The Intramolecular Aldol Condensation Route to Fused Bi- and Tricyclic β-Lactams[1,2]

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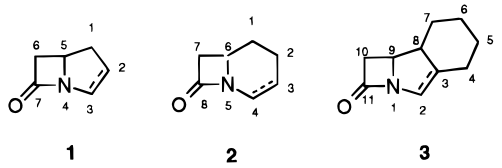
Staüdinger cycloaddition of activated acid chlorides to 1,3-ketoaldimines, prepared in quantitative yields from 1,3-ketoaldehydes and amino esters, gave in excellent yields *cis*-2-azetidinones, **6**−**8**, having the adequate functionality to obtain fused bi- and tricyclic β-lactams. Reaction of compounds **6** with LHMDS at low temperature gave a single diastereomer of fused bicyclic compounds with a carbapenam or carbacefam skeleton. Treatment of diastereomeric *cis*-2-azetidinones, **7/8**, in analogous conditions resulted either in the exclusive cyclization of one of the two diastereomers to form tricyclic [4.*n*.*m*] ($n = 5, 6$; $m = 5, 6$) compounds, or in the cyclization of both diastereomers to form tricyclic [4.*n*.7] ($n = 5, 6$) 2-azetidinones. In all cases the cyclization step was totally stereoselective. Alternatively, *trans*-carbapenams and one example of a tricyclic system having a *trans*-2-azetidinone ring have been obtained by using longer reaction times and higher temperatures. Epimerization at C3 of the 2-azetidinone nucleus occurs in these reaction conditions to obtain a single diastereomer of the final products. This approach to fused policyclic 2-azetidinones is one of the scarce syntheses of this kind of compound making use of the aldol condensation.

Introduction

The timely discovery of natural and synthetic β-lactam antibiotics of the carbapenem,[3] **1**, carbacefem,[4] **2**, and tribactam,[5] **3**, types with improved biological activity and resistance toward enzymatic degradation has promoted an impressive development of methodology to prepare these compounds (Figure 1).[6]

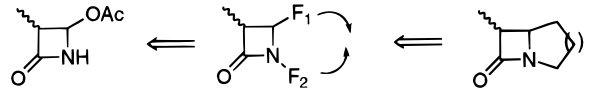
The synthesis of carbapenems and tribactams frequently begins with a functionalized β-lactam, usually a 4-acetoxy-2-azetidinone, which is either commercially available or prepared by standard methodology. This precursor is step by step functionalized to yield an advanced intermediate from which the basic bi- or tricyclic skeleton is obtained (Scheme 1). The last critical synthetic step has been approached and successfully resolved by many different methods. The rhodium carbenoid insertion onto the amide NH[7] and the Wittig-oxalimide cyclization[8] are among the most versatile and efficient cyclization procedures. Other methods[9] such as the intramolecular Dieckmann condensation,[10] the intramolecular radical reaction of enynes,[11] and palladium-catalyzed cyclizations[12] are less general.



1 **2** **3**

Figure 1.

Scheme 1



An alternative to the step by step synthesis of the key cyclization precursors is the preparation of these intermediates in a single step. β-Ketoaldimines derived from methyl glycinate or methyl β-alaninate bear the func-

[⊗] Abstract published in *Advance ACS Abstracts*, September 1, 1996.

(1) This paper is respectfully dedicated to the Memory of Professor Francisco Fariña.

(2) For a preliminary communication of a part of this work see: Alcaide, B.; Pérez-Castells, J.; Sánchez-Vigo, B.; Sierra, M. A. *BioMed. Chem. Lett.* **1993**, *3*, 2369.

(3) (a) Kropp, H.; Kahan, J. S.; Kahan, F. M.; Sudenlof, J.; Darland, G.; Birnbaum, J. *Intersci. Conf. Antimicrob. Agents Chemother.* 1976, Chicago IL. (b) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Hendlin, D.; Mochales, S.; Hernández, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1.

(4) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7585.

(5) (a) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Andreotti, D.; Gaviraghi, G.; Carlesso, R.; Bismara, C. Eur. Pat. Appl. EP0416953 A2, 1991; *Chem. Abstr.* **1992**, *116*, 235337t. (b) Perboni, A.;Rossi, T.; Gaviraghi, G.; Ursini, A.; Tarzia, G. WO 9203437, 1992; *Chem. Abstr.* **1992**, *117*, 7735m.

(6) Carbapenems: (a) Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin−Heidelberg, 1990; pp 565−612. (b) Georg, G. I. In *Studies in Natural Product Chemistry*; Rahman, A., Ed.; Elsevier Science: Amsterdam, 1989; Vol. 4, p 431. (c) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (d) Berks, A. H. *Tetrahedron* **1996**, *52*, 331. Carbacefems: (e) Cooper, R. D. G. In *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, **1992**; Chapter 8. Tribactams: (f) Pavoda, A.; Roberts, S. M.; Donati, D.; Marchioro, C.; Perboni, A. *J. Chem. Soc., Chem. Commun.* **1995**, 661. (g) Pavoda, A.; Roberts, S. M.; Donati, D.; Perboni, A.; Rossi, T. *J. Chem. Soc., Chem. Commun.* **1994**, 441. (h) Bismara, C.; Di Fabio, R.; Donati, D.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1995**, *36*, 4283. (i) Rossi, T.; Biondi, S.; Contini, S.; Thomas, R. J.; Marchioro, C. *J. Am. Chem. Soc.* **1995**, *117*, 9604. (j) Pavoda, A.; Roberts, S. M.; Donati, D.; Marchioro, C.; Perboni, A. *Tetrahedron* **1996**, *52*, 263.

(7) (a) Balkovec, J. M.; Szymonifka, M. J.; Heck, J. V.; Ratcliffe, R. W. *J. Antibiot.* **1991**, *44*, 1172. A recent modification using iodine ylides: (b) Kume, M.; Kubota, T.; Iso, Y. *Tetrahedron Lett.* **1995**, *36*, 8043.

(8) (a) Afonso, A.; Hon, F.; Weinstein, J.; Ganguly, A. K.; McPhail, A. T. *J. Am. Chem. Soc.* **1982**, *104*, 6138. (b) Yoshida, A.; Tajima, Y.; Takeda, N.; Oida, S. *Tetrahedron Lett.* **1984**, *25*, 2793. A recent example: (c) King, S. A.; Pipik, B.; Thompson, A. S.; DeCamp, A.; Verhoeven, T. R. *Tetrahedron Lett.* **1995**, *36*, 4563.

(9) For a thorough review on different cyclization methodologies, see: Kant, J.; Walker, D. G. In *The Organic Chemistry of β-Lactams*, Georg, G. I., Ed.; VCH Publishers: New York, 1993; p 121.

(10) Jackson, B. G.; Gardner, J. P.; Heath, P. C. *Tetrahedron Lett.* **1996**, *31*, 6317.

(11) Alcaide, B.; Benito, J. L.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A.; Sierra, M. A. *Tetrahedron Asymm.* **1995**, *6*, 1055 and references therein.

(12) Roland, S.; Durand, J. O.; Savignac, M.; Genet, J. P. *Tetrahedron Lett.* **1995**, *36*, 3007.

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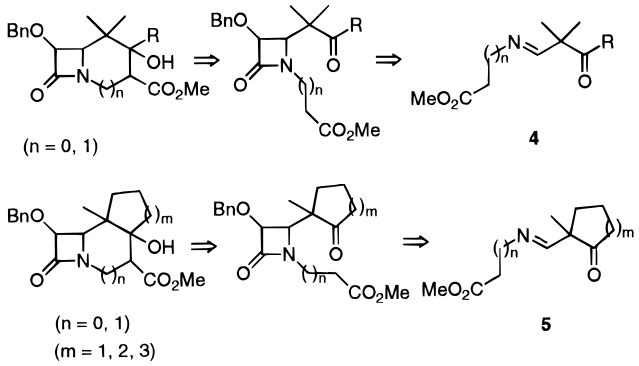
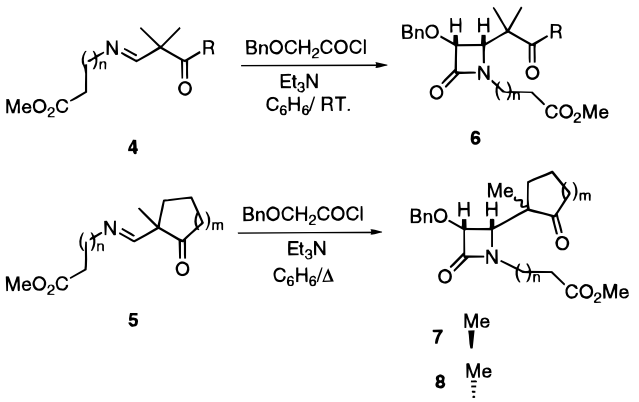
Scheme 2



Scheme 3



tionality necessary to effect the ring closure through aldol condensation, once incorporated into the 2-azetidinone ring. Then, the fully funtionalized β-lactam ring can be made in a single step by using the Staüdinger reaction of these imines with a ketene precursor. Depending on their structure, β-ketoaldimines derived from cyclic ketoaldehydes would form precursors of fused tri- or policyclic compounds (Scheme 2). This approach is developed in this paper.

The aldol approach to bicyclic β-lactams has been seldom reported.[13] Some problems associated with this approach may be, in principle, the competitive enolization for substrates with more than one enolizable position, and the retroaldol reaction favored by the ring strain. However, both points have been addressed and resolved by careful selection of the cyclization precursors and adequate reaction conditions.

Results and Discussion

1,3-Ketoaldimines **4** and **5** were prepared in quantitative yields by condensation of equimolar amounts of the corresponding 1,3-ketoaldehyde and the free amino ester. Cycloaddition of imines **4** and **5** with (benzyloxy)acetyl chloride in the presence of Et_3N gave the corresponding *cis*-2-azetidinones **6** and **7/8** in good yields (Scheme 3, Table 1).[14] Acid chloride precursors of less reactive ketenes (alkyl-substituted acid chlorides, for example) were unreactive toward both types of imines. 2-Azetidinones **6** were obtained as single *cis*-diastereomers. However, the presence of a chiral center in imines **5** resulted in the formation of diastereomeric mixtures of *cis*-2-azetidinones **7** and **8** differing in the configuration of the additional chiral center. The stereochemistry of compounds **7** and **8** is depicted in Scheme 3.[15] The structural assignment of these compounds is discussed below. Compounds **7** and **8** were obtained, in all cases, with moderate selectivities. Diastereomerically pure compounds **7** and **8** were isolated by flash chromatography in most cases.

Reaction of 2-azetidinones **6** with LHMDS at −78 °C in THF followed by acid hydrolysis gave smoothly the corresponding bicycles with a carbapenam, **9**, or carbacefam, **10**, structure in nearly quantitative yields (Scheme 4, Table 2). Analytically pure compounds were obtained by column chromatography or crystallization from the reaction mixtures. Compounds **9** and **10** were obtained as single diastereomers, showing that the aldol condensation occurs with total selectivity (see below for structural assignment).

Table 1. 4-(2-Oxoalkyl) β-Lactams 6−8

compound	R	*n*	*m*	**7/8**[a]	yield (%)[b]
6a	Me	0	−	−	70
6b	Ph	0	−	−	86
6c	*p*-$MeOC_6H_4$	0	−	−	65
6d	Me	1	−	−	75
6e	Ph	1	−	−	77
7a/8a[e]	−	0	1	70/30	56[c]
7b/8b	−	1	1	32/68	15/43[d]
7c /8c	−	0	2	59/41	47/43[d]
7d/8d	−	1	2	52/48	35/30[d]
7e/8e[e]	−	0	3	56/44	72[c]
7f/8f[e]	−	1	3	53/47	75[c]

[a] Determined by integration of well resolved signals of the ^1H NMR spectra of crude mixtures. [b] In pure compound with correct analytical and spectroscopic data. [c] Yield is for the analytically pure, inseparable mixture of both *cis*-diastereomers. [d] Yields are for each, analytically pure, separated *cis*-diastereomer. [e] In these cases the stereochemistry of each diastereomer could not be assigned. See text.

Cyclization of diastereomeric 2-azetidinones **7/8** was more demanding. When we reacted the mixture of diastereomers of β-lactams **7c/8c** with LHMDS at −78 °C a single tricyclic diastereomer **11b** and the unchanged diastereomer of the starting material **8c** were obtained. Independent cyclization of each isolated diastereomer produced identical results. Thus, compound **7c** yielded a single diastereomer of the tricyclic system, **11b**, while its diastereomer **8c** was recovered unchanged. Compound **8c** was then submitted to a systematic variation of the reaction conditions, including the base (KHMDS, LDA, DBU/LiBr), temperature, reaction time, and workup conditions. Unreacted starting material was obtained in all cases or, by forcing the reaction conditions, extensive decomposition to mixtures of unknown compounds was observed. The synthesis of the [4.6.6] system followed a similar pattern. Thus, monolactam **8d** smoothly cyclized to tricycle **12b**, while its diastereomer **7d** was unreactive. It should be pointed out that in this case the reactive diastereomer has an opposite stereochemistry at the chiral center bearing the methyl group. On the other hand, both diastereomers of monolactams **7f/8f** having a cycloheptanone moiety render the corresponding

(13) (a) Shibuya, M.; Kubota, S. *Tetrahedron Lett.* **1980**, *21*, 4009. (b) Foxton, M. W.; Mearman, R. C.; Newall, C. E.; Ward, P. *Tetrahedron Lett.* **1981**, *22*, 2497. (c) Crocker, P. J.; Karison-Andreasson, U.; Lotz, B. T.; Miller, M. J. *Heterocycles.* **1995**, *40*, 691.

(14) The *cis*-selectivity obtained in the preparation of compounds **6-8** was the expected for the imines used according to the currently accepted mechanism of the Staüdinger reaction. See: (a) Dumas, S.; Hegedus, L. S. *J. Org. Chem.* **1994**, *59*, 4967. (b) Cossio, F. P.;Arrieta, A; Lecea, B; Ugalde, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 9604.

(15) Compounds through this paper are racemic. For clarity one diastereomer is always represented.

Scheme 4

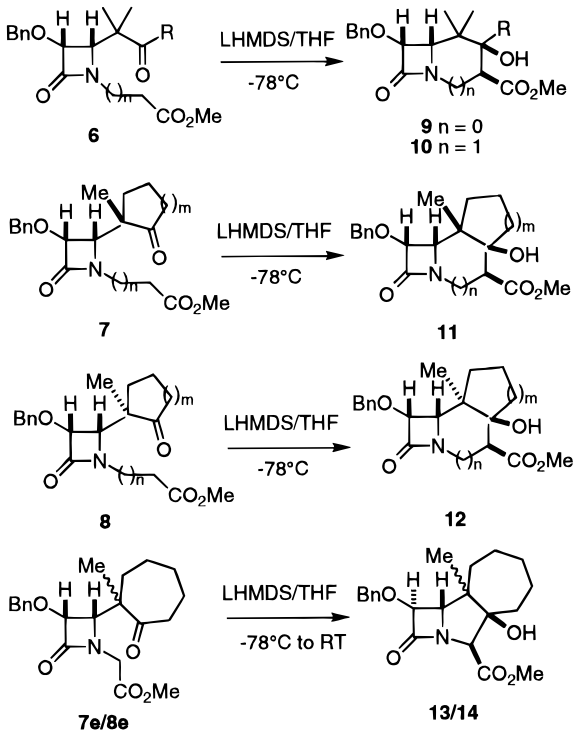


Table 2. Bi- and Tricyclic β-Lactams 9−14

starting material	product	R	*n*	*m*	yield (%)	ring system
6a	**9a**	Me	0	−	80[a]	[4.5]
6b	**9b**	Ph	0	−	70[a]	[4.5]
6c	**9c**	*p*-MeOC$_6$H$_4$	0	−	85[a]	[4.5]
6d	**10a**	Me	1	−	81[a]	[4.6]
6e	**10b**	Ph	1	−	95[a]	[4.6]
7a/8a	**11a/12a**	−	0	1	−	[4.5.5]
8b	**12a**	−	1	1	60[b]	[4.6.5]
7c	**11b**	−	0	2	95[a]	[4.5.6]
8d	**12b**	−	1	2	90[a]	[4.6.6]
7e/8e[c]	**13/14**[e]	−	0	3	80[d]	[4.5.7]
7f/8f[c]	**11d/12d**	−	1	3	50[d]	[4.6.7]

[a] In pure compound with correct analytical and spectroscopic data. [b] In crude material, spectroscopically (^{1}H NMR) pure. [c] Cyclization of the mixture of inseparable diastereomers. [d] Yield of the mixture of pure inseparable diastereomers. [e] In this case the 2-azetidinone ring has a *trans*-stereochemistry. See text.

tricyclic [4.6.7] compounds **11d/12d** as did monolactams **7e/8e**. However, the mixture of 2-azetidinones **7e/8e** formed the tricyclic [4.5.7] system, **13/14**, having a *trans*-stereochemistry at the four-membered ring (see below).[16] Finally, both diastereomers of monolactam **7a/8a** failed to produce the corresponding [4.5.5] systems. These results are listed in Table 2.

Conditions to promote the aldol condensation depended on the systems to be obtained. Thus, [4.*n*.6] (n = 5, 6) systems were obtained almost instantaneously at −78 °C, while temperature had to be raised to 0 °C to produce the remaining tricyclic systems. Tricyclic compounds **11** and **12** were obtained in almost quantitative yields, as determined by ^{1}H NMR, and as single diastereomers, except for compound **12a**. In this case, unreacted starting material **8b** (30%) was recovered. However, except for solid compounds which were easily purified by crystallization, extensive decomposition was observed when the reaction mixtures were purified by flash chromatography. Data collected in Table 2 show that our approach is viable for the synthesis of tricyclic 2-azetidinones with structures [4.*n*.*m*] (n = 5, 6; m = 5, 6, 7), except for tricycles [4.5.5].

It is clear from the data above that the ability of the monolactams **7** and **8** to form fused tricyclic β-lactams may be directly related both to the configuration of the angular methyl group and the size of the ring on these cyclization precursors. However, without data in hand proposing a model to account for the observed stereochemistry and reactivity based on chelated transition states,[17] this is, at this time, at least speculative.

Configuration of carbapenams **9** was deduced from NOE data obtained on compound **9a**. Irradiation on the Me group at C2 on compound **9a** resulted in a 3% increment on the vicinal H-3 ensuring a *cis*-relationship between both groups and hence a *syn*-configuration for the aldol moiety on compounds **9a**−**c**. The stereochemistry of compounds **10** was deduced from the coupling constants (J_1 = 11.3−11.7 Hz, J_2 = 6.0−6.1 Hz) of the H3 hydrogen and the vicinal methylene H4 hydrogens. These coupling constants are characteristic for an axial hydrogen in a pseudo-chair conformation.[18] This fact places the CO_2Me group in an equatorial disposition. The *syn*-relative configuration for the aldol moiety is derived from the observed minimum $\Delta\delta$ for the CH_2 attached to the lactam nitrogen between compounds **10a** and **10b**, while H3 is 1.2 ppm shielded in **10b** relative to **10a**. This effect is attributed to the shielding effect of the aromatic ring *cis* to the H3 hydrogen in compound **10b**. Hence the β-hydroxy ester moiety should be *syn*-relative.

The assignment of each proton of the six-membered ring fused to the 2-azetidinone on the [4.6.*m*] systems was not evident from their chemical shifts and coupling constants. An ^{1}H−^{13}C heteronuclear correlation experiment (HETCOR) carried out for compound **12b** allowed us to unambiguously discriminate between the methyne and methylene hydrogens. A pseudo-chair conformation for the central six-membered ring is derived, again, from the coupling constants of the hydrogen α to the methoxycarbonyl group and its vicinal CH_2 group (J_1 = 11.6, J_2 = 6.2 Hz). Irradiation under NOE conditions on the angular methyl group at δ = 1.16 in compound **12b** resulted in an NOE increment of 6% on the CH at δ = 2.81 indicative of a relative *syn*-disposition for both groups (Figure 2). The absence of NOE increment on H-10 is indicative of an *anti* relationship between this proton and the angular methyl group. These results are confirmed by analogous experiments on compounds **11d/12d**. Thus, an increment of 5% was observed on the H-3 hydrogen of diastereomer **12d** upon irradiation of the angular methyl group. No increment was observed for this hydrogen on compound **11d**, instead of a 4% increment on H-11 was obtained. Therefore, a *syn*-relative disposition was assigned for the angular methyl group and the H3 hydrogen for **11d**. Diastereomer **12d** should be the *anti* isomer (Figure 2). It should be noted that configuration at the $CHCO_2Me$ center remains unaltered in both isomers as derived from their coupling constants with the vicinal CH_2 which are again coherent for an

(16) The *trans*-stereochemistry at the 2-azetidinone ring depicted in the Scheme 4 for tricycles **13/14** is based on the epimerization at the most acid center (the C3 position at the four membered ring) of the precursor monolactams. See ref. 19.

(17) See, for example: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, p 111.

(18) Günther, H *NMR Spectroscopy;* John Wiley and Sons: Chichester, 1995.

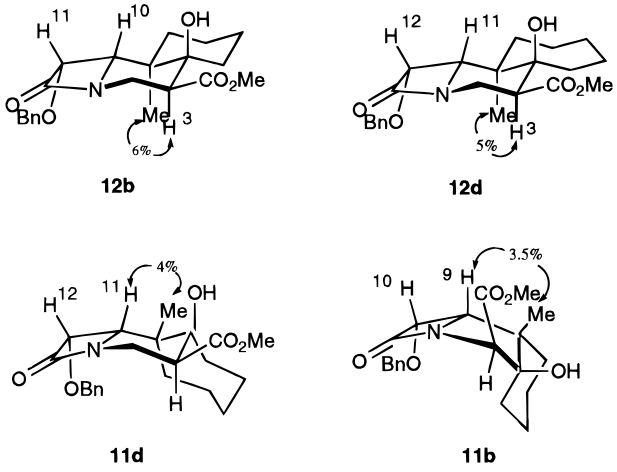


Figure 2.

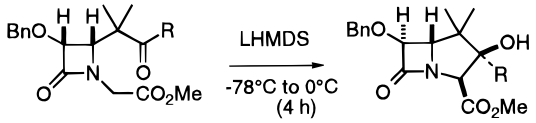
axial disposition. Configuration of the [4.6.5] system was deduced in a similar way.

For the [4.5.6] system no increment was observed on H2 upon irradiation of the angular methyl group on compound **11b**. However, a 3.5% increment on the H-9 hydrogen was observed (Figure 2) showing a *syn*-relationship between the methyl group and the four-membered ring hydrogens. The *syn* relative configuration for the aldol moiety has been assumed for all the tricyclic compounds by analogy with bicyclic derivatives **9** and **10**. Finally, configuration of monolactams **7/8** is immediately derived from their cyclized products provided that separated diastereomers could be obtained and cyclized (**7b/8b**, **7c/8c**, and **7d/8d**). The stereochemistry of the components of inseparable mixtures of diastereomers (**7a/8a**, **7e/8e**, **7f/8f**) could not be assigned.

All the tricyclic compounds above, except for **13/14**, have a *cis*-stereochemistry in the 2-azetidinone ring which is placed by the first cycloaddition step. To date, most polycyclic, biologically active β-lactams have a *trans*-2-azetidinone ring in their structures. It would be desirable that the scope of the approach to β-lactams reported here could be extended to prepare compounds with a *trans*-stereochemistry without need of additional isomerization steps. It is known[19] that *cis*−*trans*-isomerization at the 2-azetidinone nucleus occurs in the presence of base. Therefore prolonged reaction times or increased amounts of base may promote both cyclization and *cis*−*trans*-isomerization of the precursor monolactams. In fact, when compounds **6a**,**b** were reacted with LHMDS at −78 °C for 5 h, bicycles *trans*-**15a**,**b** were obtained in a 65% yields (Scheme 5). As stated previously, cyclization of the diastereomeric mixture of monolactams **7e/8e** produces exclusively the *trans*-tricyclic lactams **13/14**.

The synthesis of bicycles **15a**,**b** and their *cis*-isomers **9a**,**b** deserves some additional comments. 2-Azetidinones *cis*-**9a**,**b** were the sole reaction products when short reaction times (ca 15 min.) were used. Longer reaction times (5 h) and higher temperatures (−78 °C to 0 °C) formed the *trans*-isomers **15a**,**b**. These results pointed to that cyclization preceded isomerization. However, basic epimerization on bicycles **9a**,**b** may not account for

Scheme 5



6a R = Me
6b R = Ph

15a (65%)
15b (65%)

formation of *trans*-**15a**,**b**. Treatment of **9b** with LHMDS under conditions analogous to those used to obtain *trans*-**15b** from monolactam **6b** resulted in the formation of complex reaction mixtures. Furthermore, when cyclization of **6a** was monitored by ^{1}H NMR a new product with spectroscopic data coherent for the *trans*-isomer of **6a** was detected. These data may be explained by epimerization of *cis*-**6a** to *trans*-**6a** prior to its cyclization to the final *trans*-**15a**. To explain the exclusive formation of *cis*-**6a** when short reaction times are used, it is necessary to propose an aldol−retroaldol equilibrium between the cyclized compound **9a** and the monocyclic *cis*-lactam **6a**, with this last compound being isomerized to the *trans*-isomer in the reaction medium. These results show that the approach reported here is viable to prepare bi- and tricyclic *trans*-β-lactams by using the appropriate reaction conditions. This fact expands the scope and versatility of this cyclization.

In conclusion, a highly stereoselective, two-step synthesis of carbapenams, carbacefams, and fused tricyclic β-lactams has been developed. The structural requisites, scope, and shortcomings of this approach have been studied. Efforts to extend this easy entry to other policyclic 2-azetidinones and to overcome the limitations of our approach are now under study.

Experimental Section

General. Melting points were taken on a Gallemkamp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded, except when otherwise stated in $CDCl_3$, on a Varian XL-300S (300 and 75.43 MHz) and a Bruker 250-AM (250 and 62.5 MHz) spectrometer. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). The multiplicity for each signal is indicated as follows; s: singlet; d: doublet; t: triplet; q: quadruplet; qt: quintuplet; sex: sextuplet; dt: duplet of triplets; td: triplet of duplets, ddd: duplet of duplet of duplets, m: multiplet. Spectral data for inseparable mixtures of diastereomers are listed from the spectra of pure mixture with correct analytical data. IR spectra were taken on a Perkin-Elmer 781 spectrometer. Elemental analyses were obtained from the UCM Microanalysis Service (Facultad de Farmacia, UCM, Madrid).

All solvents used in this work were purified by distillation. Tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled from Na-benzophenone. Benzene and CH_2Cl_2 were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. For purification of crude reaction mixtures by flash chromatography, Merck silica-gel (230−400 Mesh) or Florisil were used as the stationary phase. Identification of products was made by TLC (Kiesegel 60F-254). UV light (λ = 254 nm) and 5% phosphomolybdic acid solution in 95% EtOH were use to develop the plates.

All commercially available compounds were used without further purification, except for Et_3N and hexamethyldisilazane which were distilled from CaH_2 before use. The following chemicals were prepared according to literature procedures: 2,2-dimethyl-3-oxobutanal, 2,2,5-trimethyl-3-oxo-4-hexenal, 2,2-dimethyl-3-oxo-3-phenylpropanal, and 2,2-dimethyl-3-oxo-3-(*p*-methoxyphenyl)propanal,[20] 2-formylcyclopentanone,[21] 2-for-

(19) See, for example: (a) Alcaide, B.; Domínguez, G.; Escobar, G.; Parreño, U.; Plumet, J. *Heterocycles* **1986**, *24*, 1579. (b) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575. (c) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A. *J. Org. Chem.* **1992**, *57*, 5921.

mylcyclohexanone, 2-formylcycloheptanone, and 2-formyl-2-methylcycloalcanones.[22]

Synthesis of Iminoketones 4 and 5. Procedure A. A slurry of the corresponding amino ester hydrochloride (13 mmol) in anhydrous benzene (50 mL) in a two-necked flask was treated with Et_3N (15 mmol), and the resulting slurry was stirred for 6 h at room temperature. After this time the flask was attached to a Dean−Stark apparatus, and the solution was heated under reflux. The corresponding aldehyde dissolved in anhydrous benzene (10 mL) was added in one portion to the boiling solution, and the resulting mixture was refluxed during 12 h. After this time the solution was cooled to room temperature and diluted with Et_2O, and most of the solvent was eliminated under vacuo. The residue was diluted again in Et_2O and filtered through a short path of Celite. The filtrate was concentrated to dryness under vacuo, and the residue containing the spectroscopically pure imine was used without further purification. Imines **4** and **5** were obtained in quantitative yields as unstable oils and must be used inmediately.

Procedure B. Et_3N (15 mmol) was added to a slurry of the corresponding amino ester hydrochloride (13 mmol) in anhydrous ether (50 mL). The resulting slurry was stirred for 6 h at room temperature. After this time, the corresponding aldehyde dissolved in anhydrous Et_2O (10 mL) and $MgSO_4$ (17 g) were added. The resulting mixture was stirred at room temperature during 12 h. Imines **4** and **5** were obtained in quantitative yield upon filtration and evaporation of the solvent under vacuo as unstable oils and must be used inmediately.

Methyl 3-Aza-5,5-dimethyl-6-oxo-3-heptenoate, 4a. Method B. Yellow oil. ^{1}H NMR: δ 1.33 (s, 6H), 2.18 (s, 3H), 3.74 (s, 3H), 4.24 (d, 2H, J = 1.2 Hz), 7.67 (t, 1H, J = 1.2 Hz). ^{13}C NMR: δ 212.8, 171.5, 170.0, 61.0, 53.8, 51.8, 26.0, 21.6, 17.9. IR ($CHCl_3$): ν 1760, 1720, 1670.

Methyl 3-Aza-5,5-dimethyl-6-oxo-6-phenyl-3-hexenoate, 4b. Method B. Yellow oil. ^{1}H NMR: δ 1.49 (s, 6H), 3.72 (s, 3H), 4.26 (d, 2H, J = 0.9 Hz), 7.38−7.41 (m, 5H), 7.83 (d, 1H, J = 0.9 Hz). ^{13}C NMR: δ 201.1, 171.9, 169.9, 135.9, 132.6, 129.5, 128.0, 61.3, 53.2, 51.9, 23.4, 18.9. IR ($CHCl_3$): ν 1750, 1690, 1660.

Methyl 4-Aza-6,6-dimethyl-7-oxo-4-octenoate, 4c. Method B. Yellow oil. ^{1}H-NMR: δ 1.28 (s, 6H), 2.19 (s, 3H), 1.82−1.95 (m, 3H), 2.12−2.14 (m, 2H), 2.60−2.70 (m, 1H), 3.60 (s, 3H), 3.65−3.78 (m, 1H), 6.15 (s, broad, 1H), 7.69 (s, broad, 1H).

Methyl 6-(*p*-Anisyl)-3-aza-5,5-dimethyl-6-oxo-3-hexenoate, 4d. Method B. Yellow oil. ^{1}H-NMR: δ 1.25 (s, 6H), 4.75 (s, 3H), 3.83 (s, 3H), 4.27 (s, 2H), 6.65 (AB, 2H, J_{AB} = 9 Hz), 7.82 (s, 1H), 8.00 (AB, 2H, J_{AB} = 9 Hz).

Methyl 3-Aza-4-(1-methyl-2-oxocyclopentyl)-3-butenoate, 5a. Method A. Yellow oil. ^{1}H-NMR: δ 1.20 (s, 3H), 1.70−2.06 (m, 3H), 2.64 (m, 2H), 3.63 (s, 3H), 3.70 (m 2H), 7.68 (s, 1H). ^{13}C-NMR: δ 218.8, 174.0, 169.9, 61.1, 55.1, 51.9, 37.6, 33.7, 20.2, 18.7. IR ($CHCl_3$): ν 1740, 1715, 1670.

Methyl 4-Aza-5-(1-methyl-2-oxocyclopentyl)-4-pentenoate, 5b. Method A. Yellow oil. ^{1}H-NMR: δ 1.17 (s, 3H), 1.45−1.75 (m, 1H), 1.80−1.95 (m, 2H), 2.00−2.25 (m, 2H), 2.25−2.40 (m, 1H), 2.40−2.60 (m, 2H), 3.6 (s, 3H), 7.5 (s, 1H). ^{13}C-NMR: δ 218.9, 172.0, 166.3, 56.0, 54.6, 51.3, 37.4, 34.8, 33.8, 19.9, 18.5. IR ($CHCl_3$): ν 1740, 1670.

Methyl 3-Aza-4-(1-methyl-2-oxocyclohexyl)-3-butenoate, 5c. Method A. Yellow oil. ^{1}H-NMR: δ 1.16 (s, 3H), 1.53−1.78 (m, 4H), 1.85−1.97 (m, 1H), 2.06−2.16 (m, 1H), 2.29−2.41 (m, 1H), 2.56−2.62 (m, 1H), 3.67 (s, 3H), 4.14 (AB, 2H, J_{AB} = 15.7 Hz), 7.57 (s, 1H). ^{13}C-NMR: δ 213.6, 172.5, 170.4, 61.3, 55.1, 52.1, 40.1, 37.7, 27.5, 21.8, 21.1. IR ($CHCl_3$): ν 1745, 1710, 1670.

Methyl 4-Aza-5-(1-methyl-2-oxocyclohexyl)-4-pentenoate, 5d. Method A. Yellow oil. ^{1}H-NMR: δ 1.10 (s, 3H), 1.50−1.70 (m, 4H), 1.75−2.20 (m, 2H), 2.25−2.45 (m, 2H), 2.56 (td, 2H, J_1 = 6.6 Hz, J_2 = 2.7 Hz), 3.57 (s, 3H), 3.52−3.60 (m, 2H), 7.57 (s, 1H). ^{13}C-NMR: δ 212.4, 172.5, 168.9, 56.5, 54.7, 51.6, 40.2, 37.8, 34.9, 27.5, 21.9, 21.3. IR ($CHCl_3$): ν 1740, 1710, 1670.

Methyl 3-Aza-4-(1-methyl-2-oxocycloheptyl)-3-butenoate, 5e. Method A. Yellow oil. ^{1}H-NMR: δ 1.19 (s, 3H), 1.30−1.79 (m, 5H), 2.12−2.34 (m, 2H), 2.34−2.64 (m, 3H), 3.66 (s, 3H), 4.14 (s, 2H), 7.67 (s, 1H). ^{13}C-NMR: δ 213.9, 171.7, 170.2, 61.2, 57.0, 51.9, 43.6, 41.0, 34.2, 30.2, 26.1, 24.5, 22.1.

Methyl 4-Aza-5-(1-methyl-2-oxocycloheptyl)-4-pentenoate, 5f. Method A. Yellow oil. ^{1}H-NMR: δ 1.20 (s, 3H), 1.40−1.80 (m, 6H), 2.00−2.25 (m, 2H), 2.30−2.53 (m, 3H), 2.60 (t, 2H, J = 6.6 Hz), 3.62−3.68 (m, 1H), 3.64 (s, 3H), 7.69 (s, 1H).

General Procedure for the Synthesis of 2-Azetidinones 6 and 7. Procedure A. (Benzyloxy)acetyl chloride (7.5 mmol) in anhydrous benzene (25 mL) was added dropwise via syringe to a boiling solution of the corresponding imine (5 mmol) and Et_3N (15 mmol) in benzene (25 mL). The resulting mixture was refluxed until the imine was consumed (TLC). The crude mixture was cooled to room temperature, diluted with $CHCl_3$ (50 mL), and washed with saturated $NaHCO_3$ (2 × 40 mL) and brine (2 × 40 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under vacuo. The crude compound was purified by crystallization (EtOAc/hexanes) or flash chromatography (EtOAc/hexanes mixtures). For diastereomeric mixtures, flash chromatography resulted, except otherwise stated, in the separation of both pure diasteromers.

Procedure B. This method was identical to procedure A except for that the reaction was carried out at room temperature.

***cis*-3-(Benzyloxy)-1-[(methoxycarbonyl)methyl]-4-(1,1-dimethyl-2-oxopropyl)-2-azetidinone, 6a. Procedure B.** Reaction time: 24 h. Pale yellow oil after purification by flash chromatography (hexanes/EtOAc 2:1). Yield 70%. ^{1}H-NMR: δ 1.27 (s, 3H), 1.28 (s, 3H), 2.08 (s, 3H), 3.62 (d, 1H, J = 17.4 Hz), 3.72 (s, 3H), 4.33 (d, 1H, J = 5.4 Hz), 4.34 (d, 1H, J = 17.4 Hz), 4.60 (d, 1H, J = 11.4 Hz), 4.79 (d, 1H, J = 5.4 Hz), 4.86 (d, 1H, J = 11.4 Hz), 7.31 (m, 5H). ^{13}C-NMR: δ 213.3, 169.2, 168.5, 137.0, 128.4, 127,9, 127.7, 82.3, 73.4, 63.4, 52.3, 49.0, 25.2, 22,0, 20.5. IR ($CHCl_3$): ν 1760, 1740, 1700. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.61; H, 6.79; N, 4.47.

***cis*-3-(Benzyloxy)-1-[(methoxycarbonyl)methyl]-4-(1,1-dimethyl-2-oxo-2-phenylethyl)-2-azetidinone, 6b. Procedure B.** Reaction time: 24 h. Pale yellow oil after purification by flash chromatography (hexanes/EtOAc 2:1). Yield 86%. ^{1}H-NMR: δ 1.48 (s, 3H), 1.59 (s, 3H), 3.70 (d, 1H, J = 17.7 Hz), 3.76 (s, 3H), 4.43 (d, 1H, J = 17.7 Hz), 4.49 (d, 1H, J = 5.8 Hz), 4.64 (d, 1H, J = 13.6 Hz) 4.86 (d, 1H, J = 5.8 Hz), 4.90 (d, 1H, J = 11.5 Hz), 7.31−7.48 (m, 8H), 7.58 (d, 2H). ^{13}C NMR: δ 208.1, 169.3, 168.4, 137.6, 136.9, 131.1, 128.4, 128.3, 128.0, 127.8, 127.7, 82.2, 73.4, 64.4, 52.3, 48.9, 21.5. IR ($CHCl_3$): ν 1770, 1755, 1710. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.87; H, 6.32; N, 3.54. Found: C, 69.92, H, 6.18; N, 3.33.

***cis*-3-(Benzyloxy)-1-[(methoxycarbonyl)methyl]-4-[2-(*p*-anisyl)-1,1-dimethyl-2-oxoethyl]-2-azetidinone, 6c. Procedure B.** Reaction time: 12 h. Pale yellow oil after purification by flash chromatography (hexanes/EtOAc 2:1). Yield 65%. ^{1}H-NMR: δ 1.52 (s, 3H), 1.56 (s, 3H), 3.67 (AB, 1H, J_{AB} = 17.5 Hz), 3.74 (s, 3H), 3.83 (s, 3H), 4.39 (AB, 1H, J_{AB} = 17.5 Hz), 4.58 (d, 1H, J = 5.4 Hz), 4.63 (AB, 1H, J_{AB} = 11.7 Hz), 4.86 (d, 1H, J = 5.4 Hz), 4.89 (AB, 1H, J_{AB} = 11.7 Hz), 6.85 (d, 2H, J = 9.1 Hz), 7.24−7.38 (m, 5H), 7.76 (d, 2H, J = 9.1 Hz). ^{13}C-NMR: δ 205.2, 169.5, 168.5, 162.2, 137.0, 131.1, 128.3, 128.0, 127.7, 127.6, 113.2, 82.3, 73.3, 64.5, 55.3, 52.3, 48.6, 42.7, 23.1, 21.9. IR ($CHCl_3$): ν 1760, 1740, 1700. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.10; H, 6.41; N, 3.38.

***cis*-3-(Benzyloxy)-1-[(2-methoxycarbonyl)ethyl]-4-(1,1-dimethyl-2-oxopropyl)-2-azetidinone, 6d. Procedure B.** Reaction time:12 h. Pale yellow oil after purification by flash chromatography (hexanes/EtOAc 2:1). Yield 75%. ^{1}H-NMR: δ 1.29 (s, 6H), 2.08 (s, 3H), 2.54−2.78 (m, 2H), 3.13 (dt, 1H, J_1 = 14.0 Hz, J_2 = 7.0 Hz), 3.68 (s, 3H), 3.84 (dt, 1H, J_1 = 14.0 Hz, J_2 = 7.0 Hz), 4.22 (d, 1H, J = 5.1 Hz), 4.56 (AB, 1H, J_{AB}

(20) Inukai, T.; Yoshizawa, R. *J. Org. Chem.* **1967**, *32*, 404.
(21) Eaton, P. E.; Jobe, P. G. *Synthesis* **1983**, 796.
(22) Ainsworth, C. *Org. Synth.* **1963**, *4*, 536.

= 12.0 Hz), 4.64 (d, 1H, J = 5.1 Hz), 4.82 (AB, 1H, J_{AB} = 12.0 Hz), 7.31−7.35 (m, 5H). ^{13}C-NMR: δ 212.5, 171.1, 168.1, 136.7, 127.9, 127.4, 127.2, 81.4, 72.9, 63.0, 51.4, 48.2, 37.1, 31.4, 25.3, 23.4, 19.8. IR ($CHCl_3$): ν 1750, 1700. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.92; H, 7.12; N, 3.91.

***cis*-3-(Benzyloxy)-1-[2-(methoxycarbonyl)ethyl]-4-(1,1-dimethyl-2-oxo-2-phenylethyl)-2-azetidinone, 6e. Procedure B.** Reaction time:12 h. Pale yellow oil after purification by flash chromatography (hexanes/EtOAc 2:1). Yield 77%. ^{1}H-NMR: δ 1.46 (s, 3H), 1.53 (s, 3H), 2.60−2.80 (m, 2H), 3.20 (dt, 1H, J_1 = 14.1 Hz, J_2 = 7.1 Hz), 3.69 (s, 3H), 3.88 (dt, 1H, J_1 = 14.1 Hz, J_2 = 7.1 Hz), 4.48 (d, 1H, J = 4.9 Hz), 4.58 (AB, 1H, J_{AB} = 11.6 Hz), 4.65 (d, 1H, J = 4.9 Hz), 4.83 (AB, 1H, J_{AB} = 11.6 Hz), 7.20−7.53 (m, 10H). ^{13}C-NMR: δ 208.9, 171.7, 168.9, 138.4, 137.1, 131.0, 128.6, 128.4, 128.1, 127.9, 127.8, 81.7, 73.5, 64.4, 52.1, 48.8, 37.8, 32.0, 25.5, 21.4. IR ($CHCl_3$): ν 1750, 1670. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.07; H, 6.47; N, 3.29.

***cis*-3-(Benzyloxy)-1-[(methoxycarbonyl)methyl]-4-(1-methyl-2-oxocyclopentyl)-2-azetidinones, 7a/8a. Procedure A.** Reaction time: 2 h. An inseparable mixture of both *cis*-diastereomers (70:30) was obtained as pale yellow oil after purification by flash chromatography (hexanes/EtOAc 2:1). Yield 56%. Major isomer: ^{1}H-NMR: δ 1.00 (s, 3H), 1.66−2.12 (m, 4H), 2.12−2.35 (m, 2H), 3.46 (AB, 1H, J_{AB} = 18.0 Hz), 3.65 (s, 3H), 4.05 (AB, 1H, J_{AB} = 18.0 Hz), 4.15 (d, 1H, J = 5.4 Hz), 4.60 (AB, 1H, J_{AB} = 11.7 Hz), 4.80 (d, 1H, J = 5.4 Hz), 4.88 (AB, 1H, J_{AB} = 11.7 Hz), 7.22−7.38 (m, 5H). ^{13}C-NMR: δ 222.8, 169.0, 168.3, 137.2, 128.1, 128.0, 127.8, 82.3, 73.2, 62.5, 52.4, 49.9, 42.5, 36.6, 30.8, 19.5, 18.3. Minor isomer: ^{1}H-NMR: δ 1.04 (s, 3H), 1.66−2.12 (m, 4H), 2.12−2.35 (m, 2H), 3.67 (s, 3H), 3.87 (AB, 1H, J_{AB} = 18.0 Hz), 4.04 (AB, 1H, J_{AB} = 18.0 Hz), 4.07 (d, 1H, J = 5.1 Hz), 4.54 (AB, 1H, J_{AB} = 11.7 H), 4.70 (d, 1H, J = 5.1 Hz),4.77 (AB, 1H, J_{AB} = 11.7 Hz), 7.22−7.38 (m, 5H). ^{13}C-NMR: δ 128.1, 128.0, 127.8, 82.5, 73.5, 62.8, 52.3, 50.0, 42.8, 37.1, 32.9, 19.8, 19.1. IR ($CHCl_3$): ν 1750, 1740, 1715. Anal. Calcd for $C_{19}H_{23}NO_5$: C; 66.07; H,6.71; N, 4.06. Found: C, 65.90; H, 6.43; N, 3.81.

***cis*-3-(Benzyloxy)-1-[2-(methoxycarbonyl)ethyl]-4-(1-methyl-2-oxocyclopentyl)-2-azetidinones, 7b/8b. Procedure A.** Reaction time: 2 h. Both *cis*-diastereomers (68:32) were separated as pure compounds after purification by flash chromatography (hexanes/EtOAc 3:1). **7b**: Pale yellow oil. Yield 15%. ^{1}H NMR: δ 1.21 (s, 3H), 1.68−2.16 (m, 4H), 2.16−2.30 (m, 2H), 2.50−2.76 (m, 2H), 3.42 (dt, 1H, J_1 = 14.2 Hz, J_2 = 7.0 Hz), 3.68 (s, 3H), 3.84 (dt, 1H, J_1 = 14.2 Hz, J_2 = 7.0 Hz), 3.97 (d, 1H, J = 5.1 Hz), 4.55 (AB, 1H, J_{AB} = 11.4 Hz), 4.58 (d, 1H, J = 5.1 Hz), 4.75 (AB, 1H, J_{AB} = 11.4 Hz), 7.31−7.36 (m, 5H). ^{13}C-NMR: δ 222.0, 171.4, 168.5, 136.7, 128.2, 127.9, 127.8, 81.5, 73.4, 63.2, 51.9, 49.9, 37.6, 37.3, 32.3, 31.9, 21.6, 18.7. IR ($CHCl_3$): ν 1760, 1740, 1710. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 67.14; H, 6.85; N, 3.72. **8b**: Pale yellow oil. Yield 43%. ^{1}H NMR: δ 1.06 (s, 3H), 1.80−2.20 (m, 5H), 2.30−2.45 (m, 1H), 2.55 (t, 2H, J = 7.4 Hz), 2.77 (dt, 1H, J_1 = 14.4 Hz, J_2 = 7.4 Hz), 3.66 (s, 3H), 3.74 (dt, 1H, J_1 = 14.4 Hz, J_2 = 7.4 Hz), 4.09 (d, 1H, J = 5.1 Hz), 4.64 (AB, 1H, J_{AB} = 11.6 Hz), 4.72 (d, 1H, J = 5.1 Hz), 4.94 (AB, 1H, J_{AB} = 11.6 Hz), 7.20−7.40 (m, 5H). ^{13}C-NMR: δ 222.6, 171.5, 168.4, 137.3, 128.5, 127.9, 127.7, 81.9, 73.1, 60.9, 52.0, 49.7, 37.0, 36.9, 31.3, 30.6, 19.4, 18.5. IR ($CHCl_3$): ν 1760, 1740. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 67.08; H, 7.00; N, 3.65.

***cis*-3-(Benzyloxy)-1-[(methoxycarbonyl)methyl]-4-(1-methyl-2-oxocyclohexyl)-2-azetidinones, 7c/8c. Procedure A.** Reaction time: 3 h. Both *cis*-diastereomers (41/59) were separated as pure compounds after purification by flash chromatography (hexanes/EtOAc 3:1). **7c**: Pale yellow oil. Yield 47%. ^{1}H-NMR: δ 1.29 (s, 3H), 1.46−1.94 (m, 4H), 1.96−2.10 (m, 1H), 2.16−2.32 (m, 2H), 2.50−2.67 (td, 1H), 3.58 (AB, 1H, J_{AB} = 17.4 Hz), 3.75 (s, 3H), 4.26 (AB, 1H, J_{AB} = 17.4 Hz), 4.39 (d, 1H, J = 5.7 Hz), 4.68 (AB, 1H, J_{AB} = 11.7 Hz), 4.87 (d, 1H, J = 5.7 Hz), 4.92 (AB, 1H, J_{AB} = 11.7 Hz), 7.30−7.35 (m, 5H). ^{13}C-NMR: δ 204.8, 169.6, 168.7, 137.2, 128.9, 127.9, 127.8, 82.3, 73.4, 62.3, 52.4, 50.5, 42.9, 38.5, 32.9, 27.3, 20.7, 19.4. IR ($CHCl_3$): ν 1750, 1700, 1220. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.57; H, 7.17; N, 4.01. **8c**: Pale yellow oil. Yield 43%. ^{1}H-NMR: δ 1.23 (s, 3H), 1.45−1.82 (m, 4H), 1.89−2.04 (m, 2H), 2.20−2.26 (m, 1H), 2.44−2.61 (m, 1H), 3.65 (AB, 1H, J_{AB} = 17.8 Hz), 3.76 (s, 3H), 4.30 (d, 1H, J = 5.3 Hz), 4.43 (AB, 1H, J_{AB} = 17.8 Hz), 4.61 (AB, 1H, J_{AB} = 11.5 Hz), 4.83 (d, 1H, J = 5.3 Hz), 4.87 (AB, 1H, J_{AB} = 11.5 Hz), 7.27−7.37 (m, 5H). ^{13}C-NMR: δ 214.2, 169.4, 168.7, 137.1, 128.4, 127.8, 127.7, 82.5, 73.5, 63.6, 52.3, 50.1, 42.8, 38.4, 33.4, 26.4, 20.7, 20.6. IR ($CHCl_3$): ν 1750, 1700. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.77; H, 7.32; N, 4.22.

***cis*-3-(Benzyloxy)-1-[2-(methoxycarbonyl)ethyl]-4-(1-methyl-2-oxocyclohexyl)-2-azetidinones, 7d/8d. Procedure A.** Reaction time: 3 h. Both *cis*-diastereomers (52/48) were separated as pure compounds after purification by flash chromatography (hexanes/EtOAc 3:1). **7d**: Pale yellow oil. Yield 35%. ^{1}H-NMR: δ 1.29 (s, 3H), 1.50−1.85 (m, 4H), 1.95−2.10 (m, 1H), 2.19−2.35 (m, 2H), 2.50−2.80 (m, 3H), 2.92 (dt, 1H, J_1 = 14.5 Hz, J_2 = 7.4 Hz), 3.67 (s, 3H), 3.78 (dt, 1H, J_1 = 14.5 Hz, J_2 = 7.4 Hz), 4.31 (d, 1H, J = 5.4 Hz), 4.65 (AB, 1H, J_{AB} = 11.8 Hz), 4.71 (d, 1H, J = 5.4 Hz), 4.90 (AB, 1H, J_{AB} = 11.8 Hz), 7.27−7.34 (m, 5H). ^{13}C-NMR: δ 214.7, 171.8, 168.9, 137.4, 128.5, 127.9, 127.7, 81.9, 73.3, 61.2, 51.9, 50.2, 38.5, 37.3, 33.1, 31.9, 27.2, 20.6, 19.5. IR ($CHCl_3$): ν 1750, 1710, 1220. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.37; H, 6.99; N, 3.89. **8d**: Colorless solid (sublimes at 160 °C). Yield 30%. ^{1}H-NMR: δ 1.33 (s, 3H), 1.60−1.90 (m, 4H), 1.95−2.05 (m, 2H), 2.07−2.12 (m, 1H), 2.17−2.25 (m, 1H), 2.25−2.40 (m, 2H), 3.15 (dt, 1H, J_1 = 11.2 Hz, J_2 = 6.3 Hz), 3.67 (s, 3H), 3.83 (dt, 1H, J_1 = 11.2 Hz, J_2 = 6.3 Hz), 4.21 (d, 1H, J = 5.0 Hz), 4.52 (AB, 1H, J_{AB} = 11.4 Hz), 4.64 (d, 1H, J = 5.0 Hz), 4.74 (AB, 1H, J_{AB} = 11.4 Hz), 7.27−7.32 (m, 5H). ^{13}C-NMR: δ 214.9, 171.5, 168.7, 136.9, 128.2, 127.8, 127.7, 81.8, 73.6, 64.2, 51.8, 49.1, 38.5, 37.6, 32.9, 31.9, 25.3, 22.1, 20.7. IR ($CHCl_3$): ν 1750, 1700. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.73; H, 6.96; N, 3.54.

***cis*-3-(Benzyloxy)-1-[(methoxycarbonyl)methyl]-4-(1-methyl-2-oxocycloheptyl)-2-azetidinones, 7e/8e. Procedure A.** Reaction time: 3 h. An inseparable mixture of both *cis*-diastereomers (56/44) was obtained as pale yellow oil after purification by flash chromatography (hexanes/EtOAc 2:1). Yield 72%. Major isomer: ^{1}H-NMR: δ 1.27 (s, 3H), 1.42−1.82 (m, 4H), 2.00−2.10 (m, 1H), 2.20−2.41 (m, 2H), 2.42−2.76 (m, 3H), 3.55 (AB, 1H, J_{AB} = 17.8 Hz), 3.77 (s, 3H), 4.35 (d, 1H, J = 5.3 Hz), 4.36 (AB, 1H, J_{AB} = 17.8 Hz), 4.64 (AB, 1H, J_{AB} = 12.1 Hz), 4.84 (AB, 1H, J_{AB} = 12.1 Hz), 4.85 (d, 1H, J = 5.3 Hz), 7.29−7.35 (m, 5H). ^{13}C-NMR: δ 216.3, 169.8, 168.6, 137.1, 128.3, 128.0, 127.8, 82.5, 73.5, 62.0, 53.0, 52.4, 42.9, 40.6, 33.4, 30.3, 25.8, 25.3, 20.9. Minor isomer: ^{1}H-NMR: δ 1.29 (s, 3H), 1.42−1.82 (m, 4H), 2.00−2.10 (m, 1H), 2.20−2.41 (m, 2H), 2.42−2.76 (m, 3H), 3.68 (AB, 1H, J_{AB} = 18.3 Hz), 3.74 (s, 3H), 4.29 (d, 1H, J = 5.6 Hz), 4.37 (AB, 1H, J_{AB} = 18.3 Hz), 4.66 (AB, 1H, J_{AB} = 11.9 Hz), 4.91 (d, 1H, J = 5.3 Hz), 4.95 (AB, 1H, J_{AB} = 11.9 Hz), 7.29−7.35 (m, 5H). ^{13}C-NMR: δ 217.3, 169.2, 168.9, 137.2, 128.2, 127.9, 127.7, 82.8, 73.3, 63.4, 53.6, 52.5, 42.5, 40.0, 32.4, 30.6, 26.6, 24.2, 18.9. IR ($CHCl_3$): ν 1765, 1750, 1700. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.78; H, 7.09; N, 3.95.

***cis*-3-(Benzyloxy)-1-[2-(methoxycarbonyl)ethyl]-4-(1-methyl-2-oxocycloheptyl)-2-azetidinones, 7f/8f. Procedure A.** Reaction time: 3 h. An inseparable mixture of both *cis*-diastereomers (53/47) was obtained as pale yellow oil after purification by flash chromatography. Yield 75%. Major isomer: ^{1}H-NMR: δ 1.28 (s, 3H), 1.44−1.94 (m, 7H), 2.10−2.19 (m, 1H), 2.35−2.42 (m, 1H), 2.50−2.72 (m, 3H), 3.10 (dt, 1H, J_1 = 12.4 Hz, J_2 = 6.3 Hz), 3.67 (s, 3H), 3.82 (dt, 1H, J_1 = 12.4 Hz, J_2 = 6.3 Hz), 4.22 (d, 1H, J = 5.1 Hz), 4.63 (AB, 1H, J_{AB} = 11.8 Hz), 4.68 (d, 1H, J = 5.1 Hz), 4.85 (AB, 1H, J_{AB} = 11.8 Hz), 7.29−7.36 (m, 5H). ^{13}C-NMR: δ 216.8, 171.6, 168.9, 136.9, 128.3, 127.7, 127.5, 81.8, 73.2, 63.2, 52.1, 51.7, 40.8, 37.7, 31.8, 29.6, 25.9, 24.9, 24.0, 19.9. Minor isomer: ^{1}H-NMR: δ 1.29 (s, 3H), 1.44−1.94 (m, 7H), 2.10−2.19 (m, 1H), 2.35−2.42 (m, 1H), 2.50−2.72 (m, 3H), 3.10 (dt, 1H, J_1 = 12.4 Hz, J_2 = 6.3 Hz), 3.66 (s, 3H), 3.82 (dt, 1H, J_1 = 12.4 Hz, J_2 = 6.3 Hz), 4.13 (d, 1H, J = 5.4 Hz), 4.60 (AB, 1H, J_{AB} = 11.8 Hz), 4.67

(d, 1H, J = 5.4 Hz), 4.90 (AB, 1H, J_{AB} = 11.8 Hz), 7.29−7.36 (m, 5H). ^{13}C-NMR: δ 215.8, 171.5, 168.5, 137.1, 128.2, 127.6, 127.4, 82.1, 73.1, 62.7, 52.4, 51.8, 40.9, 37.1, 34.4, 31.6, 30.5, 25.0, 24.0, 19.2. IR ($CHCl_3$): ν 1760, 1740, 1700. Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.51; H, 7.13; N, 3.48.

General Procedure for the Synthesis of Compounds 9−15. BuLi (4.8 mmol, 1.6 M in hexane) was added dropwise via syringe to a cooled (−78 °C) solution of hexamethyldisilazane (5.2 mmol) in anhydrous THF (15 mL) under argon. After 30 min, the resulting solution was transferred via cannula to a cooled solution (−78 °C) of the corresponding β-lactam (2 mmol) in anhydrous THF (15 mL) by using argon pressure. Depending on the case, the reaction was maintained at −78 °C or the temperature raised to 0 °C until complete disappearance (TLC) of the starting 2-azetidinone. The reaction mixture was quenched with NH_4Cl (3 mL of saturated aqueous solution) and diluted with 20 mL of $CHCl_3$. The organic layer was washed with water (2 × 20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo, and the crude compounds were purified as indicated.

***cis*-6-(Benzyloxy)-2-hydroxy-3-(methoxycarbonyl)-1,1,2-trimethylcarbapenam, 9a.** Reaction time: 5 min (−78 °C). Colorless crystalline solid. Mp 182−184 °C (EtOAc/hexanes). Yield 80%. ^{1}H-NMR: δ 1.00 (s, 3H), 1.02 (s, 3H), 1.35 (s, 3H), 3.74 (s, 3H), 3.87 (d, 1H, J = 5.1 Hz), 4.27 (s, 1H), 4.57 (d, 1H, J = 11.7 Hz), 4.80 (d, 1H, J = 11.7 Hz), 4.92 (d, 1H, J = 5.1 Hz), 7.33 (m, 5H). ^{13}C-NMR: δ 177.4, 170.1, 136.7, 128.5, 128.1, 128.0, 90.1, 80.4, 73,7, 66.8, 65.1, 52.5, 48.9, 19.6, 18.7, 18.5. IR ($CHCl_3$): ν 3480, 1770, 1760. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.86; H, 6.91; N, 4.20. Found: C, 64.65; H, 6.80; N, 4.10.

***cis*-6-(Benzyloxy)-2-hydroxy-3-(methoxycarbonyl)-1,1-dimethyl-2-phenylcarbapenam, 9b.** Reaction time: 5 min (−78 °C). Colorless crystaline solid. Mp 185−187 °C (EtOAc/hexanes). Yield 70%. ^{1}H-NMR: δ 0.76 (s, 3H), 1.01 (s, 3H), 3.67 (s, 3H), 4.13 (d, 1H, J = 5.1 Hz), 4.60 (d, 1H, J = 12 Hz), 4.82 (d, 1H, J = 12 Hz), 4.95 (d, 1H, J = 5.1 Hz), 5.14 (s, 1H), 7.24−7.44 (m, 10H). ^{13}C-NMR: δ 178.3, 170.5, 137.7, 136.7, 128.5, 128.2, 128,2, 128.0, 126.9, 92.9, 80.3, 73,7, 66.0, 64.2, 52.8, 50.1, 19.0, 18.9. IR ($CHCl_3$): ν 3350, 1770, 1730. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.87; H, 6.33; N, 3.54. Found: C, 69.56; H, 6.28; N, 3.50.

***cis*-2-(*p*-Anisyl)-6-(benzyloxy)-2-hydroxy-3-(methoxycarbonyl)-1,1-dimethylcarbapenam, 9c.** Reaction time: 1 h (−78 °C). Colorless crystalline solid. Mp 197−199 °C (EtOAc/hexanes). Yield 85%. ^{1}H-NMR: δ 0.69 (s, 3H), 0.94 (s, 3H), 3.3 (s, 1H), 3.62 (s, 3H), 3.74 (s, 3H), 4.05 (d, 1H, J = 4.8 Hz), 4.55 (AB, 1H, J_{AB} = 11.7 Hz), 4.76 (AB, 1H, J_{AB} = 1.7 Hz), 4.89 (d, 1H, J = 4.8 Hz), 5.03 (s, 1H), 6.80 (d, 2H, J = 9.1 Hz), 7.18−7.34 (m, 7H). ^{13}C-NMR: δ 178.5, 170.6, 159.4, 136.8, 129.8, 128.6, 128.3, 128.2, 128.1, 113.4, 92.9, 80.4, 73.8, 66.0, 64.2, 55.0, 52.9, 50.2, 19.0, 18.4. IR (KBr): ν 3300, 1760, 1750. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.60; H, 6.04; N, 3.37.

***cis*-7-(Benzyloxy)-2-hydroxy-3-(methoxycarbonyl)-1,1,2-trimethylcarbacefam, 10a.** Reaction time: 5 min (−78 °C). Colorless crystalline solid. Mp 142−144 °C (EtOAc/hexanes). Yield 81%. ^{1}H-NMR: δ 1.07 (s, 6H), 1.16 (s, 3H), 2.88 (dd, 1H, J_1 = 13.0 Hz, J_2 = 6.0 Hz), 3.13 (ddd, 1H, J_1 = 13.0 Hz, J_2 = 11.7 Hz, J_3 = 1.6 Hz), 3.32 (s, 1H), 3.72 (s, 3H), 3.81 (d, 1H, J = 4.7 Hz), 3.89 (dd, 1H, J_1 = 11.7 Hz, J_2 = 6.0 Hz), 4.64 (AB, 1H, J_{AB} = 11.8 Hz), 4.74 (dd, 1H, J_1 = 4.7 Hz, J_2 = 1.6 Hz), 4.87 (AB, 1H, J_{AB} = 11.8 Hz), 7.31−7.35 (m, 5H). ^{13}C-NMR: δ 174.7, 167.7, 137.2, 128.3, 127.7, 127.5, 83.1, 74.3, 73.3, 56.7, 52.1, 45.2, 39.4, 36.7, 21.2, 19.3, 17.4. IR ($CHCl_3$): ν 3500, 1750, 1720. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.90; H, 7.08; N, 4.10.

***cis*-7-(Benzyloxy)-2-hydroxy-3-(methoxycarbonyl)-1,1-dimethyl-2-phenylcarbacefam, 10b.** Reaction time: 5 min (−78 °C). Colorless crystalline solid. Mp 149−151 °C (EtOAc/hexanes). Yield 95%. ^{1}H-NMR: δ 0.84 (s, 3H), 1.05 (s, 3H), 3.27 (ddd, 1H, J_1 = 12.8 Hz, J_2 = 11.3 Hz, J_3 = 1.6 Hz), 3.49 (s, 3H), 3.71 (dd, 1H, J_1 = 11.3 Hz, J_2 = 6.1 Hz), 3.99 (d, 1H, J = 4.8 Hz), 4.07 (s, 1H), 4.11 (dd, 1H, J_1 = 12.8 Hz, J_2 = 6.1 Hz), 4.65 (AB, 1H, J_{AB} = 11.7 Hz), 4.82 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.6 Hz), 4.87 (AB, 1H, J_{AB} = 11.7 Hz), 7.26−7.33 (m, 10H). ^{13}C-NMR: δ 174.6, 167.7, 141.4, 137.3, 128.5, 127.9, 127.7, 127.5, 83.5, 78.7, 73.6, 57.8, 52.3, 44.0, 40.2, 37.1, 20.3, 16.9. IR (KBr): ν 3500, 1760, 1720. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N: 3.42. Found: C, 70.13; H, 6.38; N, 3.37.

10-(Benzyloxy)-3-hydroxy-2-(methoxycarbonyl)-8-methyl-1-azatricyclo[4.5.6]undecane, 11b. Reaction time: 5 min (−78 °C). Colorless crystalline solid. Mp 207−210 °C (EtOAc). Yield 95%. ^{1}H-NMR: δ 1.10 (s, 3H), 1.16−1.57 (m, 4H), 1.72−1.74 (m, 1H), 1.86−1.92 (m, 1H), 2.17−2.20 (m, 2H), 2.20 (s, 1H,), 3.75 (s, 3H), 3.92 (d, 1H, J = 4.8 Hz), 4.56 (s, 1H), 4.58 (AB, 1H, J_{AB} = 11.4 Hz), 4.80 (AB, 1H, J_{AB} = 11.4 Hz), 4.92 (d, 1H, J = 4.8 Hz), 7.27−7.39 (m, 5H). ^{13}C-NMR: δ 177.9, 170.0, 136.9, 128.6, 128.2, 128.1, 89.5, 80.5, 73.8, 66.6, 64.0, 52.6, 49.0, 31.0, 30.0, 23.2, 20.7, 16.6. IR (KBr): ν 3460, 1760, 1740. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H: 7.01; N, 3.90. Found: C, 66.52; H, 6.72; N, 3.60.

10-(Benzyloxy)-4-hydroxy-3-(methoxycarbonyl)-8-methyl-1-azatricyclo[4.6.5]undecane, 12a. Reaction time: 2 h (−78 °C to 0 °C, slow). Pale yellow oil. Yield of spectroscopically (^{1}H-NMR) pure material 60%. The product is unstable and decomposed extensively upon chromatography. An analytically pure sample was obtained by flash chromatography (hexanes/EtOAc 3:1). ^{1}H-NMR: δ 1.07 (s, 3H), 1.17−1.39 (m, 4H), 1.62−1.90 (m, 2H), 2.76 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.7 Hz), 3.06 (td, 1H, J_1 = 12.6 Hz, J_2 = 1.2 Hz), 3.52 (d, 1H, J = 4.8 Hz), 3.67 (s, 1H), 3.75 (s, 3H), 3.91 (dd, 1H, J_1 = 13.2 Hz, J_2 = 5.7 Hz), 4.65 (AB, 1H, J_{AB} = 11.7 Hz), 4.79 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.2 Hz), 4.86 (AB, 1H, J_{AB} = 11.7 Hz), 7.25−7.33 (m, 5H). IR ($CDCl_3$): ν 3340, 1760, 1720. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 71.02; H, 6.91; N, 4.07.

11-(Benzyloxy)-4-hydroxy-3-(methoxycarbonyl)-9-methyl-1-azatricyclo[4.6.6]dodecane, 12b. Reaction time: 5 min (−78 °C). Colorless crystalline solid. Mp 100−102 °C (EtOAc/hexanes). Yield 90%. ^{1}H-NMR: δ 1.16 (s, 3H), 1.23−1.44 (m, 2H), 1.50−1.54 (m, 3H), 1.63−1.85 (m, 3H), 2.81 (dd, 1H, J_1 = 13.0 Hz, J_2 = 6.2 Hz), 2.99 (s, 1H), 3.21 (ddd, 1H, J_1 = 12.3 Hz, J_2 = 11.6 Hz, J_3 = 1.5 Hz), 3.71 (s, 3H), 3.82 (d, 1H, J = 4.8 Hz), 3.93 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.2 Hz), 4.62 (AB, 1H, J_{AB} = 11.8 Hz), 4.72 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.5 Hz), 4.84 (AB, 1H, J_{AB} = 11.8 Hz), 7.25−7.39 (m, 5H). ^{13}C-NMR: δ 174.7, 168.2, 137.4, 128.5, 127.9, 127.7, 83.1, 73.4, 73.3, 57.8, 52.3, 44.9, 39.5, 37.0, 31.5, 31.4, 20.8, 20.4, 16.6. IR (KBr): ν 3500, 1750. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.55; H, 7.28; N, 3.60.

12-(Benzyloxy)-4-hydroxy-3-(methoxycarbonyl)-10-methyl-1-azatricyclo[4.6.7]tridecane, 11d/12d. Reaction time: 2 h (−78 °C to 0 °C, slow). An inseparable mixture of both *cis*-diastereomers (53/47) was obtained as yellow oil by flash chromatography (hexanes/EtOAc 3:1). Yield 50%. **11d**: ^{1}H-NMR: δ 1.10 (s, 3H), 1.20−1.80 (m, 7H), 1.85−2.07 (m, 2H), 2.08−2.30 (m, 1H), 3.07−3.22 (m, 2H), 3.42 (s, 1H), 3.72 (s, 3H), 3.78 (d, 1H, J = 5.4 Hz), 3.94 (dd, 1H, J_1 = 11.4 Hz, J_2 = 4.8 Hz), 4.64 (AB, 1H, J_{AB} = 12.0 Hz), 4.72 (d, 1H, J = 5.4 Hz), 4.83 (AB, 1H, J_{AB} = 12.0 Hz), 7.25−7.34 (m, 5H). ^{13}C-NMR: δ 175.0, 167.1, 137.3, 128.5, 127.9, 127.7, 83.5, 76.6, 73.6, 58.7, 52.4, 43.1, 42.9, 37.1, 34.6, 29.7, 26.2, 21.6, 21.1, 17.2. **12d**: ^{1}H-NMR: δ 1.07 (s, 3H), 1.20−1.80 (m, 7H), 1.85−2.07 (m, 2H), 2.08−2.30 (m, 1H), 2.80 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.1 Hz), 3.02 (s, 1H) 3.11 (broad dd, 1H, J_1 = 12.9 Hz, J_2 = 11.6 Hz), 3.70 (s, 3H), 3.75 (d, 1H, J = 5.4 Hz), 3.86 (dd, 1H, J_1 = 12.9 Hz, J_2 = 6.3 Hz), 4.60 (AB, 1H, J_{AB} = 12.0 Hz), 4.71 (d, 1H, J = 5.4 Hz), 4.86 (AB, 1H, J_{AB} = 12.0 Hz), 7.25−7.34 (m, 5H). ^{13}C-NMR: δ 175.5, 167.9, 137.4, 128.5, 127.9, 127.7, 83.3, 76.2, 73.7, 57.5, 52.3, 45.8, 42.5, 38.2, 36.8, 29.3, 26.2, 21.1, 20.1, 14.6. IR ($CHCl_3$): ν 3500, 1740, 1710. Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 67.99; H, 7.26; N, 3.98.

11-(Benzyloxy)-3-hydroxy-2-(methoxycarbonyl)-9-methyl-1-azatricyclo[4.5.7]dodecanes, 13/14. Reaction time: 2 h (−78 °C to 0 °C, slow). An inseparable mixture of both *trans* diastereomers (56/44) was obtained as yellow oil. Yield 80%. This mixture was unstable, decomposing after few minutes at room temperature. Major isomer: ^{1}H-NMR: δ 1.18 (s, 3H), 1.44−1.90 (m, 9H), 2.18−2.34 (m, 1H), 3.05 (s, 1H), 3.71 (s,

3H), 3.73 (d, 1H, $J = 1.9$ Hz), 3.81 (d, 1H, $J = 1.9$ Hz), 4,12 (s, 1H), 4.70 (AB, 1H, $J_{AB} = 12.4$ Hz), 5.03 (AB, 1H, $J_{AB} = 12.4$ Hz), 7.19−7.30 (m, 5H). Minor isomer: ^{1}H-NMR: δ 1.19 (s, 3H), 1.44−1.90 (m, 9H), 2.18−2.34 (m, 1H), 3.06 (s, 1H), 3.70 (s, 3H), 3.76 (s, 1H), 3.81 (d, 1H, $J = 1.9$ Hz), 3.84 (d, 1H, $J = 1.9$ Hz), 4.70 (AB, 1H, $J_{AB} = 12.4$ Hz), 5.02 (AB, 1H, $J_{AB} = 12.4$ Hz), 7.19−7.30 (m, 5H).

***trans*-6-(Benzyloxy)-2-hydroxy-3-(methoxycarbonyl)-1,1,2-trimethylcarbapenam, 15a.** Reaction time: 4 h (−78 °C → −10 °C). Yellow oil. Yield 65%. ^{1}H NMR: δ 1.11 (s, 3H), 1.13 (s, 3H), 1.43 (s, 3H), 3.17 (d, 1H, $J = 1.5$ Hz), 3.77 (s, 3H), 3.85 (s, 1H), 3.87 (d, 1H, $J = 1.5$ Hz), 4.75 (d, 1H, $J = 12$ Hz), 5.07 (d, 1H, $J = 12$ Hz), 7.24−7.34 (m, 5H). ^{13}C NMR: δ 172.2, 170.5, 137.6, 128.4, 127.8, 127.7, 91.5, 79.1, 73,8, 66.0, 64.8, 52.9, 44.0, 23.7, 16.7, 15.9. IR ($CHCl_3$): ν 3300, 1740. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.86; H, 6.90; N, 4.20. Found: C, 64.81; H, 6.87; N, 4.16.

***trans*-6-(Benzyloxy)-2-hydroxy-3-(methoxycarbonyl)-2-phenyl-1,1-dimethylcarbapenam, 15b.** Reaction time: 4 h (−78 °C → −10 °C). Yellow crystalline solid. Mp 128−130 °C (EtOAc/hexanes). Yield 65%. ^{1}H NMR: δ 0.97 (s, 3H), 1.06 (s, 3H), 3.34 (d, 1H, $J = 1.8$ Hz), 3.52 (s, 3H), 4.02 (d, 1H, $J = 1.8$ Hz), 4.72 (s, 1H), 4.80 (d, 1H, $J = 12$ Hz), 5.12 (d, 1H, $J = 12$ Hz), 7.36−7.50 (m, 8H), 7.49 (d, 2H). ^{13}C NMR: δ 172.2, 170.1, 137.5, l33.3, 128.3, 128.1, 127.7, 127.6, 127.5, 126.9, 94.6, 78.7, 73.7, 65.3, 65.2, 52.6, 45.9, 24.0, 16.7. IR ($CHCl_3$) ν 3700, 1760, 1750. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.87; H, 6.33; N, 3.54. Found: C, 69.54; H, 6.19; N, 3.29.

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