinal chemistry because of their likely metabolic instability.

However, the results collected allow us to try to rationalize the outcome of these Mitsunobu reactions. Scheme 6 shows a general mechanistic hypothesis that can be applied to the nucleophiles described in this paper (sulfonamides and hydroxamates) but also to the previously described phenols.<sup>11</sup> We think that side reactions as well as the recovery of starting material (observed in the case of phenols as nucleophiles) can be explained through the formation of an oxazolinium ion intermediate **30**.

The starting materials exist in two interconverting conformers deriving from rotation around the tertiary amide bond. Only one of these conformers (**25**) can be converted into the desired cyclization product **28** (path A). On the other hand, in the other conformation **26**, activation of the hydroxy group will give the intermediate **29**. In this structure only the oxygen of the tertiary amide can act as a nucleophile, forming the oxazolinium cation **30** (path B). Intermediate **29** is obviously in equilibrium with the conformer **27**. Therefore the competition between the two paths depends on various factors, such as the position of the conformational equilibrium, the ring size formed from path A, and the acidity of the NuH group. The scale of acidity should be: aromatic sulfonamides, phenols, aliphatic sulfonamides, hydroxamates. Therefore aromatic sulfonamides and phenols form an anion more easily and path A predominates, especially

in the presence of a base ( $\text{Et}_3\text{N}$ ), which increases the amount of the anion present in solution.

On the other hand, with aliphatic sulfonamides and hydroxamates, the alternative path B becomes predominant and the oxazolinium ion **30** is formed preferentially. The same oxazolinium ion can be formed also through a third pathway (path C), where the system DEAD/ $\text{PPh}_3$  acts on the cyclic intermediate **31** provoking a formal elimination of water.

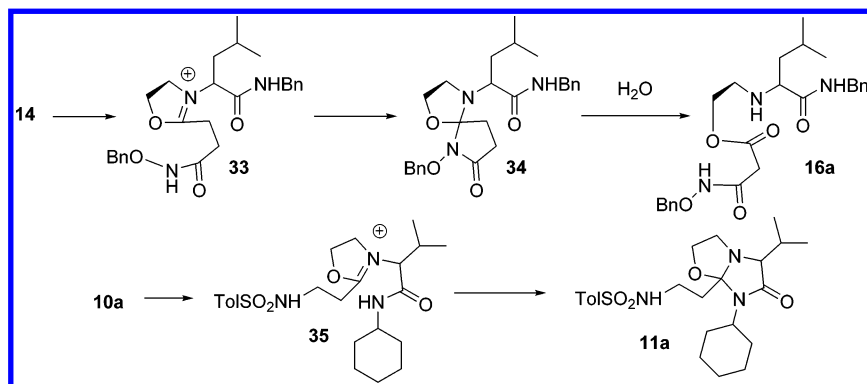
The fate of the oxazolinium ion **30** depends on the overall structure. In the case of the hydroxamates studied in this work (Scheme 7), the length of the chain bearing the NuH group allows attack by this group to the  $\text{C}=\text{N}$  bond to give the spiro compounds **34**. Although this product was not isolated starting from the simpler substrate **14**, we think that it may undergo a facile hydrolysis during workup to give the ester **16a**. On the contrary, starting from the more complex substrate **22b**, a spiro compounds analogue to **34** could be isolated. The higher bulkiness of substituents and the presence of the additional pyrrolidine ring makes this adduct more stable, although we observed its facile hydrolysis on standing (see above).

In the case of aliphatic sulfonamides, this type of cyclization would lead to a four-membered ring and is disfavored. Therefore the oxazolinium ion **34** is attacked by the secondary amide to give **11a**.

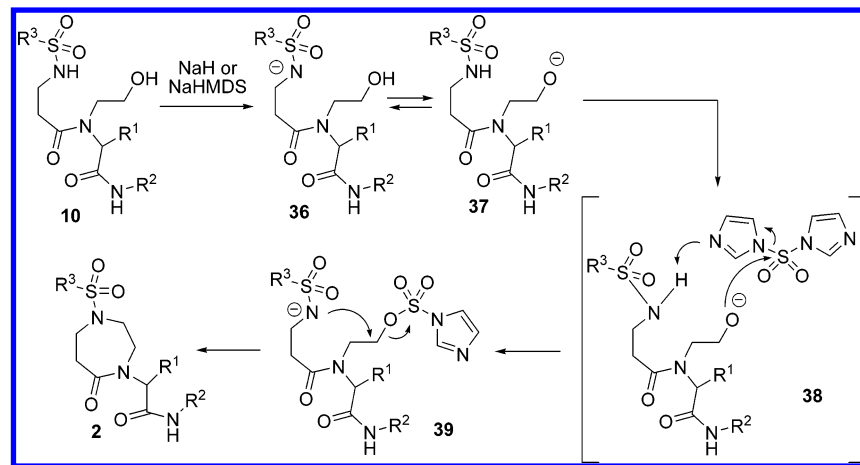
Finally, in the case of phenols derived from salicylic acid,<sup>11</sup> probably because of conjugation of the aryl with the  $\text{C}=\text{N}$  double bond in the oxazolinium ions **30**, both type of cyclization are disfavored and **30** is hydrolyzed during workup giving back the starting material.

The competition between path A and paths B or C is expected to be operating also using other activation methods. Actually, as already stated above, reaction of **10a** with methanesulfonyl chloride and  $\text{Et}_3\text{N}$  gave exclusively the bicyclic adduct **11**. A mechanism analogous to path B can account for this behavior. A question now arises: why the situation is completely reversed with sulfonyl diimidazole? After all, sulfonyl imidazole is believed to react with alcohols under basic conditions to give sulfonyl derivatives not very different from methanesulfonates.<sup>32</sup> However we think that the mechanism of the reaction of alcohols

SCHEME 7



SCHEME 8



with sulfonyl diimidazole may be different from that with sulfonyl chlorides. The imidazolidine anion is a poor leaving group and therefore reaction with the alkoxide should be accelerated if an acid species protonates the pyridine-type imidazole nitrogen during substitution. Under the conditions employed there are only two possible acid species: the sulfonamide and the secondary amide, the former being much more acidic. Scheme 8 shows a possible mechanism.

In this hypothesis the rate-limiting step is the formation of the activated alcohol **39**. For its formation the sulfonamido group plays the double role of basic catalyst (provoking the formation of the alcoholate **37**) and of acid catalyst, favoring imidazole expulsion during the nucleophilic attack of the alcoholate to sulfonyl diimidazole. Therefore only the “correct” conformation may react. In this conformation only path A is possible, because path B will require a conformational change. Also the formation of ketopiperazines can be explained by this picture. In this case it is the secondary amide that plays the role of basic-acid catalyst. It is interesting to note that the reaction promoted by the secondary amide may take place in both conformations. The side reaction leading to ketopiperazines should be disfavored by the lower acidity of the amide compared to the sulfonamides. However, the fact that it forms a six-membered ring (instead of a seven-membered ring) and that it can occur on both conformers, makes it competitive in some cases with the desired pathway, especially when the amide acidity is increased, such as in entries 21 and 22 of Table 2.

## Conclusions

The results discussed in this paper show the power of coupling Ugi MCRs with post-condensation transformations for the rapid

obtainment of relatively complex heterocyclic scaffolds in few steps. Although coupling the Ugi reaction with a known organic transformation like the Mitsunobu reaction may seem a trivial exercise, one should always bear in mind that we are working on complex highly functionalized structures, and that the two amidic groups arising from the Ugi reaction do not always behave as mere spectators: they can indeed heavily interfere with the “normal” expected course of the reaction. Fine-tuning of the conditions and a thorough assessment of the scope of these synthetic methodologies have to be pursued before claiming the synthetic utilities of these tandem reactions. In our case, we have proved that the very short (2 steps) synthesis of tetrahydrobenzo[*e*]-1,4-diazepin-1-ones and of 1-sulfonyl 1,4-diazepan-5-ones with 3 diversity inputs is indeed possible by coupling Ugi and Mitsunobu reactions. The addition of further diversity inputs (using substituted ethanolamines and substituted anthranilic acids) is in progress. On the contrary, the attempted synthesis of 1,4-diazocane-5,8-diones was less successful. In any case the collected results allowed us to propose a possible mechanistic rationalization, which may be precious for future developments.

## Experimental Section

**General Procedure for the Synthesis of Imines 5–Oxazolidines 6 from Aliphatic Aldehydes and Ethanolamine. 2-(2-Methylpropylideneamino)ethanol 5a/2-Isopropylloxazolidine 6a.** A solution of isobutyraldehyde (5 mL, 54.8 mmol) in dry diethyl ether (50 mL) was treated, at room temperature, with ethanolamine (3.30 mL, 54.8 mmol) and powdered 4-Å molecular sieves (10 g). After 1 h the mixture was filtered and the filtrate distilled at 250–300 mbar first and then at 34 mbar to give the pure imine as a

colorless liquid (3.892 g, 62%) (bp 60–64 °C at 34 mbar). <sup>1</sup>H NMR showed a 17:83 ratio between **5a** and **6a**. **5a**: δ 1.07 [6 H, d, CH(CH<sub>3</sub>)<sub>2</sub>, J 6.9]; 2.43 (mc) [1 H, m, CH(CH<sub>3</sub>)<sub>2</sub>]; 3.50 (mc) [2 H, m, CH<sub>2</sub>OH]; 3.79 [2 H, t, CH<sub>2</sub>N, J 5.3]; 7.61 [1 H, d, CH=N, J 4.2]. **6a**: δ 0.98 and 1.00 [2 × 3 H, 2d, CH(CH<sub>3</sub>)<sub>2</sub>, J 6.6]; 1.77 [1 H, octuplet, CH(CH<sub>3</sub>)<sub>2</sub>, J 6.3]; 3.00 [1 H, dt, CHH–N, J<sub>t</sub> 7.6, J<sub>d</sub> 11.7]; 3.23 [1 H, ddd, CHH–N, J 4.8, 6.6, 11.7]; 3.60–3.76 [2 H, m, CH<sub>2</sub>O]; 4.07 [1 H, d, O–CH–N, J 6.3]. GC-MS: *R*<sub>f</sub> 2.46; *m/z* 115 (M<sup>+</sup>, 0.9); 100 (2.9); 84 (31.4); 72 (100.0); 70 (21.8); 56 (11.8); 55 (11.2); 45 (25.8); 44 (30.6); 43 (9.8); 42 (10.6); 41 (15.8); 39 (9.3).

**General Procedure for the Synthesis of Imines 5 from Aromatic Aldehydes and Ethanolamine.** As above, but, after filtration of molecular sieves, the solution was evaporated to dryness. After further stripping at 1 mbar for 2–3 h, the crude imine was used as such for the Ugi reaction. NMR in selected cases showed that only the imine form **5** was present.

**General Procedure for the Ugi Reactions to give 9–10.** The freshly prepared imine is dissolved in dry MeOH (0.7 M) and added with powdered 3-Å molecular sieves (30 mg/mL). Acid **7** or **8** (0.9 equiv) and the appropriate isocyanide (0.8 eq) are then added in sequence. After 24 h the solution is filtered and evaporated. It is taken up in AcOEt or CH<sub>2</sub>Cl<sub>2</sub> (when the residue is not soluble in AcOEt) and washed with saturated aqueous NaHCO<sub>3</sub>. After drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation, the crude product is chromatographed on silica gel (220–400 mesh) with CH<sub>2</sub>Cl<sub>2</sub>/Me<sub>2</sub>CO (about 85:15) or petroleum ether/Me<sub>2</sub>CO (about 6:4). The purity of the Ugi products was assessed by <sup>1</sup>H and <sup>13</sup>C NMR as well as by TLC. The NMR spectra showed a double set of signals due to conformational equilibria. Only at 110 °C did the coalescence occur. However, some signals were still broad. For this reason we preferred to carry out the complete characterization on the cyclized products **1** and **2**.

**General Procedure for the Intramolecular Mitsunobu: To Give Compounds 1. Method A.** A solution of **9** (0.414 mmol) in dry THF (5 mL) was cooled to 0 °C and treated with PPh<sub>3</sub> (177 mg, 0.675 mmol), Et<sub>3</sub>N (115 μL, 0.83 mmol), and DEAD (98 μL, 0.62 mmol). After 5 min the cooling bath was removed and the mixture stirred at room temperature for 1–6 h until disappearance of the substrate. The solvent was evaporated and the crude product immediately chromatographed through 220–400 mesh silica gel (petroleum ether/acetone) to give the pure product.

**Method B.** Exactly as above but using TBAD instead of DEAD.

**Method C.** Exactly as above but without addition of Et<sub>3</sub>N.

**General Procedure for the Cyclization of 10 to Give 2 (Method D).** The substrate **10** was dissolved in DMF (0.18 M) and treated subsequently with 1.5 equiv of *N,N'*-sulfuryldiimidazole and 1.2 equiv of NaH (60% in mineral oil) or sodium hexamethyldisilazide (0.6 M in toluene). After 18 h, the reaction was quenched with 5% aqueous NH<sub>4</sub>H<sub>2</sub>PO<sub>4</sub> + 1 M HCl (10:1). The pH was adjusted to 3. Extraction with AcOEt, drying (Na<sub>2</sub>SO<sub>4</sub>), and evaporation gave a crude product that was chromatographed on silica gel (220–400 mesh) typically with CH<sub>2</sub>Cl<sub>2</sub>/Me<sub>2</sub>CO 95/5 or 9/1 or with petroleum ether/AcOEt 4/6 + 1–2% EtOH. The latter solvent mixture was better suited when separation from the side product **12** turned difficult. In most cases, analytically pure samples could be obtained by trituration from Et<sub>2</sub>O/PE.

**Selected Data for Compounds 1–2. *N*-Cyclohexyl-2-(2,3-dihydro-5-oxo-1-tosyl-1H-benzo[e][1,4]diazepin-4(5H)-yl)-4-methylpentanamide 1a.** White solid. Mp: 158.8–161.5 °C. *R*<sub>f</sub> 0.43 (PE/AcOEt 6:4). Found: C, 65.4; H, 7.3; N, 8.1. C<sub>28</sub>H<sub>37</sub>N<sub>3</sub>O<sub>4</sub>S requires C, 65.73; H, 7.29; N, 8.21. <sup>1</sup>H NMR: δ 0.72–0.85 [1 H, m, CHH*i*Pr]; 0.86 [3 H, d, CH<sub>3</sub>, J 6.6]; 0.89 [3 H, d, CH<sub>3</sub>, J 6.3]; 1.03–1.48 [7 H, m, CH<sub>2</sub> cyclohexyl + CH(CH<sub>3</sub>)<sub>2</sub>]; 1.50–1.80 [4 H, m, CH<sub>2</sub> cyclohexyl]; 1.80–1.95 [1 H, m, CHH*i*Pr]; 2.41 [3 H, s, CH<sub>3</sub>]; 3.17 [1 H, ddd, CHHN, J 4.2, 11.4, 15.6]; 3.50–3.62 [1 H, m, CHHN]; 3.60–3.72 [1 H, m, *cy*Hex-CHN]; 3.73–3.84 [1 H, m, CHHN]; 3.95 [1 H, dt, CHHN, J<sub>d</sub> 4.8, J<sub>t</sub> 12.00]; 4.59 [1 H, dd, CHCH<sub>2</sub>, J 4.2, 10.5]; 6.16 [1 H, d, NH, J 8.4]; 7.23 [2 H, d, H

ortho to CH<sub>3</sub>, J 8.1]; 7.40–7.60 [5 H, m, aromatics]; 7.65 [1 H, d, H ortho to C=O, J 7.5]. <sup>13</sup>C NMR: δ 21.6 [CH<sub>3</sub>Ar]; 22.0, 23.3 [(CH<sub>3</sub>)<sub>2</sub>CH]; 24.5 (2), 25.4, 32.6, 32.7 [CH<sub>2</sub> cyclohexyl]; 25.1 [CH(CH<sub>3</sub>)<sub>2</sub>]; 41.7 [CH<sub>2</sub>N]; 48.0 [*cy*Hex-CHNH]; 53.3 [CH<sub>2</sub>N]; 54.4 [*i*Bu-CHN]; 127.5 [CH ortho to SO<sub>2</sub>]; 128.9 [CH meta to C=O] 129.7 [CH meta to SO<sub>2</sub>]; 130.4 [CH ortho to C=O]; 131.4 [CH meta to C=O]; 132.3 [CH para to C=O]; 134.3, 134.4, 136.5, 143.7 [quaternary aromatic]; 168.8, 169.5 [C=O]. IR: *ν*<sub>max</sub> 3419 (broad), 2996, 2935, 2854, 1663, 1630, 1598, 1504, 1449, 1406, 1348, 1256, 1155, 1116, 1086, 1050 cm<sup>-1</sup>.

***N*-Cyclohexyl-3-methyl-2-(7-oxo-4-tosyl-1,4-diazepan-1-yl)butanamide 2a.** Foam. *R*<sub>f</sub> 0.51 in PE/AcOEt 4:6. Found: C, 61.7; H, 7.9; N, 9.25. C<sub>23</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub>S requires C, 61.44; H, 7.85; N, 9.35. <sup>1</sup>H NMR: δ 0.78 and 0.91 [2 × 3H, 2d, (CH<sub>3</sub>)<sub>2</sub>CH J 6.9, 6.3]; 1.00–1.85 [10H, m, cyclohexyl]; 2.19 [1H, d of septuplet, CH(CH<sub>3</sub>)<sub>2</sub>, J<sub>s</sub> 6.5, J<sub>d</sub> 11.1]; 2.42 [3H, s, ArCH<sub>3</sub>]; 2.36–2.48 [1H, m, H-3]; 2.56 [1H, t, H-7, J=11.5]; 2.74 [1H, dd, H-6, J 14.7, 6.9]; 2.86 [1H, ddd, H-6, J 14.7, 10.8, 1.8]; 3.50–3.64 [2H, m, CHNH of cyclohexyl + H-2]; 3.73–3.92 [3H, m, H-2, H-7, H-3]; 4.35 [1H, d, *i*PrCHNH, J=11.1]; 5.82 [1H, d, NH, J=8.1]; 7.31 [2 H, d, CH ortho to CH<sub>3</sub>, J 8.1]; 7.61 [2 H, CH meta to CH<sub>3</sub>, J 8.1]. <sup>13</sup>C NMR: δ 18.5 and 19.4 [CH(CH<sub>3</sub>)<sub>2</sub>]; 21.5 [Ar-CH<sub>3</sub>]; 24.6 [2 × CH<sub>2</sub> cyclohexyl]; 25.3 [CH<sub>2</sub> cyclohexyl]; 25.9 [CH(CH<sub>3</sub>)<sub>2</sub>]; 32.66 and 32.68 [2C, CH<sub>2</sub> cyclohexyl]; 37.9 [C-6 of the ring]; 43.7 [C-7 of the ring]; 43.9 [C-2 of the ring]; 47.8 [CHN cyclohexyl]; 49.2 [C-3 of the ring]; 62.7 [*i*Pr-CHN]; 127.4 and 129.8 [aromatic CH]; 133.6 and 143.8 [aromatic C quat.]; 168.7 and 174.3 [C=O]. IR: *ν*<sub>max</sub> 3685, 3419, 3028, 2930, 2855, 2402, 1667, 1638, 1504, 1434, 1364, 1340, 1307, 1242, 1158, 1094, 971, 905, 821 cm<sup>-1</sup>.

***N*'-(1-(Benzylcarbamoyl)-3-methylbutyl)-*N*'-(benzyloxy)-*N*'-(2-hydroxyethyl)succinamide 14.** It was prepared in 50% yield from **5b/6b** and acid **13** following the general procedure for Ugi reactions. *R*<sub>f</sub> 0.32 (CH<sub>2</sub>Cl<sub>2</sub>/Me<sub>2</sub>CO 7:3). Found: C, 66.3; H, 7.45; N, 8.85. C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>5</sub> requires C, 66.50; H, 7.51; N, 8.95. <sup>1</sup>H NMR: (DMSO-*d*<sub>6</sub>, 110 °C): δ 0.91, 0.93 [2 × 3H, 2 d, (CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub> J 5.4, 6.0]; 1.48–1.66 [2H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>]; 1.84 [1H, octuplet, CH(CH<sub>3</sub>)<sub>2</sub> J 7.2]; 2.37 [2 H, t, CH<sub>2</sub>C=O, J 6.9]; 2.56–2.76 [2H, m, CH<sub>2</sub>C=O]; 3.30–3.65 [4H, m, OCH<sub>2</sub>CH<sub>2</sub>N]; 4.31 [2H, d, HNCH<sub>2</sub>Ph J 5.7]; 4.52, 4.66 [2H, 2 s (broad), CHN and OH]; 4.82 [2H, s, PhCH<sub>2</sub>O]; 7.18–7.45 [10H, m, CH aromatics]; 7.99 [1H, s, NHCH<sub>2</sub>Ph]; 10.55 [1H, s, NH hydroxamate]. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 110 °C): δ 21.5, 21.9 [(CH<sub>3</sub>)<sub>2</sub>CH]; 24.0 [CH(CH<sub>3</sub>)<sub>2</sub>]; 27.4, 27.5 [2 × CH<sub>2</sub>C=O]; 37.7 [CH<sub>2</sub>N]; 42.0 [CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>]; 46.8 [PhCH<sub>2</sub>N]; 56.7 [CHN]; 59.2 [CH<sub>2</sub>OH]; 76.6 [PhCH<sub>2</sub>O]; 125.9, 126.5, 127.3, 127.4, 127.5, 127.9 [aromatic CH]; 135.5, 138.7 [aromatic quat. C]; 169.6, 170.2, 171.9 [3 × C=O].

**Mitsunobu Reaction of Compound 14.** It was carried out under the conditions of method A described above. Chromatography (PE/acetone 7:3 to 6:4) gave compounds **15a** (faster eluting, 25%) plus compound **16a** (35%). It should be noted that **16a** tended to decompose in part during chromatography giving **17** or **14**.

***N*-Benzyl-2-(8-benzyloxyimino-5-oxo-1,4-oxazocan-4-yl)-4-methylpentanamide 15a.** *R*<sub>f</sub> 0.63 in CH<sub>2</sub>Cl<sub>2</sub>/AcOEt 1:1. Found: C, 69.0; H, 7.45; N, 9.15. C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub> requires C, 69.16; H, 7.37; N, 9.31. <sup>1</sup>H NMR: δ 0.90, 0.93 [2 × 3H, 2 × d, (CH<sub>3</sub>)<sub>2</sub>CH, J 6.6]; 1.41–1.62 [2H, m, CHH–CH(CH<sub>3</sub>)<sub>2</sub> and CH(CH<sub>3</sub>)<sub>2</sub>]; 1.81 [1H, dt, CHH–CH(CH<sub>3</sub>)<sub>2</sub>, J<sub>t</sub> 7.5, J<sub>d</sub> 13.5]; 2.47–2.74 [4H, m, H-6 and H-7]; 3.51 [1H, dt, H-3, J<sub>t</sub> 3.9, J<sub>d</sub> 16.5]; 3.62 [1H, ddd, H-3, J 3.0, 8.1, 16.2]; 4.08 [1H, ddd, H-2, J 3.0, 8.4, 12.3]; 4.38 [1H, ddd, H-2, J 3.3, 4.8, 12.3]; 4.30 and 4.44 [2H, AB part of ABX system, CH<sub>2</sub>Ph, J<sub>AB</sub> 14.7, J<sub>AX</sub> 5.6, J<sub>BX</sub> 6.1]; 4.98 [2H, s, PhCH<sub>2</sub>O]; 5.03 [1H, t, CHN, J 7.5]; 6.96 [1H, t, NH, J 5.85]; 7.20–7.40 [10H, m, aromatic CH]. <sup>13</sup>C NMR: δ 22.4, 22.8 [CH<sub>3</sub>]; 24.7 [CH(CH<sub>3</sub>)<sub>2</sub>]; 30.5, 32.7 [C-6 and C-7]; 36.6 [C-3]; 43.5 [CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>]; 45.2 [NCH<sub>2</sub>Ph]; 54.4 [CHN]; 68.5 [CH<sub>2</sub>O (C-2)]; 76.3 [PhCH<sub>2</sub>O]; 127.4, 127.7, 128.0, 128.1, 128.4, 128.6 [CH benzyll]; 137.1 e 137.9 [quat.]; 156.2 [C=N]; 171.0, 175.1 [C=O].

**2-(1-(Benzylcarbamoyl)-3-methylbutylamino)ethyl 3-(Benzyl-oxy-carbamoyl)propanoate 16a.** Note: it is difficult to obtain in



completely pure form this compound, because it tends to convert into 17 or back into 14. We could obtain a nearly pure sample by fast chromatography and examine it as soon as possible exclusively at NMR.  $^1\text{H}$  NMR (DMSO- $d_6$ , room temperature):  $\delta$  0.84, 0.87 [2  $\times$  3H, 2 d, ( $\text{CH}_3$ ) $_2\text{CH}$ , J 6.6]; 1.23–1.41 [2H, m,  $\text{CH}_2\text{CH}(\text{CH}_3)$ ]; 1.66 [1H, nonuplet,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$  J 6.6]; 2.24 [2H, t,  $\text{CH}_2\text{C}=\text{O}$ ]; 2.50–2.75 [2H, m,  $\text{CH}_2\text{C}=\text{O}$ ]; 3.08 [1 H, t, CHN, J 7.3]; 3.20–3.50 [2 H, m,  $\text{CH}_2\text{N}$  (covered by the water signal)]; 4.03 [2 H, t,  $\text{CH}_2\text{O}$ , J 5.8]; 4.30 [2 H, d,  $\text{NHCH}_2\text{Ph}$ ]; 4.77 [2 H, s,  $\text{OCH}_2\text{Ph}$ ]; 7.20–7.43 [10 H, m, aromatics]; 8.43 [1 H, t, NH, J 6.2]; 11.07 [1 H, s, NHO]. Note: the NH signal of the secondary amine is not seen because it exchanges rapidly with water contained in DMSO- $d_6$ .  $^{13}\text{C}$  NMR (DMSO- $d_6$ , room temperature):  $\delta$  22.3, 22.8 [ $\text{CH}_3\text{-CH}$ ]; 24.3 [ $\text{CH}(\text{CH}_3)_2$ ]; 26.9, 28.5 [ $\text{CH}_2\text{C}=\text{O}$ ]; 41.8, 42.6, 45.9 [ $\text{CH}_2\text{N} + \text{CH}_2\text{CH}(\text{CH}_3)_2$ ]; 60.2 [CHN]; 63.8 [ $\text{CH}_2\text{O}$ ]; 76.8 [ $\text{PhCH}_2\text{O}$ ]; 126.7, 127.1, 128.21 (2 superimposed signals), 128.24, 128.7 [aromatic CH]; 135.9, 139.6 [quat.]; 168.2, 172.1, 174.4 [ $\text{C}=\text{O}$ ].

**tert-Butyl (S)-3-((Benzyloxy)carbonyl)-1-((5*R*,*S*)-2-(benzylcarbamoyl)-5-(tert-butylidimethylsilyl(oxy)methyl)pyrrolidin-1-yl)-1-oxopropan-2-ylcarbamates 20a,b.** Compound **18** (453 mg, 2.12 mmol) was dissolved in dry MeOH (7.1 mL). Then benzyl isocyanide (310  $\mu\text{L}$ , 2.54 mmol) and Boc-L-Asp(OBn)-OH **19** (755 mg, 2.33 mmol) were added, and the resulting solution was stirred at room temperature for 1.25 h. After solvent evaporation under reduced pressure, the residue was dissolved in AcOEt and washed with saturated  $\text{NaHCO}_3$ ; the organic layer was finally washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . After solvent removal the crude was purified by chromatography with  $\text{CH}_2\text{Cl}_2/\text{AcOEt}$  95:5  $\rightarrow$   $\text{CH}_2\text{Cl}_2/\text{AcOEt}$  4:6 + 1% MeOH to give **20a,b** (1.180 g, 85%) as a white foam. D.r., determined by HPLC, was 34:66 **20a** (*cis*,  $R_t$  14.82 min): **20b** (*trans*,  $R_t$  13.56 min).

The following transformations have been performed on the diastereomeric mixture. However, analytically pure samples of both **20a** and **20b** have been obtained by chromatography and were independently characterized. **Compound 20a.**  $R_f$  0.23 in  $\text{CH}_2\text{Cl}_2/\text{AcOEt}$  8:2 + 0.5% MeOH. Found: C, 64.35; H, 7.90; N, 6.50.  $\text{C}_{35}\text{H}_{51}\text{N}_3\text{O}_7\text{Si}$  requires C, 64.29; H, 7.86; N, 6.43.  $[\alpha]_D = -35.8$  (c 3.14).  $^1\text{H}$  NMR: (taken in DMSO- $d_6$  at 200 MHz. At room temperature, two conformations in a 77 (M = major):23 (m = minor) ratio were observed; at 100  $^\circ\text{C}$  just one conformer but with very broad signals can be detected):  $\delta$  (room temperature) 0.002 [6H, s,  $\text{Si}(\text{CH}_3)_2$ ]; 0.84 [9H, s,  $\text{SiC}(\text{CH}_3)_3$ ]; 1.37 [9H, s,  $\text{OC}(\text{CH}_3)_3$ ]; 1.53–2.82 [6H, m,  $\text{CH}_2\text{CO}_2$ , *H*-3, *H*-4]; 3.44–4.46 [7H, m,  $\text{CH}_2\text{-OSi}$ , CHNHBoc,  $\text{NHCH}_2\text{Ph}$ , *H*-2, *H*-5]; 4.68–5.08 [2H, m,  $\text{PhCH}_2\text{O}$ ]; 7.10 (m) [1H, d, NHBoc, J=7.6]; 7.18–7.40 [10H, m, aromatics]; 7.48 (M) [1H, d, NHBoc, J=7.2]; 8.10 (M) [1H, broad s, CONHCH $_2$ ]; 8.35 (m) [1H, broad s, CONHCH $_2$ ];  $^{13}\text{C}$  NMR (taken in DMSO- $d_6$  at 50 MHz at r. t.):  $\delta$  -5.7 and -5.6 [2C,  $\text{Si}(\text{CH}_3)_2$ ]; 17.9 [ $\text{SiC}(\text{CH}_3)_3$ ]; 25.7 [3C,  $\text{SiC}(\text{CH}_3)_3$ ]; 26.7 (M), 26.8 (M) and 29.6 (m) [2C, *C*-3, *C*-4]; 28.0 [3C,  $\text{OC}(\text{CH}_3)_3$ ]; 36.2 [ $\text{CH}_2\text{CO}_2\text{Bn}$ ]; 41.8 (M), and 42.6 (m) [ $\text{NHCH}_2\text{Ph}$ ]; 48.1 (M) and 49.2 (m) [CHNHBoc]; 58.9 (M), 59.8 (m), 60.5 (M), and 61.0 (m) [2C, *C*-2, *C*-5]; 63.0 (M), 63.6 (m), and 65.5 (M+m) [2C,  $\text{CH}_2\text{OSi}$ ,  $\text{OCH}_2\text{-Ph}$ ]; 78.4 (M) and 78.5 (m) [ $\text{OC}(\text{CH}_3)_3$ ]; 126.5, 126.7, 127.1, 127.7, 127.9, 128.1, 128.2, and 128.3 [10C, aromatic CH]; 135.8 (M+m), 139.0 (m), and 139.2 (M) [2C, aromatic quat.]; 155.0 [ $\text{C}=\text{O}$  Boc]; 169.9, 170.1, 170.8, and 171.3 [3C,  $\text{C}=\text{O}$ ]. IR:  $\nu_{\text{max}}$  3675, 3421, 3005, 2954, 2856, 1721, 1655, 1494, 1420, 1367, 1292, 1188, 1161, 1094, 811  $\text{cm}^{-1}$ . **Compound 20b.**  $R_f$  0.40 in  $\text{CH}_2\text{Cl}_2/\text{AcOEt}$  8:2 + 0.5% MeOH. Found: C, 64.50; H, 7.80; N, 6.55.  $\text{C}_{35}\text{H}_{51}\text{N}_3\text{O}_7\text{Si}$  requires C, 64.29; H, 7.86; N, 6.43.  $[\alpha]_D = +28.7$  (c 2.10).  $^1\text{H}$  NMR: (taken in DMSO- $d_6$  at 200 MHz. At room temperature, two conformations in a 70 (M = major):30 (m = minor) ratio were observed; they do not collapse even at 100  $^\circ\text{C}$ ):  $\delta$  (room temperature) -0.001 and 0.025 [2  $\times$  3H, 2s,  $\text{Si}(\text{CH}_3)_2$ ]; 0.85 (M) and 0.84 (m) [9H, s,  $\text{SiC}(\text{CH}_3)_3$ ]; 1.37 (M) and 1.33 (m) [9H, s,  $\text{OC}(\text{CH}_3)_3$ ]; 1.67–2.86 [6H, m,  $\text{CH}_2\text{CO}_2$ , *H*-3, *H*-4]; 3.23–4.88 [7H, m,  $\text{CH}_2\text{OSi}$ , CHNHBoc,  $\text{NHCH}_2\text{Ph}$ , *H*-2, *H*-5]; 4.82 and 4.91 (m) [2H, AB system,  $\text{PhCH}_2\text{O}$   $J_{\text{AB}}=12.8$ ]; 5.03 and 5.09 (M) [2H,

AB system,  $\text{PhCH}_2\text{O}$   $J_{\text{AB}}=12.6$ ]; 7.16–7.34 [11H, m, aromatics, NHBoc]; 8.11 (m) [1H, broad t, CONHCH $_2$ , J=5.3]; 8.71 (M) [1H, broad t, CONHCH $_2$ , J=5.5].  $^{13}\text{C}$  NMR (taken in DMSO- $d_6$  at 50 MHz at room temperature):  $\delta$  -5.70, -5.63, and -5.58 [2C,  $\text{Si}(\text{CH}_3)_2$ ]; 17.8 [ $\text{SiC}(\text{CH}_3)_3$ ]; 24.7 (M), 26.7 (m), 27.0 (m), and 30.1 (M) [2C, *C*-3, *C*-4]; 25.6 (m) and 25.7 (M) [3C,  $\text{SiC}(\text{CH}_3)_3$ ]; 28.0 [3C,  $\text{OC}(\text{CH}_3)_3$ ]; 35.1 (M) and 36.1 (m) [ $\text{CH}_2\text{CO}_2\text{Bn}$ ]; 41.8 (m) and 42.2 (M) [ $\text{NHCH}_2\text{Ph}$ ]; 48.4 (m) and 48.8 (M) [CHNHBoc]; 58.3 (m), 59.2 (M), 60.2 (M), and 60.4 (m) [2C, *C*-2, *C*-5]; 61.6 (M), 63.5 (m), 65.3 (M), and 65.4 (m) [2C,  $\text{CH}_2\text{OSi}$ ,  $\text{OCH}_2\text{Ph}$ ]; 78.0 (M) and 78.6 (m) [ $\text{OC}(\text{CH}_3)_3$ ]; 126.5, 126.6, 126.7, 127.0, 127.5, 127.7, 127.8, 128.09, 128.15, and 128.2 [10C, aromatic CH]; 135.9 (m), 136.0 (M), 138.9 (M), and 139.3 (m) [2C, aromatic quat.]; 155.0 (M) and 155.2 (m) [ $\text{C}=\text{O}$  Boc]; 169.9, 170.0, 170.4, 171.2, 171.5, and 171.8 [3C,  $\text{C}=\text{O}$ ]. IR:  $\nu_{\text{max}}$  3425, 2951, 2926, 2855, 1727, 1649, 1493, 1426, 1368, 1245, 1157, 1109, 835  $\text{cm}^{-1}$ .

**tert-Butyl (S)-3-(((Benzyloxy)amino)carbonyl)-1-((5*R*,*S*)-2-(benzylcarbamoyl)-5-(hydroxymethyl)pyrrolidin-1-yl)-1-oxopropan-2-ylcarbamates 22a,b.** (1) Hydrogenolysis of benzyl ester. A solution of **20a,b** (316 mg, 0.48 mmol) in 95% EtOH (6 mL) was treated with 10% Pd/C (36 mg) and hydrogenated at room temperature for 3.5 h. The catalyst was filtered and the solvent removed in vacuo. The oily residue was taken up twice, first with dry toluene and then with dry  $\text{CH}_2\text{Cl}_2$  to give a white solid that was directly submitted to the following coupling.  $R_f$  0.28 (*cis*) and 0.43 (*trans*) in PE/AcOEt 1:1 + 2% AcOH. (2) Coupling reaction to give **21a,b**. Crude acid was dissolved in dry  $\text{CH}_2\text{Cl}_2/\text{DMF}$  3:1 (12 mL) and treated with *N*-benzylhydroxylamine hydrochloride (116 mg, 0.72 mmol) and triethyl amine (370  $\mu\text{L}$ , 2.66 mmol). After cooling to 0  $^\circ\text{C}$ , PyBOP [(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate] (302 mg, 0.58 mmol) was added and the resulting solution was allowed to stir at room temperature for 1 h. The mixture was partitioned between water and AcOEt and extracted. The organic layers were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed, and the crude was purified by chromatography with PE/AcOEt 1:1 + 2% *i*PrOH  $\rightarrow$  2:8 + 2% *i*PrOH to give **21a,b** (288 mg, 89%) as a white foam.  $R_f$  0.38 (*cis*) and 0.50 (*trans*) in PE/AcOEt 1:1 + 2% *i*PrOH. (3) Silyl ether removal. A solution of **21a,b** (288 mg, 0.43 mmol) in  $\text{CH}_3\text{CN}$  (2.5 mL) was cooled to 0  $^\circ\text{C}$  and treated with HF (40%, 125  $\mu\text{L}$ ). After 1.5 h at 0  $^\circ\text{C}$ , the reaction was quenched with solid  $\text{NaHCO}_3$  (250 mg), diluted with water, and extracted with AcOEt. The organic layers were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed, and the crude product was purified by chromatography with  $\text{CH}_2\text{Cl}_2$  + 8% *i*PrOH  $\rightarrow$   $\text{CH}_2\text{Cl}_2$  + 10% *i*PrOH to give **22a** (80 mg) and **22b** (144 mg) as white foams, with a 94% overall yield. **Compound 22a.**  $R_f$  0.46 in  $\text{CH}_2\text{Cl}_2$  + 8% *i*PrOH. Found: C, 62.55; H, 6.80; N, 10.15.  $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_7$  requires C, 62.80; H, 6.91; N, 10.10.  $[\alpha]_D = -32.9$  (c 2.12).  $^1\text{H}$  NMR: (taken in DMSO- $d_6$ . At room temperature two prevailing conformations in a 83 (M = major):17 (m = minor) ratio were observed; at 100  $^\circ\text{C}$  just one conformer but with very broad signals can be detected):  $\delta$  (room temperature) 1.38 [9H, s,  $\text{OC}(\text{CH}_3)_3$ ]; 1.72–2.48 [6H, m,  $\text{CH}_2\text{-CONHOBn}$ , *H*-3, *H*-4]; 3.23–4.78 [9H, m,  $\text{CH}_2\text{OH}$ ,  $\text{PhCH}_2\text{O}$ , CHNHBoc,  $\text{NHCH}_2\text{Ph}$ , *H*-2, *H*-5]; 5.01 (m) [1H, broad t, OH, J=4.8]; 5.07 (M) [1H, broad t, OH, J=4.7]; 6.85 [1H, d, NHBoc (m or M), J=7.5]; 7.19–7.39 [11H, m, aromatics, NHBoc (m or M)]; 8.32 (M) [1H, broad t, CONHCH $_2$ , J=5.7]; 8.61 (m) [1H, broad t, CONHCH $_2$ , J=5.9]; 11.04 (M) [1H, broad s, ONHCO]; 11.08 (m) [1H, broad s, ONHCO].  $^{13}\text{C}$  NMR (taken in DMSO- $d_6$  at room temperature):  $\delta$  27.3 (M), 27.5 (M), 28.9 (m), and 29.7 (m) [2C, *C*-3, *C*-4]; 28.0 [3C,  $\text{OC}(\text{CH}_3)_3$ ]; 34.8 [ $\text{CH}_2\text{CONHOBn}$ ]; 41.7 (M) and 42.5 (m) [ $\text{NHCH}_2\text{Ph}$ ]; 48.2 (M) and 49.3 (m) [CHNHBoc]; 59.5, 60.4, and 61.1 [2C, *C*-2, *C*-5]; 62.1 [ $\text{CH}_2\text{OH}$ ]; 76.8 [ $\text{OCH}_2\text{Ph}$ ]; 78.3 [ $\text{OC}(\text{CH}_3)_3$ ]; 126.5, 126.7, 127.0, 128.1, 128.2, and 128.7 [10C, aromatic CH]; 135.8 (M+m), 138.9 (m), and 139.2 (M) [2C, aromatic quat.]; 155.5 (m) and 155.0 (M) [ $\text{C}=\text{O}$  Boc]; 166.5 (m) and 166.6 (M) [CONHOBn]; 170.8, 171.5, and 172.0 [2C,  $\text{C}=\text{O}$ ]. IR:  $\nu_{\text{max}}$  3677, 3353, 2975, 1695, 1655, 1493, 1434,

1368, 1159, 1073  $\text{cm}^{-1}$ . Compound **22b**.  $R_f$  0.27 in  $\text{CH}_2\text{Cl}_2$  + 8%  $i\text{PrOH}$ . Found: C, 62.85; H, 6.85; N, 10.20.  $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_7$  requires C, 62.80; H, 6.91; N, 10.10.  $[\alpha]_D = +19.9$  (c 0.85).  $^1\text{H}$  NMR: (taken in  $\text{DMSO}-d_6$ . At room temperature two prevailing conformations in about a 1:1 ratio were observed; they do not collapse even at 100  $^\circ\text{C}$ ):  $\delta$  (room temperature) 1.30 and 1.37 [9H, 2s,  $\text{OC}(\text{CH}_3)_3$ ]; 1.73–2.54 [6H, m,  $\text{CH}_2\text{CONHOBn}$ ,  $H$ -3,  $H$ -4]; 3.07–4.87 [10H, m,  $\text{CH}_2\text{OH}$ ,  $\text{PhCH}_2\text{O}$ ,  $\text{CHNHBoc}$ ,  $\text{NHCH}_2\text{Ph}$ ,  $H$ -2,  $H$ -5,  $\text{OH}$  one conformer]; 4.99 [1H, broad t,  $\text{OH}$  one conformer,  $J=4.8$ ]; 7.10 [1H, d,  $\text{NHBoc}$  one conformer,  $J=7.8$ ]; 7.15 [1H, d,  $\text{NHBoc}$  one conformer,  $J=6.6$ ]; 7.21–7.40 [10H, m, aromatics]; 7.93 [1H, broad t,  $\text{CONHCH}_2$  one conformer,  $J=5.7$ ]; 8.71 [1H, broad s,  $\text{CONHCH}_2$  one conformer]; 10.80 [1H, broad s,  $\text{ONHCO}$  one conformer]; 10.99 [1H, broad s,  $\text{ONHCO}$  one conformer].  $^{13}\text{C}$  NMR (taken in  $\text{DMSO}-d_6$  at room temperature):  $\delta$  24.5, 26.7, 27.2, and 29.7 [2C,  $C$ -3,  $C$ -4]; 28.0 and 28.0 [3C,  $\text{OC}(\text{CH}_3)_3$ ]; 33.3 and 34.4 [ $\text{CH}_2\text{CONHOBn}$ ]; 41.7 and 42.4 [ $\text{NHCH}_2\text{Ph}$ ]; 48.5 and 48.9 [ $\text{CHNHBoc}$ ]; 58.9, 59.7, 60.0, and 60.6 [2C,  $C$ -2,  $C$ -5]; 62.4 [ $\text{CH}_2\text{-OH}$ ]; 76.9 [ $\text{OCH}_2\text{Ph}$ ]; 78.2 and 78.6 [ $\text{OC}(\text{CH}_3)_3$ ]; 126.46, 126.55, 126.7, 127.0, 127.2, 128.1, 128.17, 128.24, 128.69, and 128.74 [10C, aromatic CH]; 135.8, 135.9, 139.0, and 139.3 [2C, aromatic quat.]; 155.0 and 155.4 [ $\text{C=O Boc}$ ]; 166.6 and 166.7 [ $\text{CONHOBn}$ ]; 170.0, 170.7, 171.4, and 171.8 [2C,  $\text{C=O}$ ]. IR:  $\nu_{\text{max}}$  3667, 3362, 3005, 1680, 1490, 1429, 1368, 1190, 1023  $\text{cm}^{-1}$ .

**tert-Butyl (5S,8S,10aR)-8-(Benzylcarbamoyl)-3-benzoyloximinooctahydro-6-oxo-1H-pyrrolo[2,1-c][1,4]oxazocin-5-ylcarbamate 23a.** A solution of **22a** (80 mg, 0.14 mmol) in dry THF (10 mL) was treated with  $\text{PPh}_3$  (113 mg, 0.43 mmol) and DEAD (64  $\mu\text{L}$ , 0.41 mmol). After 1.5 h of stirring at room temperature the solvent was removed in vacuo, and the crude was purified by chromatography with  $\text{PE}/\text{AcOEt}$  4:6 + 0.7% MeOH to give **23a** (54 mg, 70%) as a white foam.  $R_f$  0.40 in  $\text{PE}/\text{AcOEt}$  4:6 + 0.7% MeOH. Found: C, 64.85; H, 6.90; N, 10.30.  $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_6$  requires C, 64.91; H, 6.76; N, 10.44.  $[\alpha]_D = +43.3$  (c 0.88).  $^1\text{H}$  NMR: (taken in  $\text{DMSO}-d_6$ . At room temperature two conformations in a 87 (M = major):13 (m = minor) ratio were observed; at 90  $^\circ\text{C}$  the signals almost collapsed to give one rotamer):  $\delta$  (90  $^\circ\text{C}$ ) 1.40 [9H, s,  $\text{OC}(\text{CH}_3)_3$ ]; 2.01–2.18 [2H, m,  $H$ -3 or  $H$ -4]; 1.85–1.97 [1H, m,  $H$ -3 or  $H$ -4]; 1.74–1.78 [1H, m,  $H$ -3 or  $H$ -4]; 2.45 and 2.79 [2H, AB part of ABX system,  $\text{CH}_2\text{CHNHBoc}$ ,  $J_{\text{AB}}=14.5$ ,  $J_{\text{AX}}=11.7$ ,  $J_{\text{BX}}=5.2$ ]; 4.12 [1H, dd,  $\text{CHHO}$ ,  $J=1.8$ , 11.4]; 4.30 and 4.37 [2H, AB part of ABX system,  $\text{NHCH}_2\text{Ph}$ ,  $J_{\text{AB}}=15.2$ ,  $J_{\text{AX}}=6.1$ ,  $J_{\text{BX}}=5.8$ ]; 4.28–4.42 [1H, m,  $H$ -5]; 4.49 [1H, d,  $\text{CHHO}$ ,  $J=11.7$ ]; 4.59 [1H, t,  $H$ -2,  $J=6.9$ ]; 4.70 [1H, center of m,  $\text{CHNHBoc}$ ]; 4.86 and 4.95 [2H, AB system,  $\text{OCH}_2\text{Ph}$ ,  $J=11.7$ ]; 6.59 [1H, broad s,  $\text{CHNHBoc}$ ]; 7.21–7.80 [10H, m, aromatics]; 7.87 [1H, broad s,  $\text{CONHCH}_2$ ].  $^{13}\text{C}$  NMR (taken in  $\text{DMSO}-d_6$  at room temperature):  $\delta$  26.8, 27.7, and 27.8 [2C,  $C$ -3,  $C$ -4]; 28.1 [3C,  $\text{OC}(\text{CH}_3)_3$ ]; 34.5 (m) and 35.3 (M) [ $\text{CH}_2\text{CHNHBoc}$ ]; 41.9 [ $\text{NHCH}_2\text{Ph}$ ]; 49.2 [ $\text{CHNHBoc}$ ]; 59.8 and 61.1 [2C,  $C$ -2,  $C$ -5]; 73.5, 73.9, and 75.0 [2C,  $\text{CH}_2\text{O}$ ]; 78.2

(M) and 79.1 (m) [ $\text{OC}(\text{CH}_3)_3$ ]; 126.6, 126.9, 127.6, 128.1, 128.16, and 128.21 [10C, aromatic CH]; 137.3 and 139.2 [2C, aromatic quat.]; 153.5, 154.8, 170.4, and 171.0 [4C,  $\text{C=O}$  (or N)]. IR:  $\nu_{\text{max}}$  3685, 3462, 3000, 1703, 1670, 1631, 1602, 1492, 1416, 1368, 1292, 1159, 1017, 859, 720  $\text{cm}^{-1}$ .

**Compound 24b.** The same conditions used for the preparation of **23a** were used, starting from **22b** (74 mg, 0.13 mmol), but employing DIAD (74  $\mu\text{L}$ , 0.37 mmol) instead. Chromatography with  $\text{PE}/\text{Et}_2\text{O}$  7:3 + 2% MeOH afforded **24b** (49 mg, 68%) as a pale-yellow foam.  $R_f$  0.41 in  $\text{Et}_2\text{O}$  + 2% MeOH. Found: C, 64.95; H, 6.70; N, 10.50.  $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_6$  requires C, 64.91; H, 6.76; N, 10.44.  $[\alpha]_D = +25.8$  (c 2.39).  $^1\text{H}$  NMR: (taken in  $\text{DMSO}-d_6$ . At room temperature two epimers in a 65 (M = major):35 (m = minor) ratio were observed; at 90  $^\circ\text{C}$  the same ratio was maintained but the signals become sharper):  $\delta$  (90  $^\circ\text{C}$ ) 1.20–2.44 [4H, m,  $H$ -3,  $H$ -4]; 1.42 and 1.44 [9H, s,  $\text{OC}(\text{CH}_3)_3$ ]; 1.83 and 2.57 (M) [AB part of ABX system,  $\text{CH}_2\text{CHNHBoc}$ ,  $J_{\text{AB}}=11.1$ ,  $J_{\text{AX}}=6.0$ ,  $J_{\text{BX}}=5.7$ ]; 2.33 and 2.61 (m) [AB part of ABX system,  $\text{CH}_2\text{CHNHBoc}$ ,  $J_{\text{AB}}=16.4$ ,  $J_{\text{AX}}=8.1$ ,  $J_{\text{BX}}=8.9$ ]; 3.48 (t,  $J = 7.4$ ), 3.66 (dt,  $J = 8.0$  and 12.6), 3.91 (quintuplet,  $J = 7.0$ ), 3.98 (quintuplet,  $J = 9.4$ ), 4.08 (t,  $J = 7.2$ ), 4.17–4.38 (m) and 4.56 (quadruplet,  $J = 8.8$ ) [7H,  $\text{CH}_2\text{O}$ ,  $\text{CHNHBoc}$ ,  $\text{NHCH}_2\text{Ph}$ ,  $H$ -2,  $H$ -5]; 4.91 and 5.05 (m) [2H, AB system,  $\text{OCH}_2\text{Ph}$ ,  $J_{\text{AB}}=10.0$ ]; 5.06 and 5.12 (M) [2H, AB system,  $\text{OCH}_2\text{Ph}$ ,  $J_{\text{AB}}=9.9$ ]; 6.68 (m) [1H, broad s,  $\text{NHBoc}$ ]; 6.89 (M) [1H, broad d,  $\text{NHBoc}$ ,  $J=8.1$ ]; 7.16–7.48 [10H, m, aromatics]; 7.84 (m) [1H, broad s,  $\text{CONHCH}_2$ ]; 8.36 (m) [1H, broad s,  $\text{CONHCH}_2$ ].  $^{13}\text{C}$  NMR (taken in  $\text{DMSO}-d_6$  at room temperature):  $\delta$  28.0 (m) and 28.1 (M) [3C,  $\text{OC}(\text{CH}_3)_3$ ]; 28.6 (M), 29.4 (m), 30.1 (m), and 30.3 (M) [2C,  $C$ -3,  $C$ -4]; 33.5 (m) and 34.7 (M) [ $\text{CH}_2\text{-CHNHBoc}$ ]; 41.9 (M) and 42.1 (m) [ $\text{NHCH}_2\text{Ph}$ ]; 45.1 (m) and 49.5 (M) [ $\text{CHNHBoc}$ ]; 60.5 (M), 60.9 (m), 63.4 (m), and 64.8 (M) [2C,  $C$ -2,  $C$ -5]; 70.3 (M) and 74.4 (m) [ $\text{CH}_2\text{O}$  ring]; 78.4 (m) and 79.1 (M) [ $\text{OCH}_2\text{Ph}$ ]; 78.6 [ $\text{OC}(\text{CH}_3)_3$ ]; 108.4 (M) and 109.7 (m) [ $\text{OCN-N(C)}]$ ; 126.6, 126.7, 127.0, 128.17, 128.21, 128.24, 128.4, 128.6, 128.77, 128.80, and 129.3 [10C, aromatic CH]; 134.4 (M), 135.2 (m), 139.0 (m), and 139.1 (M) [2C, aromatic quat.]; 154.8 [ $\text{C=O Boc}$ ]; 165.2 (M) and 166.0 (m), 172.6 (m), and 173.3 (M) [2C,  $\text{C=O}$ ]. IR:  $\nu_{\text{max}}$  3673, 3422, 3371, 3000, 1708, 1603, 1492, 1367, 1247, 1159, 1041, 907, 862  $\text{cm}^{-1}$ .

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**Supporting Information Available:** General experimental methods. Characterizations of all compounds **5–6**, **1**, and **2** as well as of compounds **11a** and **12b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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