Diastereoselective Route to Novel Fused or Bridged Tricyclic β-Lactams through Intramolecular Nitrone–Alkene Cycloaddition of 2-Azetidinone-Tethered Alkenylaldehydes – Synthetic Applications to Carbacephams and Cyclic β-Amino Acid Derivatives

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Dedicated to Prof. José Elguero on the occasion of his 70th birthday

Keywords: Lactams / Nitrogen heterocycles / Cycloaddition / Polycycles / Aldehydes / Amino acids / Amino alcohols

A convenient, regio- and stereoselective direct route to optically pure unusually fused or bridged tricyclic β-lactams has been developed by use of intramolecular nitrone–alkene cycloaddition (INAC) reactions of easily available monocyclic 2-azetidinone-tethered alkenylaldehydes as the key synthetic step. The regioselectivity of the cycloaddition can be tuned by moving the alkene substituent from N1 to C3 on the 2-azetidinone ring. In addition, some simple, interesting transformations were tested on representative examples of the different types of tricyclic systems prepared, in order to demonstrate their potential as intermediates in the preparation of differently polyfunctionalized compounds, including carbacepham derivatives and related unconventional bicyclic systems containing medium-sized rings fused to the β-lactam nucleus, as well as several types of cyclic β-amino acid derivatives.

Introduction

β-Lactam antibiotics have occupied a central role in defense against bacterial infections over the past several decades.[1] The various families of β-lactam antibiotics differ in their spectra of antibacterial activity and in their susceptibilities to β-lactamase enzymes, which constitute the most common, and growing, form of antibacterial resistance.[2] The bacterial resistance to β-lactam antibiotics caused by their widespread use during the past decades has motivated a growing interest in the preparation and biological evaluation of new types of β-lactams intended to overcome the defense mechanisms of the bacteria. Tricyclic β-lactam antibiotics, generally referred to as trinems, are a new class of synthetic antibacterial agents featuring good resistance to β-lactamases and dehydropeptidases.[3] Additionally, the ever growing new applications of 2-azetidinones, in fields ranging from enzyme inhibition[4] to the use of these products as starting materials to develop new synthetic methodologies,[5] has triggered a renewed interest in the synthesis of new β-lactam systems in an attempt to move away from the classical β-lactam antibiotic structures.[6]

Since the pioneering work by LeBel,[7] the intramolecular nitrone–alkene cycloaddition (INAC) of alkenylaldehydes has been a powerful entry to complex heterocyclic systems.[8] The interest in the preparation of structurally novel bicyclic and polycyclic β-lactams[9] makes these compounds attractive targets for synthetic approaches based on INAC reactions. However, although other related intramolecular azide–olefin[10] and nitrile oxide–olefin[11] cycloadditions in the β-lactam series have occasionally been used to prepare fused bi- and tricyclic β-lactams, there is no report involving INAC reactions of 2-azetidinone-tethered alkenylaldehydes. In contrast, INAC reactions of acyclic 5-hexenyl and 5-heptenyl nitrones have been successfully used for the synthesis of key monocyclic intermediates of both thienamycin and its 1β-methyl derivative.[12] A notable feature of such processes is their propensity towards the predominant or exclusive formation of the fused bicyclic systems, as opposed to the bridged systems. In our ongoing project directed toward the synthesis of potentially bioactive 2-azetidinones[13] we recently introduced 2-azetidinone-tethered alkenylaldehydes (type **I**) as starting materials for the synthesis of fused bi- and tricyclic β-lactams, by both cyclization and intramolecular cycloaddition methodologies.[14] We envisaged that nitrones formed from such aldehydes might undergo INAC reactions to provide the alkene substituent on

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the 2-azetidinone ring, thus providing a novel, rapid route to unusual fused or bridged tricyclic β-lactams (types **II** and/or **III**) (Figure 1). The aim of our original project was to gain access to different ring connectivities on the four-membered ring in a highly regio- and stereoselective fashion, starting from easily available precursors. Our interest in such reactions was further stimulated by the potential for selective functionalization of the fused bicyclic β-lactam systems by ring cleavage of the isoxazolidine moiety.[15] In this paper we report in full[16] a general study into the use of monocyclic 2-azetidinone-tethered alkenylaldehydes as substrates for INAC reactions. In addition, applications to the preparation of polyfunctionalized, enantiopure carbacepham[17] derivatives and unconventional bicyclic systems containing medium-sized rings fused to the β-lactam nucleus, as well as several types of cyclic β-amino acid derivatives, are also described.

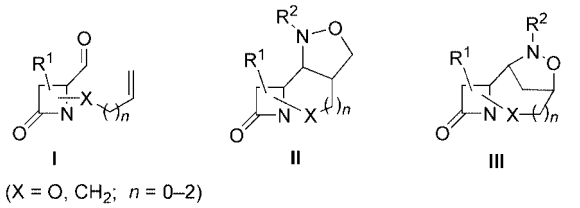


Figure 1. 2-Azetidinone-tethered alkenylaldehydes (**I**), fused tricyclic β-lactams (**II**), and bridged tricyclic β-lactams (**III**).

Results and Discussion

Starting Materials

In order to assess the scope and the regio- and stereochemistry of INAC reactions to access different tricyclic β-lactams, a series of 2-azetidinone-tethered alkenyl aldehydes **1**–**7** with variable lengths of their linking chains, different connectivity patterns of the reactive sites, and different *cis*/*trans* stereochemistry was prepared by standard methodologies (Figure 2 and Scheme 1). The cycloaddition precursor compounds racemic **4a**[18] and **4b**[14g] and optically pure (+)-**3**[14f] were known, while the enantiopure 2-azetidinones (+)-**5c** and (+)-**5e** were obtained as single *cis* enantiomers in the same manner as (+)-**5a**,[14g] (+)-**5b**,[14e] and (+)-**5d**[14e] from the corresponding imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N.[19] Standard acetonide hydrolysis (PTSA, THF/H_2O/Δ) of compounds (+)-**5c** and (+)-**5e** followed by oxidative cleavage ($NaIO_4$/CH_2Cl_2/$NaHCO_3$) provided optically pure *cis*-4-oxoazetidine-2-carbaldehydes (+)-**1c** and (+)-**1e** in the same manner as previously used for (+)-**1a**,[14g] (+)-**1b**,[14e] and (+)-**1d**[14e] in excellent yields. The *trans*-aldehyde (+)-**2b** was prepared in the same manner as (+)-**2a**[20] through our chemoselective C2 epimerization by treatment of *cis* compound (+)-**1d** with sodium carbonate in acetonitrile/water. Access to substrates **6a**, **6b**, and **7** was achieved from *N*-allyl-2-azetidinone (+)-**5a** as a common precursor (Scheme 1). Dihydroxylation (OsO_4/Me_3NO), followed by oxidative cleavage ($NaIO_4$/CH_2Cl_2/$NaHCO_3$) of the resulting diol, gave aldehyde (+)-**8** in excellent yield (98%), and this provided the homoallylic alcohols **9a** and **9b** as an equimolecular mixture of diastereomers after a Sakurai reaction (allyltrimethylsilane/$SnCl_4$/CH_2Cl_2/–78 °C; 50% yield after chromatographic purification).[14f] Both epimers at the carbinolic center, (+)-**9a** and (+)-**9b**, could be obtained analytically pure after a second chromatographic separation; their configurational assignment is discussed below. Finally, the mixture of epimeric alcohols **9a** and **9b** gave the lactol mixture **6a/6b** in nearly quantitative yield after acidic treatment to remove the isopropylidene group and oxidative cleavage of the 1,2-diol moiety. Moreover, independent transformation of the pure isolated isomers (+)-**9a** and (+)-**9b** afforded the corresponding lactols **6a** and **6b**, respectively. Compounds **6a** and **6b** were characterized by ^1H and ^{13}C NMR as complex mixtures of ring-chain tautomers, δ-lactols (major components), and δ-hydroxyaldehydes. Because of the considerable loss of material during chromatographic purification, the crude mixtures of lactols **6** were used without further purification for the INAC reactions.

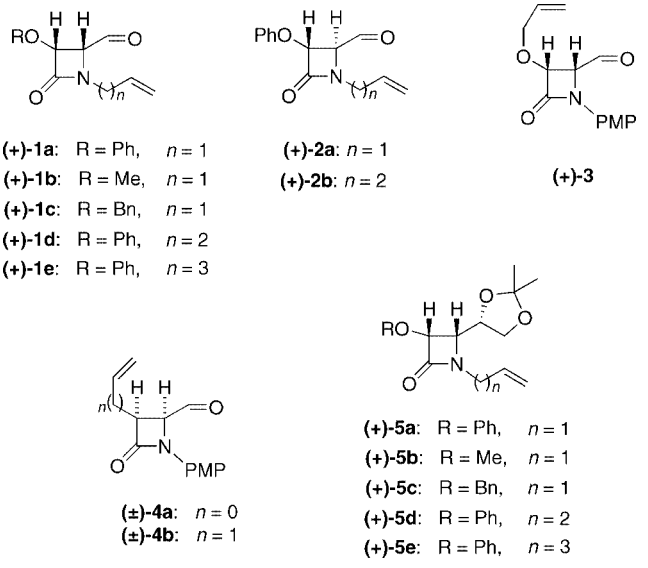
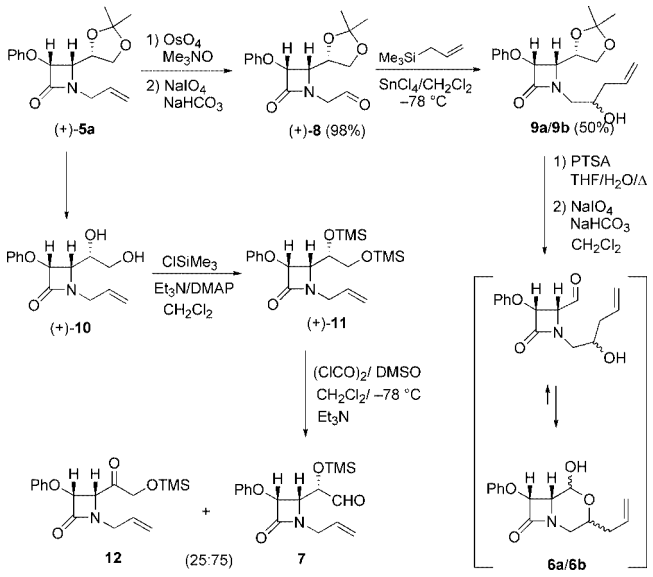


Figure 2. Starting 2-azetidinones **1**–**5**.

On the other hand, aldehyde **7** was prepared from dihydroxy-2-azetidinone (+)-**10** by a procedure reported for related non β-lactam 1,2-diols.[23] Protection of the hydroxy groups with an excess of trimethylsilyl chloride/triethylamine/DMAP (cat.) followed by Swern oxidation of the resulting disilylderivative (+)-**11** gave an inseparable mixture of the required aldehyde **7** and the isomeric ketone **12** in a 75:25 ratio (Scheme 1). The alkene-aldehydes having been obtained, the next stage was to carry out the intramolecular cycloadditions on the corresponding nitrones.

INAC Reaction of *N*-Alkenyl-β-lactams 1a–e, 2a–b, 6a–b, and 7

We first studied the INAC reactions of 3,4-*cis*-*N*-alkenylaldehydes **1a**–**e**, and the results are shown in Table 1. After



Scheme 1.

several experiments with different solvents and temperatures (Entries 1–5), we found that the best results were obtained on heating a mixture of the aldehyde (+)-**1a** (1 equiv.) with *N*-methylhydroxylamine hydrochloride (1.5 equiv.) and triethylamine (1.5 equiv.) at reflux in toluene for 30 min (Entry 3). The bridged carbacepham cycloadduct (–)-**13a** was exclusively obtained in excellent yield (80%). Similar results were obtained for the different 3-substituted aldehydes (**1b** to **1e**) (Entries 6–9) and when (+)-**1a** and *N*-benzylhydroxylamine were used (Entry 10). Both the regio- and the stereoselectivity of the INAC reaction were independent of the substituents on either the β-lactam ring or the hydroxylamine. In the case of (+)-**13d** lower selectivity was observed (mixture of two *cis* bridged diastereoisomers in a 95:5 ratio).

To extend this approach to the synthesis of other more functionalized tricyclic β-lactams, lactols **6a** and **6b** were investigated next, together with alkenylaldehyde **7**, in which the formyl group is separated from the C4 position of the four-membered ring by a methylene group. The results of intramolecular 1,3-dipolar cycloadditions of nitrones generated in situ from alcohols **9a** and **9b** (via lactols **6a** and **6b**) and aldehyde **7** are shown in Scheme 2. After several experiments with different solvents and temperatures (Entries 1–5), we found that the best results were obtained on heating a mixture of the aldehyde (+)-**1a** (1 equiv.) with *N*-methylhydroxylamine hydrochloride (1.5 equiv.) and triethylamine (1.5 equiv.) at reflux in toluene for 30 min (Entry 3). The bridged carbacepham cycloadduct (–)-**13a** was exclusively obtained in excellent yield (80%). Similar results were obtained for the different 3-substituted aldehydes (**1b** to **1e**) (Entries 6–9) and when (+)-**1a** and *N*-benzylhydroxylamine were used (Entry 10). Both the regio- and the stereoselectivity of the INAC reaction were independent of the substituents on either the β-lactam ring or the hydroxylamine. In the case of (+)-**13d** lower selectivity was observed (mixture of two *cis* bridged diastereoisomers in a 95:5 ratio).

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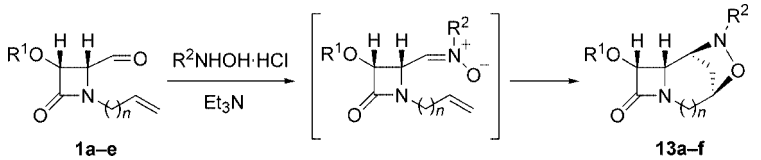
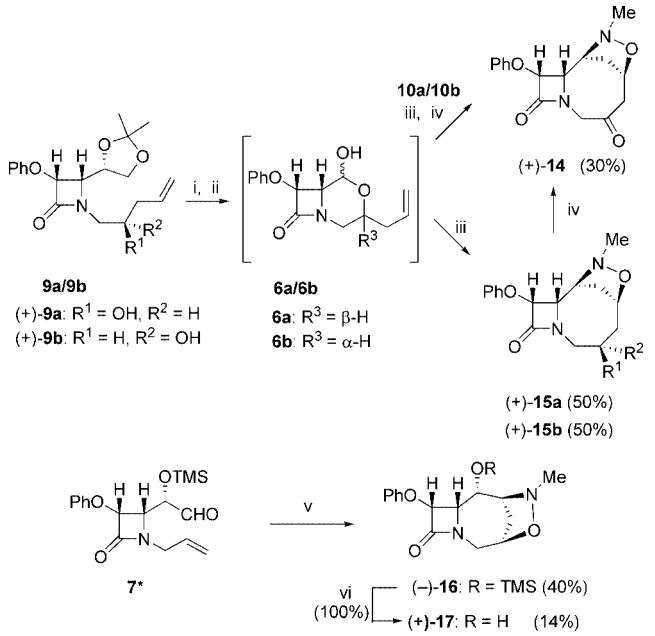
Table 1. Synthesis of bridged cycloadducts **13** from regio- and stereoselective INAC reactions of alkenylaldehydes **1**.



Entry	Substrate	*n*	R^1	R^2	Conditions	*t* [h]	Product	Yield [%][a]
1	(+)-**1a**	1	Ph	Me	benzene, r.t.	24	(–)-**13a**	70
2	(+)-**1a**	1	Ph	Me	benzene, Δ	1	(–)-**13a**	70
3	(+)-**1a**	1	Ph	Me	toluene, Δ	0.5	(–)-**13a**	80
4	(+)-**1a**	1	Ph	Me	acetonitrile, Δ	0.5	(–)-**13a**	75
5	(+)-**1a**	1	Ph	Me	methanol, r.t.	0.5	(–)-**13a**[b]	40
6	(+)-**1b**	1	Me	Me	toluene, Δ	0.5	(+)-**13b**	70
7	(+)-**1c**	1	Bn	Me	toluene, Δ	0.5	(+)-**13c**	70
8	(+)-**1d**	2	Ph	Me	toluene, Δ	2	(+)-**13d**[c]	75
9	(+)-**1e**	3	Ph	Me	toluene, Δ	3	(+)-**13e**	70
10	(+)-**1a**	1	Ph	Bn	toluene, Δ	0.5	(+)-**13f**	62

[a] Yield of pure, isolated product with correct analytical and spectroscopic data. [b] Together with major compound **13a** (65%); cycloadducts **18** and **19** arising from prior *cis*/*trans* isomerization of starting aldehyde **1a** (see later; Scheme 3) were observed as minor components (35%) as determined from ^1H NMR spectra (300 MHz) of the crude reaction mixture before purification. [c] Together with a minor stereoisomer (5% yield).



Scheme 2. (i) PTSA, THF/H_2O, Δ. (ii) $NaIO_4$, $NaHCO_3$, CH_2Cl_2, r.t. (iii) MeNHOH·HCl, Et_3N, toluene, Δ, 21–24 h. (iv) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, Et_3N. (v) MeNHOH·HCl, Et_3N, toluene, Δ, 0.5 h. (vi) TBA, THF, r.t. * In mixture with 25% of unreactive compound **12**.

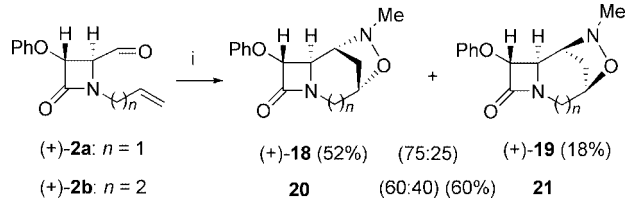
Furthermore, independent cycloaddition of isolated lactols **6a** or **6b**, prepared in situ from alcohols, exclusively provided the corresponding tricyclic alcohols (+)-**15a** and (+)-**15b**, respectively, in 50% isolated yield in both cases. Swern oxidation of each of these two epimeric alcohols quantitatively afforded compound (+)-**14** as a common product, thus confirming their epimeric nature at the carbinolic center. On the other hand, aldehyde **7**, as a 75:25 mixture together with the unreactive ketone **12**, underwent smooth cycloaddition after 30 minutes, providing an 80:20 mixture of tricyclic silylether (–)-**16** and its corresponding alcohol (+)-**17** in 40% and 14% isolated yields, respectively. Quantitative desilylation (TBAF/THF/r.t.) of compound (–)-**16** to (+)-**17** confirmed the same regio- and stereochemistry for both compounds.

The results above demonstrate that INAC reactions of *cis*-2-azetidinone-tethered *N*-alkenylaldehydes **1a**–**e**, **6a**, **6b**, and **7** are regio- and stereoselective, efficient routes to different enantiopure functionalized tricyclic β-lactams with bridged structures and containing six- to eight-membered central rings. No isomeric fused tricyclic cycloadducts were observed in any instance.

The exclusive formation of the bridged-ring products **13**–**17** is worthy of note because only fused-ring products have been found in INAC reactions of *N*-alkenyl-2-prolinaldehyde,[21] while variable mixtures of both bridged and fused-ring products were obtained from alkenylnitrones derived from aza-heteroaromatic aldehydes.[22] In our case, it is possible that, because of the rigid angular disposition imparted by the planar lactam group in a small cycle, the fused-ring transition state increases in energy, thereby becoming uncompetitive with the usually disfavored bridged-ring transition state.

Influence of cisltrans Stereochemistry or Other INAC Reaction Conditions

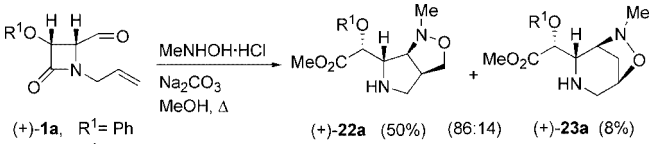
In order to study the influence of the stereochemistry of the starting substrate on both the regio- and the stereoselectivity of the INAC reaction, we investigated the reactions of *trans*-alkenylaldehydes (+)-**2a** and (+)-**2b** under similar conditions as before. Substrate (+)-**2a** provided a 75:25 mixture of bridged diastereoisomers (+)-**18** and (+)-**19**, in 52% and 18% yield as pure isolated compounds (Scheme 3), whereas aldehyde (+)-**2b** gave an inseparable 60:40 mixture of isomers, **20** and **21**.



Scheme 3. (i) MeNHOH·HCl, Et_3N, toluene, Δ, 1–2 h.

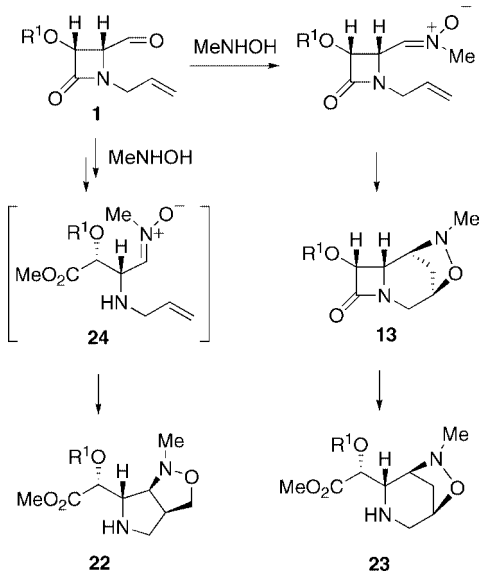
These results demonstrate that the stereochemistry (*cis* or *trans*) of the starting β-lactam has a remarkable influence on the stereoselectivity (*de*: 90–100 for *cis* isomers to 20–50 for *trans* isomers) without affecting the regioselectivity of the cycloaddition reaction, the bridged isomers being the only formed products in all cases.

On another common base/solvent treatment with an excess of sodium carbonate in methanol for 30 min,[24] alkenylaldehydes (+)-**1a** and (+)-**1c** gave the fused bicyclic pyrrolidyl acetates (+)-**22a** and (+)-**22c**, respectively, each isolated as the major component in reasonable yield (50% as pure product), instead of the expected bridged tricyclic β-lactams (–)-**13a** and (+)-**13c**. The piperidyl derivatives (+)-**23a** and (+)-**23c** were the only isolated by-products (8% in both cases) (Scheme 4).[17b] As discussed below (see Scheme 14), compounds (+)-**23a** and (+)-**23c** were easily obtained in quantitative yield from their corresponding adducts (–)-**13a** and (+)-**13c** by treatment with sodium carbonate in methanol at reflux. Hence, this different regioselectivity may be due to prior opening of the β-lactam ring and further cycloaddition of the resulting acyclic α-allylamino nitrone **24** (Scheme 5).[13,22]



Scheme 4.

Once the rigid angular disposition imparted by the planar lactam group in **1a** or **1c** has disappeared, the transition state leading to the fused pyrrolidyl ring might be steri-

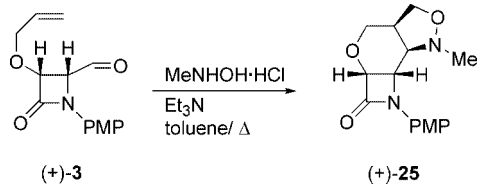


Scheme 5.

cally less demanding. Products, **22a**, **22c**, **23a**, and **23c** have been used previously for us in a divergent, concise route to both indolizidine and quinolizidine derivatives, respectively, with substituents and stereochemistry preadjusted at the β-lactam stage.[17b]

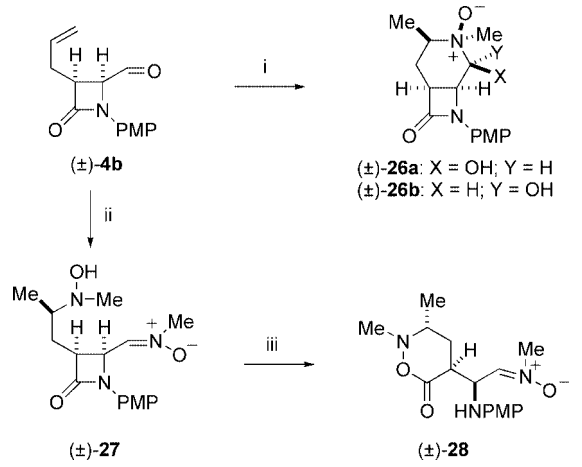
INAC Reactions of *cis*-3-Alkenyl-4-oxoazetidine-2-carbaldehydes 3, 4a, and 4b

An interesting and useful aspect of both the reactivity and the regioselectivity of the INAC reaction was discovered when the alkene substituent was moved from N1 in the β-lactam ring to C3. A dramatic change in the regioselectivity was observed and the fused tricyclic cycloadduct (+)-**25** was formed as the exclusive product (65% yield) from enantiopure compound (+)-**3** (Scheme 6).

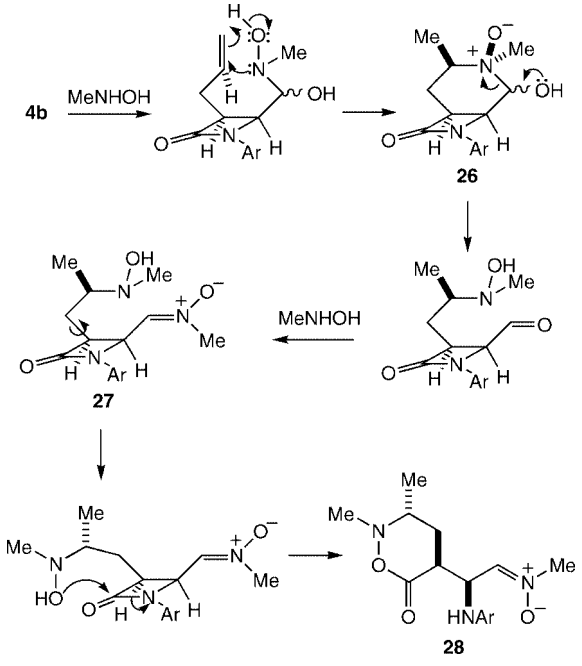


Scheme 6.

Different results were observed with *cis*-3-allyl-4-formyl-2-azetidinone (±)-**4b**, which would allow a direct comparison with the 1-allyl derivative (+)-**1a**. Compound (±)-**4b**, under nitrone formation conditions[13d] (stirring with an equimolar mixture of MeHNOH·HCl and Et_3N at room temperature in benzene for 5 h), afforded instead of the expected nitrone a 1.5:1 mixture of bicyclic *N*-oxides (±)-**26a** and (±)-**26b**, products of a reverse-Cope cyclization of the intermediate α-hydroxyhydroxylamine, in excellent yield (Scheme 7).[25] Only the major isomer (±)-**26a** was isolated analytically pure. Interestingly, this reaction with a threefold excess of *N*-methylhydroxylamine for 3 d gave the hydroxylamino nitrone (±)-**27** in a 50% yield. This nitrone is unstable in chloroform and after one week, the oxazinone nitrone (±)-**28** was obtained in quantitative yield (^1H NMR monitoring). The formation of compounds **26**–**28** may be accounted for as shown in Scheme 8.

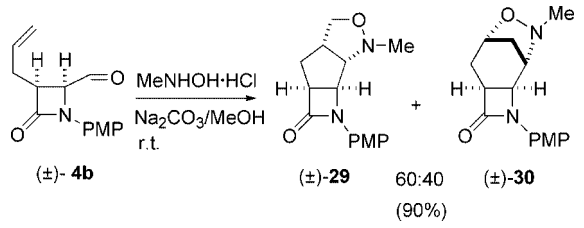


Scheme 7. (i) MeNHOH·HCl (1 equiv.), Et_3N, benzene, r.t., 5 h; (ii) MeNHOH·HCl (3 equiv.), Et_3N, benzene, r.t., 3 d; (iii) chloroform, r.t., 7 d.



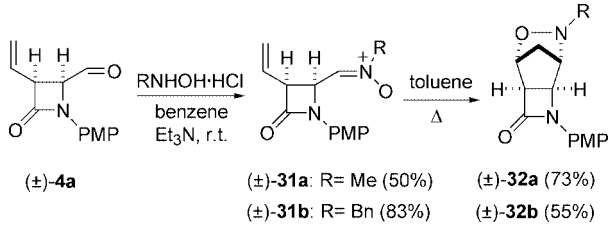
Scheme 8.

The cycloaddition process was observed with a different base/solvent system (MeHNOH·HCl (3 equiv.) and Na_2CO_3 (3 equiv.) in methanol at room temperature for 24 h), giving an isomeric mixture of fused adduct (±)-**29** and bridged isoxazolidine (±)-**30** in a 1.5:1 ratio (Scheme 9) without β-lactam ring opening.



Scheme 9.

We had previously reported that compound (±)-**4a**, with one carbon atom fewer, reacted with *N*-methylhydroxylamine or *N*-benzylhydroxylamine under these nitrone formation conditions to give nitrones (±)-**31a** and (±)-**31b** in good yields.[13d] Nitrones (±)-**31** smoothly formed the corresponding bridged cycloadducts (±)-**32a** and (±)-**32b** as single diastereoisomers in 73% and 55% isolated yields when heated in boiling toluene for 18 h (Scheme 10). As far as we know, INAC reactions with alkenylaldehydes containing only two carbon atoms between the reactant groups have very seldom been studied and there is no precedent when the central bond of the linking chain belongs to a ring.[26]



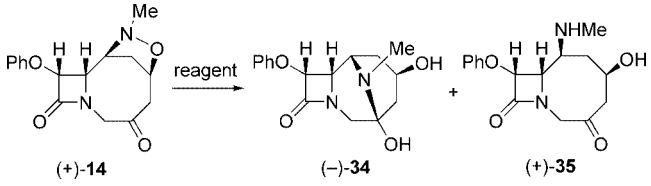
Scheme 10.

The above results clearly show that intramolecular nitrone–alkene cycloaddition with 3-alkenyl compounds is very sensitive to the structures of the initial compounds.

Synthetic Transformations of Cycloadducts

This second part is concerned with the chemoselective manipulation of selected cycloadducts as intermediates in the synthesis of carbacepham derivatives and related bicyclic systems containing medium-sized rings fused to the β-lactam nucleus. Reduction of the N–O bond was tested first, by catalytic hydrogenation of compound (–)-**13a** with 10% Pd (C). In this way, amino alcohol (+)-**33a** was obtained in moderate yield (40%) after a prolonged time (70 h). The best result was accomplished by treatment with Zn (10 equiv.) in 50% aqueous acetic acid[27] at 75 °C for 5 h to afford the 1-amino-3-hydroxycarbacepham (+)-**33a** (80%), without affecting the configurations of the different stereocenters. Under the same conditions, compounds **13c–d** and (+)-**13f** gave the corresponding bicyclic amino alcohols **33c–d** and (+)-**33f** (Table 2<tabr2" pos="x22>). However, reductive cleavage of the N–O bond in compound (+)-**13e** proved to be more difficult, even after 2 d at higher temperature. With hexacarbonylmolybdenum[28] we obtained amino alcohol (+)-**33e**, although in low yield (15%).

The outcome of the reductive cleavage of cycloadduct (+)-**14**, containing an extra oxo group, was dependent on the nature of the reagent used for ring-opening. Thus, treatment with Zn in aqueous acetic acid (60%) at 75 °C for 3 h smoothly formed the tricyclic hemiacetal **34** in 60% yield, whereas catalytic hydrogenation with Pd/C in methanol furnished the bicyclic amino alcohol **35** (50%), together with its ring tautomer **34** (20%), after 72 h (Scheme 11).

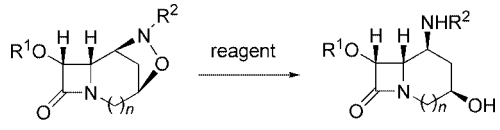


Scheme 11.

In the case of the 3,4-fused bridged cycloadducts **32a** and **32b**, reduction with Zn in AcOH/H_2O/THF (2:1:1) provided the bicyclic amino alcohols **36a** and **36b** in excellent yield in both cases (Scheme 12).

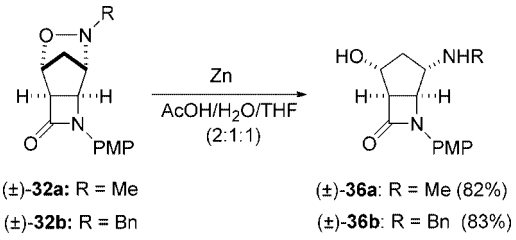
In order to achieve different functionalized carbacephams, other less frequently used procedures to open the isoxazolidine ring were also tested with cycloadduct (–)-**13a** as model (Scheme 13). Thus, treatment with an excess of

Table 2. Synthesis of bicyclic amino alcohols **36** from cycloadducts **9**.



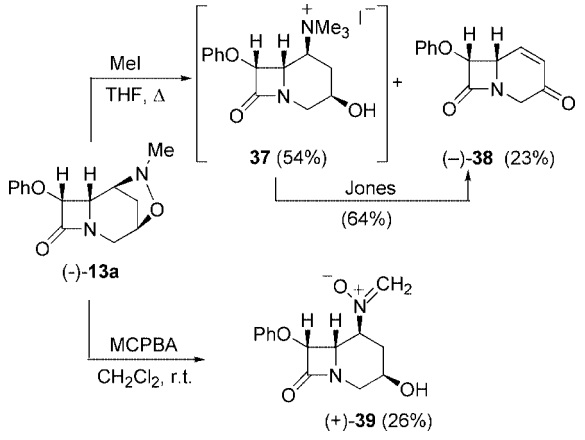
Substrate	*n*	R^1	R^2	Reagent	*t* [h]	Product	Yield [%][a]
(–)-**13a**	1	Ph	Me	Zn/AcOH/75 °C[b]	6	(+)-**33a**	80
(+)-**13c**	1	Bn	Me	Zn/AcOH/75 °C[b]	5	(+)-**33c**	76
(+)-**13d**	2	Ph	Me	Zn/AcOH/75 °C[c]	24	(+)-**33d**	66
(+)-**13e**	3	Ph	Me	$Mo(CO)_6$[d]	2.5	(+)-**33e**	15
(+)-**13f**	1	Ph	Bn	Zn/AcOH/75 °C[b]	7	(+)-**33f**	80

[a] Yield of pure, isolated product with correct analytical and spectroscopic data. [b] 10 equiv. of Zn powder were used. [c] 20 equiv. of Zn powder were used. [d] Compound (+)-**13e** (1 mmol) and $Mo(CO)_6$ (1 mmol) were heated at reflux in acetonitrile (15 mL) and water (1 mL).



Scheme 12.

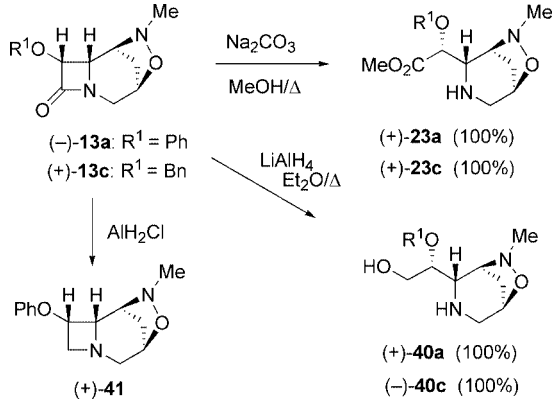
methyl iodide gave the quaternary ammonium iodide alcohol **37** (54%) and the conjugated enone (–)-**38** (23%).[29] The insoluble compound **37** could not be purified or characterized and was subsequently converted into the enone (–)-**38** by Jones' oxidation and concurrent β-elimination (64% yield). Enone (–)-**38** was also obtained by Swern oxidation of the amino alcohol (+)-**33a** in a 41% yield, through a similar tandem oxidation–elimination process. On the other hand, oxidative opening of the isoxazolidine ring with *m*-chloroperbenzoic acid[30] yielded the hydroxynitrone (+)-**39** (26%).



Scheme 13.

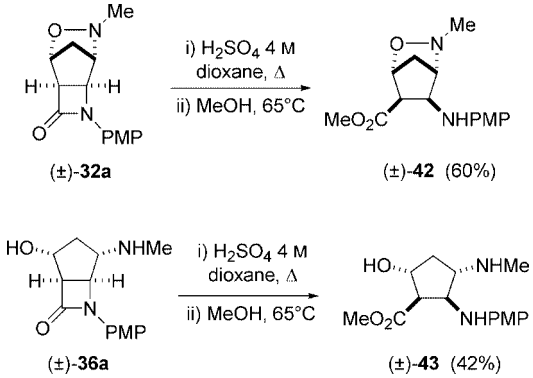
Synthetic Transformations of the β-Lactam Ring

In the reactions investigated above, the isoxazolidine ring was the only moiety affected, the β-lactam nucleus remaining unaltered. Next, we explored some reactions involving selective opening of the β-lactam ring, hoping to achieve functionalized cyclic β-amino acid derivatives, the chemistry of which has become an area of intense research activity as a consequence of their important biological profiles.[31] Compounds (–)-**13a** and (+)-**13c** were chosen as models (Scheme 14). The piperidyl ester derivatives (+)-**23a** and (+)-**23c** were easily obtained in nearly quantitative yield by treatment with sodium carbonate in refluxing methanol,[32] while reduction with $LiAlH_4$ in ether at room temperature for 1 h quantitatively provided the piperidyl alcohols (+)-**40a** and (–)-**40c**.[16b] Interestingly, reduction of (–)-**13a** with monochloroalane, generated in situ from $LiAlH_4/AlCl_3$ by a well-established procedure[33] gave the bicyclic azetidine (+)-**41** in 40% yield. Attempts to improve the reduction procedure by use of different experimental conditions (temperature, solvent, and reagent) failed, with mixtures of azetidine (+)-**41** and amino alcohol (+)-**40a** being obtained in all cases. Apart from their intrinsic interest, the bicyclic azetidine (+)-**41** may be considered a cyclic homologue of indolizidine alkaloids, which have attracted great attention thanks to their diverse and potent biological activities.[34]



Scheme 14.

Similar ring opening was tested on compounds (±)-**32** and (±)-**36**, in order to prepare their corresponding functionalized cyclic β-amino esters (±)-**42** and (±)-**43**. However, stronger reaction conditions, involving prior hydrolysis by heating at reflux with a 1:1 mixture of 4 M sulfuric acid/dioxane and subsequent esterification with boiling methanol,[35] were required to obtain the desired compounds (±)-**42** and (±)-**43** (Scheme 15). We also obtained compound (±)-**43** from (±)-**42** by reductive cleavage of the isoxazolidine ring as reported above, but the yield was lower (30%) and the crude reaction product more difficult to purify. In this way a simple synthetic method to the cyclopentane-based *cis*-β-amino esters containing extra masked [(±)-**42**] or unmasked [(±)-**43**] amino alcohol functionalities has been developed.



Scheme 15.

Although they exist in nature, as typified by the antifungal β-amino acid cispentacin,[36] there are few known examples of carbocyclic β-amino acids and so there is a need for synthetic variants. Whilst a number of methods for the synthesis of cyclic β-amino acids have been developed, stereoselective access to polyfunctionalized derivatives remains a challenge.[37]

Configurational Assignment

The structures and stereochemistries of all compounds were assigned by detailed NMR studies. The *cis* stereochemistry of the four-membered ring is set during the cyclization step to form the 2-azetidinone ring and it is transferred unaltered during the further synthetic steps.[38]

The salient feature distinguishing between bridged (**13a–f**, **14–21**, **30**, **32a**, and **32b**) and fused (**25** and **29**) regioisomers was the presence of high-field methylene carbon resonances at δ(C) = 28.2–33.6 ppm (DEPT) in the ^{13}C NMR spectra of the first class of compounds, consistent with their bridged structures.[39,40] The fused compounds showed carbon resonances at δ(C) = 68.6–71.5 ppm (DEPT) attributable to oxygen-substituted methylene carbon atoms. Regarding the stereochemistry of compounds **13**, ^{1}H NMR spectroscopic data (vicinal proton couplings and qualitative homonuclear NOE difference spectra) did not allow distinction between the two possible configurations **13a** and **13g** (Figure 3). As we have previously reported, this configurational assignment was unequivocally established as **13a** by X-ray diffraction analysis.[16a] It is therefore reasonable to assume a similar configuration (*anti* between the bridged methylene group and the 6-H hydrogen atom) for the compounds **13b-f**, **14**, and **15** derived from related *cis*-β-lactams. The configurations of the isomeric *trans* cycloadducts **18** and **19** were deduced from NOE data performed on 4-H in both compounds, resulting in a slight enhancement in the signal corresponding to both 7-H and 2-H in compound **18**, or a slight increment on the signal of 2′-H and 6-H in compound **19** (Figure 3).

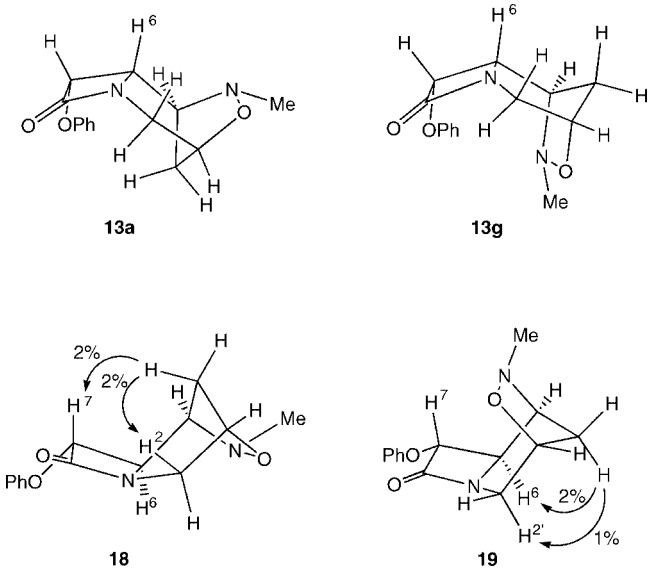


Figure 3. Selected NOE effects and stereochemistry of *cis*- and *trans*-bridged tricyclic β-lactams **13a**, **18**, and **19**.

The configurations of isomeric cycloadducts **15a** and **15b**, which differ only in the stereochemistry of the carbinolic center C3, were deduced in a similar way from NOE data obtained on both compounds (Figure 4). These results allow the assignment of a (3*R*) configuration for compound **15a** and hence the opposite (3*S*) configuration for compound **15b**. Consequently, the stereochemistry at the C3 stereogenic center in compounds **6a**, **6b**, **9a**, and **9b** could immediately be deduced by comparison with the configuration of the tricyclic compounds **15**. Finally, the configurations of cycloadducts **16** and **17** were deduced from NOE experiments performed on the hydroxy compound **17**, weak increments being observed on the signals of both 2′-H and 7-H upon irradiation of 4′-H and 2-H, respectively.

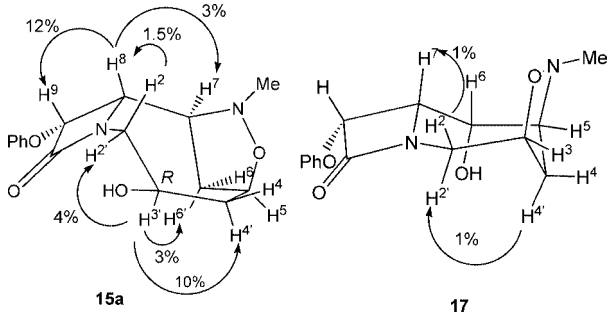


Figure 4. Selected NOE effects and stereochemistry of bridged tricyclic β-lactams **15a** and **17**.

Figure 5 shows relevant structural and stereochemical aspects for different products prepared from 3-alkenyl-4-formyl-β-lactams (compounds **25**, **26**, **29**, **30**, and **32**). All of these compounds showed $J_{2,3}$ coupling constant values in good agreement with those reported for analogous systems.[14f] Thus, *anti* relative dispositions between 2-H and 3-H were assigned for compounds **25**, **29**, **30**, and **32**, with $J_{2,3}$ = 0 Hz, while for compound **26a** the *syn* stereochemistry was deduced from the observed value of $J_{2,3}$ (5.9 Hz). Furthermore, a *trans*-diaxial disposition between hydrogen atoms 5-H, 6-H, and 7-H was assigned for compound **26a** on the basis of coupling constants ($J_{5,6}$ = 10.4, $J_{6,7}$ = 14.1 Hz). As a consequence, the methyl group on C5 has an

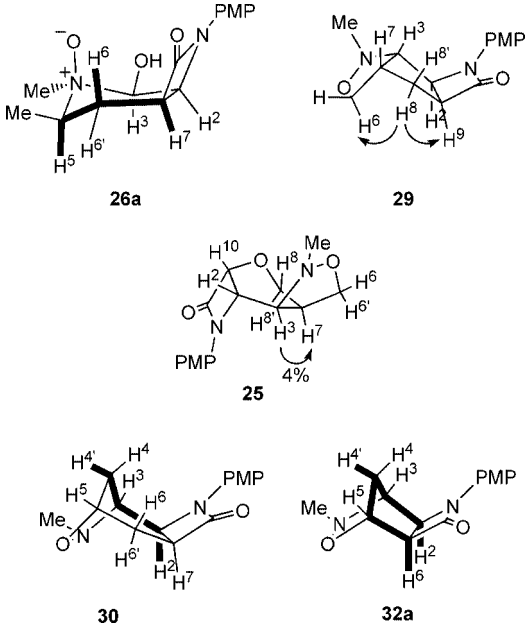


Figure 5. Relevant structural and stereochemical aspects for compounds **25a, 26**, **29**, **30**, and **32a**.

equatorial disposition, being *syn* to the *N*-oxide group due to the concerted nature of the reverse-Cope cyclization. The relative stereochemistry of the carbinol center was deduced from the $J_{2,3}$ coupling constant as well as from NOE data (see Figure 5<xfigr5" pos="x22>) indicative of a *syn* relative disposition. For fused compound **29**, the *anti* relative disposition between the isoxazolidine and the β-lactam ring was deduced from NOE enhancements on both 6-H and 9-H upon irradiation on 8-H. For cycloadducts **30** and **32a**, the existence of W coupling ($J < 1.0$ Hz) between 4′-H and 2-H for compound **30** and 4′-H and between 2-H and 6-H for compound **32a** clearly indicates that 2-H in both compounds is in the *endo* position, confirming the configurations depicted in Figure 5.[41] The *anti* relative disposition between 2-H and the bridged methylene group in compounds **30** and **32** is in agreement with that observed for compounds **13**, as we have previously stated. From these observations it seems, in all cases, that the diastereoselectivity of the different cycloaddition reactions is controlled by the C4 stereogenic center in the β-lactam ring.

Conclusions

A rapid stereocontrolled route to optically pure unusually fused or bridged tricyclic β-lactams has been developed by use of the intramolecular nitrone–alkene cycloaddition (INAC) reactions of easily available monocyclic 2-azetidinone-tethered alkenylaldehydes as the key synthetic step. The regioselectivity of the cycloaddition can be tuned by moving the alkene substituent from N1 in the 2-azetidinone ring to C3. In addition, some simple, interesting transformations were tested on representative examples of the different types of prepared tricyclic systems, which demonstrated their potential as intermediates in the preparation of differently polyfunctionalized compounds including carbacepham derivatives and several types of novel cyclic β-amino acid derivatives.

Experimental Section

General Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance 300, a Varian VRX-300S, or a Bruker AC 200. NMR spectra were recorded in $CDCl_3$ solutions, except when otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H: $\delta = 0.0$ ppm) or $CDCl_3$ (^{13}C: $\delta = 76.9$ ppm). Low- and high-resolution mass spectra were taken with an HP5989A spectrometer in chemical ionization modes (CI) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in deg per dm at 25 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification. Compounds (+)-**1a**, (+)-**1b**, (+)-**1d**, (+)-**2a**, (+)-**3**, (±)-**4a**, (±)-**4b**, (+)-**5a**, (+)-**5b**, (+)-**5d**, and (+)-**10** are known. New compounds (+)-**1c**, (+)-**1e,** (+)-**2b**, (+)-**5c**, (+)-**5e** were prepared by our previously reported methods.[13,14,18,20]

General Procedure for the Preparation of INAC Cycloadducts 13a–f, 15–21, 25, 32a, and 32b:. The appropriate *N*-alkylhydroxylamine hydrochloride (0.75 mmol) and NEt_3 (0.75 mmol) were sequentially added at room temp under Ar to a well-stirred solution of the corresponding alkenylaldehyde (0.50 mmol) in anhydrous toluene (30 mL). The resulting suspension was heated at reflux until complete disappearance of the starting material (TLC). The mixture was allowed to cool to room temp. and the solvent was then removed under reduced pressure. The residue was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with hexane/AcOEt mixtures gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of cycloadducts follow.[42]

Tricyclic 2-Azetidinone (–)-13a: Compound (+)-**1a** (110 mg, 0.47 mmol) yielded (–)-**13a** (86 mg, 80%) after 0.5 h and purification by flash chromatography (hexanes/AcOEt 1:1). White solid. M.p. 104–106 °C (hexanes/AcOEt). $[\alpha]_D^{25} = -36.0$ ($c = 2.0$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.92$ (d, $^2J_{4,4'} = 12.7$ Hz, 1 H, 4-H), 2.40 (m, 1 H, 4′-H), 2.62 (s, 3 H, NMe), 3.08 (d, $^2J_{2,2'} = 13.6$ Hz, 1 H, 2-H), 3.57 (d, $^3J_{4',5} = 4.4$ Hz, 1 H, 5-H), 3.72 (dd, $^2J_{2,2'} = 13.6$, $^3J_{2',3} = 3.3$ Hz, 1 H, 2′-H), 4.02 (d, $^3J_{6,7} = 4.7$ Hz, 1 H, 6-H), 4.56 (dd, $^3J_{3,4'} = 6.2$, $^3J_{2',3} = 3.3$ Hz, 1 H, 3-H), 5.36 (d, $^3J_{6,7} = 4.7$ Hz, 1 H, 7-H), 6.98 (m, 3 H, Ar), 7.25 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 170.9$ (C8), 157.4, 129.8, 122.5, 115.3, 81.0, 73.4, 62.2, 60.4, 49.8, 46.2 (NMe), 28.5 (C4) ppm. IR (KBr): $\tilde{\nu} = 1760$ cm^{-1}. MS (CI): *m*/*z* (%) = 261 (7) $[M + H]^+$, 260 (42) $[M]^+$, 167 (99), 84 (100). $C_{14}H_{16}N_2O_3$ (260.29): C 64.60, H 6.20, N 10.76; found C 64.55, H 6.25, N 10.78.

Tricyclic 2-Azetidinone (+)-13b: Compound (+)-**1b** (55 mg, 0.32 mmol) yielded (+)-**9b** (45 mg, 70%) as a white solid after purification by flash chromatography (CH_2Cl_2/AcOEt 1:1). White solid. M.p. 95–96 °C (hexanes/AcOEt). $[\alpha]_D^{25} = +5.0$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.78$ (d, $^2J_{4,4'} = 12.7$ Hz, 1 H, 4-H), 2.29 (m, 1 H, 4′-H), 2.59 (s, 3 H, NMe), 2.96 (d, $^2J_{2,2'} = 13.6$ Hz, 1 H, 2-H), 3.49 (d, $^3J_{4',5} = 4.8$ Hz, 1 H, 5-H), 3.56 (s, 3 H, OMe), 3.62 (dd, $^2J_{2,2'} = 13.6$, $^3J_{2',3} = 3.4$ Hz, 1 H, 2′-H), 3.78 (d, $^3J_{6,7} = 4.6$ Hz, 1 H, 6-H), 4.47 (dd, $^3J_{3,4'} = 5.9$, $^3J_{2',3} = 3.4$ Hz, 1 H, 3-H), 4.56 (d, $^3J_{6,7} = 4.6$ Hz, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 172.9$ (C8), 84.0, 73.6, 62.3, 59.9, 59.3, 49.4, 46.1 (NMe), 28.4 (C4) ppm. IR (KBr): $\tilde{\nu} = 1751$ cm^{-1}. MS (CI): *m*/*z* (%) = 199 (15) $[M + H]^+$, 198 (100) $[M]^+$. $C_9H_{14}N_2O_3$ (198.22): C 54.53, H 7.12, N 14.13; found C 54.54, H 7.12, N 14.13.

Tricyclic 2-Azetidinone (+)-13c: Compound (+)-**1c** (150 mg, 0.61 mmol), yielded (+)-**9c** (117 mg, 70%) after purification by flash chromatography (hexanes/AcOEt 1:1). White solid. M.p. 107–108 °C (hexanes/AcOEt). $[\alpha]_D^{25} = +3.0$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.82$ (d, $^2J_{4,4'} = 12.7$ Hz, 1 H, 4-H), 2.29 (m, 1 H, 4′-H), 2.53 (s, 3 H, NMe), 2.95 (d, $^2J_{2,2'} = 13.5$ Hz, 1 H, 2-H), 3.41 (d, $^3J_{4',5} = 4.5$ Hz, 1 H, 5-H), 3.63 (dd, $^2J_{2,2'} = 13.5$, $^3J_{2',3} = 3.5$ Hz, 1 H, 2′-H), 3.73 (d, $^3J_{6,7} = 4.7$ Hz, 1 H, 6-H), 4.46 (dd, $^3J_{3,4'} = 6.1$, $^3J_{2',3} = 3.5$ Hz, 1 H, 3-H), 4.58 (d, $^2J = 11.7$ Hz, 1 H, PhC*H*HO), 4.75 (dd, $^3J_{6,7} = 4.7$ Hz, 1.4 Hz, 1 H, 7-H), 4.89 (d, $^2J = 11.7$ Hz, 1 H, PhCH*H*O), 7.31 (m, 5 H, Ar) ppm. ^{13}C NMR (750 MHz, $CDCl_3$, 25 °C): $\delta = 173.0$ (C8), 136.9, 128.5, 128.2, 128.1, 81.8, 73.5, 73.3, 62.4, 60.1, 49.4, 46.1 (NMe), 28.4 (C4) ppm. IR (KBr): $\tilde{\nu} = 1741$ cm^{-1}. MS (CI): *m*/*z* (%) = 275 (2) $[M + H]^+$, 274 (11) $[M]^+$, 91 (100). $C_{15}H_{18}N_2O_3$ (274.32): C 65.68, H 6.61, N 10.21; found C 65.65, H 6.58, N 10.25.

Tricyclic 2-Azetidinone (+)-13d: Compound (+)-**1d** (90 mg, 0.37 mmol) yielded a crude mixture containing two isomers (95:5) after 2 h. The two isomers were separated as pure compounds after column chromatography (hexanes/AcOEt 1:1). In this way 75 mg (75%) of the less polar compound (+)-**13d** and 5 mg (5%) of the more polar minor compound were obtained.

Major Isomer (+)-13d: White solid. M.p. 106–107 °C (hexanes/ethyl acetate). $[\alpha]_D^{25}$ = +62.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.66 (m, 2 H, 3-H, 3′-H), 2.18 (d, $^2J_{5,5'}$ = 13.3 Hz, 1 H, 5-H), 2.60 (s, 3 H, NMe), 2.67 (m, 1 H, 5′-H), 3.00 (ddd, $^2J_{2,2'}$ = 14.6, ^3J = 11.7, ^3J = 5.4 Hz, 1 H, 2-H), 3.42 (d, $^3J_{5,6}$ = 6.4 Hz, 1 H, 6-H), 3.80 (ddd, $^2J_{2,2'}$ = 14.6, ^3J = 4.9, ^3J = 1.3 Hz, 1 H, 2′-H), 4.03 (d, $^3J_{7,8}$ = 4.7 Hz, 1 H, 7-H), 4.64 (dd, $^3J_{4,5'}$ = 9.6, ^3J = 4.9 Hz, 1 H, 4-H), 5.21 (d, $^3J_{7,8}$ = 4.7 Hz, 1 H, 8-H), 6.96 (m, 3 H, Ar), 7.23 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.7 (C9), 157.4, 129.7, 122.4, 115.4, 80.6, 74.9, 65.0, 63.2, 46.3 (NMe), 35.7, 33.6 (C5), 31.0 ppm. IR (KBr): $\tilde{\nu}$ = 1751 cm^{-1}. MS (CI): *m*/*z* (%) = 275 (2) $[M + H]^+$, 274 (100) $[M]^+$, 181 (58), 84 (93). $C_{15}H_{18}N_2O_3$ (274.32): C 65.68, H 6.61, N 10.21; found C 65.66, H 6.60, N 10.18.

Minor Isomer: Colorless oil. $[\alpha]_D^{25}$ = +19.6 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.62 (m, 1 H, 3-H), 1.97 (d, $^2J_{5,5'}$ = 12.9 Hz, 1 H, 5-H), 2.14 (m, 1 H, 3′-H), 2.52 (s, 3 H, NMe), 2.70 (ddd as dt, $^2J_{5,5'}$ = 12.9, ^3J = 7.8 Hz, 1 H, 5′-H), 2.95 (dt, $^2J_{2,2'}$ = 13.9, ^3J = 6.6 Hz, 1 H, 2-H), 3.25 (d, $^3J_{5',6}$ = 7.8 Hz, 1 H, 6-H), 3.70 (dd, $^3J_{7,8}$ = 4.4, $^3J_{6,7}$ = 0.9 Hz, 7-H), 1 H, 3.94 (ddd as dt, $^2J_{2,2'}$ = 13.9, ^3J = 6.6 Hz, 1 H, 2′-H), 4.62 (ddd as dt, ^3J = 7.8, ^3J = 4.9 Hz, 1 H, 4-H), 5.11 (dd, $^3J_{7,8}$ = 4.4, ^5J = 1.2 Hz, 1 H, 8-H), 6.90 (m, 3 H, Ar), 7.25 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.8 (C9), 157.4, 129.7, 121.9, 115.0, 78.9, 74.8, 63.0, 61.7, 46.5 (NMe), 36.6, 32.8, 29.7 (C5) ppm.

Tricyclic 2-Azetidinone (+)-13e: Compound (+)-**1e** (100 mg, 0.38 mmol) yielded (+)-**9e** (77 mg, 70%) after 3 h, after purification by flash chromatography (hexanes/AcOEt 1/2). White solid. M.p. 104–106 °C (hexanes/AcOEt). $[\alpha]_D^{25}$ = +104.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.85 (m, 4 H, 3-H, 3′-H, 4-H, 4′-H), 2.16 (dd, $^2J_{6,6'}$ = 13.3, $^3J_{5,6}$ = 4.7 Hz, 1 H, 6-H), 2.43 (ddd, $^2J_{6,6'}$ = 13.3, $^3J_{5,6'}$ = 10.0, $^3J_{6',7}$ = 7.6 Hz, 1 H, 6′-H), 2.57 (s, 3 H, NMe), 2.94 (ddd, $^2J_{2,2'}$ = 13.9, ^3J = 9.7, *J* = 2.0 Hz, 1 H, 2-H), 3.46 (d, $^3J_{6',7}$ = 7.6 Hz, 1 H, 7-H), 3.69 (dd, $^2J_{2,2'}$ = 13.9, ^3J = 6.0 Hz, 1 H, 2′-H), 4.18 (d, $^3J_{8,9}$ = 4.9 Hz, 1 H, 8-H), 4.54 (m, 1 H, 5-H), 5.15 (d, $^3J_{8,9}$ = 4.9 Hz, 1 H, 9-H), 6.98 (m, 3 H, Ar), 7.23 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.6 (C10), 157.5, 129.6, 122.3, 115.5, 80.4, 74.5, 66.3, 65.7, 43.4 (NMe), 40.1, 29.1 (C6), 28.7, 24.2 ppm. IR (KBr): $\tilde{\nu}$ = 1757 cm^{-1}. MS (CI): *m*/*z* (%) = 289 (7) $[M + H]^+$, 288 (35) $[M]^+$, 84 (100), 99 (51). $C_{16}H_{20}N_2O_3$ (288.34): C 66.65, H 6.99, N 9.72; found C 66.66, H 7.00, N 9.67.

Tricyclic 2-Azetidinone (+)-13f: Compound (+)-**1a** (100 mg, 0.43 mmol), yielded (+)-**9f** (90 mg, 62%) after purification by flash chromatography (hexanes/AcOEt 1:1). White solid. M.p. 51–52 °C (hexanes/AcOEt). $[\alpha]_D^{25}$ = +18.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.91 (d, $^2J_{4,4'}$ = 12.8 Hz, 1 H, 4-H), 2.38 (m, 1 H, 4′-H), 3.07 (d, $^2J_{2,2'}$ = 13.5 Hz, 1 H, 2-H), 3.64 (d, ^2J = 12.8 Hz, 1 H, PhC*H*H), 3.68 (d, $^3J_{4',5}$ = 4.4 Hz, 1 H, 5-H), 3.71 (dd, $^2J_{2,2'}$ = 13.5, $^3J_{2',3}$ = 3.4 Hz, 1 H, 2′-H), 3.94 (d, ^2J = 12.8 Hz, 1 H, PhCH*H*), 3.97 (d, $^3J_{6,7}$ = 4.3 Hz, 1 H, 6-H), 4.56 (dd, $^3J_{3,4'}$ = 6.1, $^3J_{2',3}$ = 3.4 Hz, 1 H, 3-H), 5.25 (dd, $^3J_{6,7}$ = 4.3, $^5J_{2,7}$ = 1.3 Hz, 1 H, 7-H), 6.91 (m, 3 H, Ar), 7.20 (m, 7 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.8 (C8), 157.2, 136.7, 129.6, 129.0, 128.5, 127.5, 122.4, 115.3, 81.0, 73.6, 62.4, 60.3, 59.7, 49.7, 28.9 (C4) ppm. IR (KBr): $\tilde{\nu}$ = 1762 cm^{-1}. MS (CI): *m*/*z* (%) = 336 (27) $[M]^+$, 91 (100). $C_{20}H_{20}N_2O_3$ (336.39): C 71.41, H 5.99, N 8.33; found C 71.49, H 5.89, N 5.91.

Tricyclic 2-Azetidinones (+)-18 and (+)-19: Compound (+)-**2a** (62 mg, 0.27 mmol) yielded the less polar compound (+)-**18** (36 mg, 52%) and the more polar compound (+)-**19** (12 mg, 18%) after column chromatography (hexanes/AcOEt, 2:1).

Tricyclic 2-Azetidinone (+)-18: White solid. M.p. 123–124 °C (hexanes/AcOEt). $[\alpha]_D^{25}$ = +105.4 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.71 (d, $^2J_{4,4'}$ = 12.5 Hz, 1H, 4-H), 2.35 (m, 1H, 4′-H), 2.63 (s, 3H, NMe), 3.06 (d, $^2J_{2,2'}$ = 14.1 Hz, 1H, 2-H), 3.63 (d, $^2J_{2,2'}$ = 14.1, $^3J_{2',3}$ = 3.6 Hz, 1H, 2′-H), 3.65 (d, $^3J_{4',5}$ = 4.6 Hz, 1H, 5-H), 3.94 (s, 1H, 6-H), 4.56 (dd, $^3J_{3,4'}$ = 5.8, $^3J_{2',3}$ = 3.6 Hz, 1H, 3-H), 4.92 (d, $^3J_{6,7}$ = 1.4 Hz, 1H, 7-H), 6.99 (m, 2H, Ar), 7.24 (m, 3H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.4 (C8), 157.2, 129.7, 122.5, 115.9, 82.2, 73.9, 63.7, 63.2, 48.9, 46.3(NMe), 27.3 (C4) ppm. IR (KBr): $\tilde{\nu}$ = 1751 cm^{-1}. MS (CI): *m*/*z* (%) = 261 (8) $[M + H]^+$, 260 (49) $[M]^+$, 167 (53), 84 (100). $C_{14}H_{16}N_2O_3$ (260.29): C 64.60, H 6.20, N 10.76; found C 64.62, H 6.15, N 10.79.

Tricyclic 2-Azetidinone (+)-19: Colorless oil. $[\alpha]_D^{25}$ = +59.3 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.94 (d, $^2J_{4,4'}$ = 12.5 Hz, 1H, 4-H), 2.46 (m, 1H, 4′-H), 2.65 (s, 3H, NMe), 2.69 (d, $^2J_{2,2'}$ = 13.1 Hz, 1H, 2-H), 3.39 (d, $^3J_{4',5}$ = 5.5 Hz, 1H, 5-H), 3.54 (s, 1H, 6-H), 3.69 (d, $^2J_{2,2'}$ = 13.1, $^3J_{2',3}$ = 3.0 Hz, 1H, 2′-H), 4.47 (dd, $^3J_{3,4'}$ = 6.4, $^3J_{2',3}$ = 3.0 Hz, 1H, 3-H), 5.32 (d, $^3J_{6,7}$ = 1.2 Hz, 1H, 7-H), 7.03 (m, 2H, Ar), 7.22 (m, 3H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.0 (C8), 157.5, 129.6, 122.0, 115.4, 82.6, 72.3, 61.0, 60.5, 47.3, 47.0 (NMe), 32.7 (C4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1750 cm^{-1}. MS (CI): *m*/*z* (%) = 261 (9) $[M + H]^+$, 260 (46) $[M]^+$, 84 (100). $C_{14}H_{16}N_2O_3$ (260.29): C 64.60, H 6.20, N 10.76; found C 64.57, H 6.23, N 10.73.

Tricyclic 2-Azetidinone (+)-25: Compound (+)-**3** (100 mg, 0.38 mmol), yielded (+)-**28** (72 mg, 65%) after purification by flash chromatography (hexanes/AcOEt 1:1). White solid. M.p. 132–133 °C (hexanes/AcOEt). $[\alpha]_D^{25}$ = +55.5 (*c* = 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.74 (s, 3 H, NMe), 2.79 (m, 1 H, 7-H), 3.28 (d, $^3J_{3,7}$ = 9.6 Hz, 1 H, 3-H), 3.74 (s, 3 H, OMe), 3.74 (dd, ^2J = 12.8, ^3J = 1.8 Hz, 1 H, OCH_2), 3.83 (dd as t, *J* = 7.9 Hz, 1 H, OCH_2), 3.94 (dd, ^2J = 12.8, ^3J = 3.1 Hz, 1 H, OCH_2), 3.97 (d, $^3J_{2,10}$ = 5.1 Hz, 1 H, 2-H), 4.14 (dd as t, *J* = 8.5 Hz, 1 H, OCH_2), 5.02 (d, $^3J_{2,10}$ = 5.1 Hz, 1 H, 10-H), 6.85 (d, *J* = 8.9 Hz, 2 H, Ar), 7.31 (d, *J* = 8.9 Hz, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.7 (C11), 156.7, 129.8, 118.4, 114.7, 78.9, 68.6, 61.9, 60.8, 55.5, 51.9, 43.8 (NMe), 37.8 ppm. IR (KBr): $\tilde{\nu}$ = 1739 cm^{-1}. MS (CI): *m*/*z* (%) = 291 (13) $[M + H]^+$, 290 (58) $[M]^+$, 98 (100). $C_{15}H_{18}N_2O_4$ (290.32): C 62.06, H 6.25, N 9.65; found C 62.05, H 6.24, N 9.69.

General Procedure for the Preparation of INAC Cycloadducts 22, 23, (±)-29, and (±)-30: The appropriate *N*-alkylhydroxylamine hydrochloride (0.75 mmol) and Na_2CO_3 (0.75 mmol) were added to a well-stirred solution of the corresponding alkenylaldehyde (0.50 mmol) in MeOH (30 mL). The reaction mixture was heated at reflux until complete disappearance of the starting aldehyde (TLC). The mixture was allowed to cool to room temp., and the solvent was then removed under reduced pressure. The residue was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of cycloadducts follow.[42]

Bicyclic Cycloadducts (+)-22a and (+)-23a: Compound (+)-**1a** (465 mg, 1.97 mmol) yielded the less polar pyrrolidyl ester (+)-**22a** (288 mg, 50%) and the more polar piperidyl ester (+)-**23a** (57 mg, 8%) after column chromatography (AcOEt/MeOH, 4:1).

Pyrrolidyl Ester (+)-22a: Colorless oil. $[\alpha]_D^{25}$ = +23.4 (*c* = 1.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.62 (s, 3 H, NMe), 2.81 (dd, $^2J_{8,8'}$ = 10.6, $^3J_{7,8}$ = 5.9 Hz, 1 H, 8-H), 3.29 (m, 1 H, 7-H), 3.42 (m, 2 H, 8′-H, 2-H), 3.53 (dd, ^3J = 8.5, ^3J = 5.5 Hz,

1 H, 3-H), 3.64 (dd, $^2J_{6,6'}$ = 8.8, $^3J_{6,7}$ = 2.9 Hz, 1 H, 6-H), 3.77 (s, 3 H, OMe), 4.07 (dd, $^2J_{6,6'}$ = 8.8, $^2J_{6',7}$ = 7.5 Hz, 1 H), 4.71 (d, ^3J = 4.9 Hz, 1 H, C*H*OPh), 6.83 (m, 2 H, Ar), 6.93 (m, 1 H, Ar), 7.23 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.4, 157.7, 129.6, 122.0, 115.0, 77.7, 75.7, 70.5, 65.8, 52.7, 52.4, 48.7, 43.8 (NMe) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1710 cm^{-1}. MS (CI): *m*/*z* (%) = 292 (30) [*M*]$^+$, 91 (100). $C_{15}H_{20}N_2O_4$ (292.33): C 61.63, H 6.90, N 9.58; found C 61.90, H 6.70, N 9.68.

Piperidyl Ester (+)-23a: Colorless oil. $[\alpha]_D^{25}$ = +5.7 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.25 (m, 1 H, 4-H), 2.39 (d, $^2J_{4,4'}$ = 11.7 Hz, 1 H, 4′-H), 2.70 (s, 3 H, NMe), 2.80 (d broad, $^2J_{6,6'}$ = 13.4 Hz, 1 H, 6-H), 2.89 (dd, $^2J_{6,6'}$ = 13.4, $^3J_{5,6'}$ = 1.7 Hz, 1 H, 6′-H), 3.17 (dd, $^3J_{3,4'}$ = 4.9, $^3J_{2,3}$ = 2.2 Hz, 1 H, 3-H), 3.44 (dd, ^3J = 5.3, $^3J_{2,3}$ = 2.2 Hz, 1 H, 2-H), 3.77 (s, 3 H, OMe), 4.47 (m, 1 H, 5-H), 4.71 (d, ^3J = 5.3 Hz, 1 H, C*H*OPh), 6.88 (m, 2 H, Ar), 7.00 (m, 1 H, Ar), 7.31 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.8, 157.6, 129.7, 121.9, 114.9, 77.8, 75.2, 63.9, 60.0, 52.5, 48.9, 46.7 (NMe), 29.6 (C4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3350, 1757 cm^{-1}. MS (CI): *m*/*z* (%) = 292 (68) [*M*]$^+$, 91 (100). $C_{15}H_{20}N_2O_4$ (292.33): C 61.63, H 6.90, N 9.58; found C 61.65, H 6.85, N 9.55.

Procedure for the Preparation of Bicyclic *N*-Oxides 26: MeNHOH·HCl (83,5 mg, 1.0 mmol) and NEt_3 (0.14 mL, 1.0 mmol) were sequentially added at room temp. under Ar to a well-stirred solution of (±)-**4b** (245 mg, 1.0 mmol) in anhydrous benzene (30 mL). The resulting suspension was stirred at room temp. for 5 h. The solvent was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. *N*-Oxide **26** was obtained in quantitative yield as a mixture (60:40) of two isomers. Both isomers were unstable and decomposed extensively upon chromatography. An analytically pure sample of major isomer **26a** was obtained by flash chromatography (AcOEt).

Bicyclic *N*-Oxide (±)-26a: Colorless oil. ^{1}H NMR (300 MHz, DMSO, 80 °C): δ = 0.97 (d, 3 H, ^3J = 6.3 Hz, Me), 1.87 (td, *J* = 14.1, *J* = 10.4 Hz, 1 H, 6-H), 1.99 (dt, $^2J_{6,6'}$ = 14.1, *J* = 5.3, 1 H, 6′-H), 2.67 (s, 3 H, NMe), 2.80 (m, 1 H, 5-H), 3.55 (ddd, $^3J_{6,7}$ = 14.1, $^3J_{2,7}$ = 5.9, $^3J_{6',7}$ = 5.3 Hz, 1 H, 7-H), 3.72 (s, 3 H, OMe), 4.15 (t, *J* = 5.9 Hz, 1 H, 2-H), 5.14 (d, $^3J_{2,3}$ = 5.9 Hz, 1 H, 3-H), 6.76 (s broad, 1 H, OH), 6.89 (d, *J* = 8.7 Hz, 2 H, Ar), 7.54 (d, *J* = 8.7 Hz, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.2 (C8), 156.0, 131.6, 118.5, 114.2, 99.0, 59.9, 55.5, 50.7, 43.1, 32.0, 22.3, 14.2 (Me) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3350, 1750 cm^{-1}. MS (CI): *m*/*z* (%) = 293 (3) [*M* + H]$^+$, 292 (12) [*M*]$^+$, 58 (100). $C_{15}H_{20}N_2O_4$ (292.33): C 61.63, H 6.90, N 9.58; found C 61.75, H 6.75, N 9.66.

General Procedure for the Reductive Cleavage of Cycloadducts. Synthesis of Cyclic Amino Alcohols 33, 34 and 36. Method A: A stirred solution of the cycloadduct (0.18 mmol) in aqueous AcOH (60%, 6 mL) was heated at 75 °C. Then excess zinc dust (10–20 equiv.) was added with vigorous stirring and the reaction mixture was maintained at 75 °C until complete disappearance of starting material (TLC). The mixture was allowed to cool to room temp., was then basified (pH = 14) by addition of KOH (6 M), and was extracted with AcOEt. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. The corresponding amino alcohol was obtained analytically pure without any further purification. **Method B:** This procedure was identical to Method A except that a mixture of aqueous AcOH (60%) (4.5 mL) and THF (1.5 mL) was used as solvent. **Method C:** Solid $Mo(CO)_6$ (1.0 mmol) was added to a solution of the cycloadduct (1.0 mmol) in a mixture of MeCN (15 mL) and water (1 mL). The mixture was heated at reflux temperature until complete disappearance of starting material (TLC). After cooling to room temp., the mixture was filtered through Celite, eluting with AcOEt, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography.

Bicyclic Amino Alcohol (+)-33a. Method A: Compound (+)-**9a** (50 mg, 0.19 mmol) yielded (+)-**33a** (40 mg, 80%) as a white solid after heating for 6 h. M.p. 58–60 °C (hexanes/AcOEt). $[\alpha]_D^{25}$ = +55.9 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.28 (m, 1 H, 4-H), 1.98 (s broad, 2 H, NH, OH), 2.26 (dt, $^2J_{4,4'}$ = 12.9, ^3J = 3.6 Hz, 1 H, 4′-H), 2.30 (s, 3 H, NMe), 2.55 (ddd, $^2J_{2,2'}$ = 12.7, $^3J_{3,2}$ = 9.3, $^5J_{2,7}$ = 1.2 Hz, 1 H, 2-H), 2.79 (ddd, $^3J_{4,5}$ = 12.0, $^3J_{5,6}$ = 8.6, $^3J_{4',5}$ = 3.6 Hz, 1 H, 5-H), 3.41 (dd, $^3J_{5,6}$ = 8.6, $^3J_{6,7}$ = 4.4 Hz, 1 H, 6-H), 3.79 (m, 1 H, 3-H), 3.99 (dd, $^2J_{2,2'}$ = 12.7, $^3J_{2',3}$ = 5.6 Hz, 1 H, 2′-H), 5.26 (dd, $^3J_{6,7}$ = 4.4, $^5J_{2,7}$ = 1.2 Hz, 1 H, 7-H), 6.98 (m, 3 H, Ar), 7.24 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.6 (C8), 157.2, 129.5, 122.3, 115.4, 80.5, 65.5, 57.4, 53.7, 44.7, 37.7, 33.4 (NMe) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3421, 1751 cm^{-1}. MS (CI): *m*/*z* (%) = 263 (100) [*M* + H]$^+$, 245 (28), 95 (58). $C_{14}H_{18}N_2O_3$ (262.3): C 64.11, H 6.92, N 10.68; found C 64.15, H 6.85, N 10.75.

Bicyclic Amino Alcohol (+)-36e. Method C: Compound (+)-**9e** (20 mg, 0.07 mmol), yielded (+)-**36e** (3 mg, 15%) as a colorless oil. $[\alpha]_D^{25}$ = +40.6 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.80 (m, 6H), 2.35 (s, 3H, NMe), 3.28 (m, 1H), 3.10 (m, 1H), 3.68 (m, 1H), 3.91 (dd, $^3J_{7,8}$ = 8.8, $^3J_{8,9}$ = 4.9 Hz, 1H, 8-H), 4.11 (m, 1H, 5-H), 5.30 (d, $^3J_{8,9}$ = 4.9 Hz, 1H, 9-H), 7.01 (m, 3H, Ar), 7.29 (m, 2H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.6 (C10), 157.2, 129.7, 122.5, 115.5, 79.7, 69.7, 62.1, 56.9, 41.9, 34.8, 33.6, 29.7, 20.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3345, 1743 cm^{-1}. MS (CI): *m*/*z*: 291 (6) [*M* + H]$^+$, 290 (100) [*M*]$^+$. $C_{16}H_{22}N_2O_3$ (290.36): C 66.19, H 7.64, N 9.65; found C 66.09, H 8.52, N 9.71.

Tricyclic Hemiacetal (–)-34. Method A: Compound (+)-**14** (35 mg, 0.13 mmol) yielded compound (–)-**34** (20 mg 60%) as a colorless oil after heating for 3 h. $[\alpha]_D^{25}$ = –9.9 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.61 (m, 2 H, 6-H, 6′-H), 2.11 (dd, $^2J_{4,4'}$ = 13.8, $^3J_{3,4}$ = 6.1 Hz, 1 H, 4-H), 2.21 (dd, $^2J_{4,4'}$ = 13.8, $^3J_{3,4'}$ = 4.2 Hz, 1 H, 4′-H), 2.45 (s, 3 H, NMe), 2.61 (s broad, 2 H, 2 x OH), 2.89 (dd, $^2J_{2,2'}$ = 13.3, $^5J_{2,9}$ = 1.7 Hz, 1 H, 2-H), 3.30 (m, 1 H, 7-H), 3.71 (d, $^2J_{2,2'}$ = 13.3 Hz, 1 H, 2′-H), 4.08 (t, $^3J_{8,9}$ = 4.4 Hz, 1 H, 8-H), 4.23 (m, 1 H, 5-H), 5.20 (dd, $^3J_{8,9}$ = 4.4, $^5J_{2,9}$ = 1.7 Hz, 1 H, 9-H), 6.99 (m, 3 H, Ar), 7.33 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 164.7 (C10), 157.9, 129.9, 122.6, 115.0, 80.6, 77.2 (C3), 64.4 (C5), 58.0, 52.6, 46.7, 43.3, 33.7 (NMe), 31.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3402, 1751 cm^{-1}. MS (CI): *m*/*z* (%) = 305 (87) [*M* + H]$^+$, 287 (80), 61 (100). $C_{16}H_{20}N_2O_4$ (304.34): C 63.14, H 6.62, N 9.20; found C 63.28, H 6.72, N 9.14.

Preparation of Tricyclic Hemiacetal (–)-34 by Catalytic Hydrogenation of Cycloadduct (+)-14: Pd(C) (10%, 10 mg) was added to a solution of (+)-**17** (50 mg, 0.16 mmol) in MeOH (15 mL). The mixture was stirred under hydrogen in a Parr apparatus at 45 psi (3 atm) until complete disappearance of the starting material (TLC; 3 d). The mixture was filtered through Celite, eluting with AcOEt, and the solvent was removed under reduced pressure. Chromatography of the residue (CH_2Cl_2/MeOH, 10:1) gave (+)-**35** (25 mg, 50%) and (–)-**34** (10 mg, 20%).

Bicyclic Amino Hydroxyketone (+)-35: $[\alpha]_D^{25}$ = +83.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.17 (m, 1 H, 6-H), 2.16 (s, 3 H, NMe), 2.37 (m, 2 H, 4-H, 6′-H), 3.67 (dd, $^3J_{6,7}$ = 10.5, $^3J_{7,8}$ = 10.2 Hz, 1 H, 7-H), 3.41 (d, $^2J_{2,2'}$ = 19.3 Hz, 1 H, 2-

H), 3.48 (dd, $^2J_{4,4'}$ = 12.0, $^3J_{4',5}$ = 4.2 Hz, 1 H, 4′-H), 3.49 (s, 1 H, OH), 3.93 (dd, $^3J_{7,8}$ = 10.2, $^3J_{8,9}$ = 4.8 Hz, 1 H, 8-H), 4.10 (m, 1 H, 5-H), 4.54 (d, $^2J_{2,2'}$ = 19.3 Hz, 1 H, 2′-H), 5.39 (d, $^3J_{8,9}$ = 4.8 Hz, 1 H, 9-H), 6.95 (t, *J* = 7.2 Hz, 1 H, Ar), 7.04 (m, 2 H, Ar), 7.33 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 208.0, 166.4 (C10), 157.8, 129.1, 122.1, 115.9, 81.7, 69.4, 61.6, 57.3, 51.6, 43.5, 40.0 (NMe), 31.7 ppm. IR ($CHCl_3$): ṽ = 3426, 1755 cm^{-1}. MS (CI): *m*/*z* (%) = 305 (3) $[M + H]^+$, 304 (100) $[M]^+$. $C_{16}H_{20}N_2O_4$ (304.34): C 63.14, H 6.62, N 9.20; found C 63.04, H 6.63, N 9.24.

Procedure for the Synthesis of Piperidyl Alcohols 40: Compound **13** (1.0 mmol) was slowly added under Ar to a suspension of $AlLiH_4$ (1.0 mmol) in anhydrous Et_2O (10 mL), and the resulting mixture was vigorously stirred and allowed to come to room temp. over 1 h. The reaction mixture was cooled to 0 °C, NH_4Cl (5 mL) was added, and the mixture was then basified (pH = 14) by addition of NaOH (50%). The reaction mixture was allowed to warm to room temp. and was extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and finally concentrated under reduced pressure. Compound **40** was obtained in analytically pure form without any further purification.

Piperidyl Alcohol (+)-40a: Compound (–)-**13a** (300 mg, 1.15 mmol) yielded compound (+)-**40a** (304 mg, 100%) as a pale colorless oil. $[\alpha]_D^{25}$ = +50.9 (*c* = 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.15 (m, 1 H, 4-H), 2.62 (d, $^2J_{4,4'}$ = 11.7 Hz, 1 H, 4′-H), 2.70 (s, 3 H, NMe), 3.04 (d, $^2J_{6,6'}$ = 13.4 Hz, 1 H, 6-H), 3.13 (s broad, 2 H, NH, OH), 3.26 (m, 3 H, 2-H, 3-H, 6′-H), 3.83 (dd, ^2J = 11.9, ^3J = 2.3 Hz, 1 H, C*H*HOH), 3.72 (dd, ^2J = 11.9, ^3J = 3.7 Hz, 1 H, CH*H*OH), 4.35 (q, *J* = 2.7 Hz, 1 H, C*H*OPh), 4.48 (dd, *J* = 5.7, *J* = 3.0 Hz, 1 H, 5-H), 7.00 (m, 3 H, Ar), 7.31 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 157.5, 129.9, 121.7, 116.6, 77.9, 75.6, 65.1, 63.4, 60.5, 49.3, 46.6 (NMe), 29.6 (C4) ppm. IR ($CHCl_3$): ṽ = 3340, 3320 cm^{-1}. MS (CI): *m*/*z* (%) = 265 (34) $[M + H]^+$, 264 (100) $[M]^+$. $C_{14}H_{20}N_2O_3$ (264.32): C 63.62, H 7.63, N 10.60; found C 63.68, H 7.70, N 10.65.

Procedure for the Preparation of Bicyclic Azetidine (+)-41: $LiAlH_4$ (7.6 mg, 0.19 mmol) was slowly added to a suspension of $AlCl_3$ (25.6 mg, 0.19 mmol) in Et_2O (3.0 mL), and the mixture was heated under reflux temperature for 30 min. The resulting suspension was allowed to cool to room temp. and solid (–)-**9a** (50 mg, 0.19 mmol) was added dropwise. After 15 min, the mixture was cooled to 0 °C, NH_4Cl (5 mL) was added, and the mixture was then basified (pH = 14) by addition of aqueous NaOH (50%). The mixture was allowed to warm to room temp. and was extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and finally concentrated under reduced pressure. Flash chromatography of the residue (AcOEt/MeOH, 2:1) gave (+)-**41** (19 mg, 40%) as a colorless oil. $[\alpha]_D^{25}$ = +78.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.45 (m, 2 H, 4-H, 4′-H), 2.56 (dd, $^2J_{2,2'}$ = 14.2, $^3J_{2,3}$ = 3.2 Hz, 1 H, 2-H), 2.63 (s, 3 H, NMe), 3.25 (d, $^2J_{2,2'}$ = 14.2 Hz, 1 H, 2′-H), 3.47 (d, $^3J_{4,5}$ = 4.4 Hz, 1 H, 5-H), 3.59 (dd, $^2J_{8,8'}$ = 8.5, $^3J_{7,8}$ = 5.6 Hz, 1 H, 8-H), 4.23 (dd, $^2J_{8,8'}$ = 8.5, $^3J_{7,8'}$ = 6.6 Hz, 1 H, 8′-H), 4.41 (d, $^3J_{6,7}$ = 6.1 Hz, 1 H, 6-H), 4.54 (dd, $^3J_{3,4}$ = 5.4, $^3J_{2,3}$ = 3.2 Hz, 1 H, 3-H), 4.95 (q, *J* = 6.6 Hz, 1 H), 6.79 (d, *J* = 7.8 Hz, 2 H, Ar), 6.99 (t, *J* = 7.3 Hz, 1 H, Ar), 7.33 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 157.3, 129.7, 121.4, 114.6, 75.4, 71.5, 67.4, 65.7, 62.4, 58.9, 46.6 (NMe), 28.3 (C4) ppm. IR ($CHCl_3$): ṽ = 2990 cm^{-1}. MS (CI): *m*/*z* (%) = 247 (4) $[M + H]^+$, 246 (100) $[M]^+$. $C_{14}H_{18}N_2O_2$ (246.31): C 68.27, H 7.37, N 11.37; found C 68.35, H 7.28, N 11.32.

Supporting Information: Supporting information for this article is available on the WWW under http://www.wiley–vch.de/home/ejoc/ or from the authors. It contains compound characterization data and experimental procedures for compounds (+)-**1c**, (+)-**1e**, (+)-**2b**, (+)-**5c**, (+)-**5e**, **7**, (+)-**8**, (+)-**9a**, (+)-**9b**, (+)-**11**, **12**, (+)-**14**, (+)-**15a**, (+)-**15b**, (–)-**16**, (+)-**17**, **20**, **21**, (+)-**22c**, (+)-**23c**, (±)-**27**, (±)-**28**, (±)-**29**, (±)-**30**, (±)-**32a**, (±)-**32b**, (+)-**33c**, (+)-**33d**, (+)-**33f**, (±)-**36a**, (±)-**36b**, (–)-**38**, (+)-**39**, (–)-**40c**, (±)-**42** and (±)-**43**.

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[37] See, for example: a) D. H. Appella, P. R. LePlae, T. L. Raguse, S. H. Gellman, *J. Org. Chem.* **2000**, *65*, 4766; b) I. B. Masesane, P. G. Steel, *Synlett* **2003**, 735; c) R. G. Soengas, J. C. Estévez, R. J. Estévez, *Org. Lett.* **2003**, *5*, 1423; d) A. D. Abell, J. Gardiner, *Org. Lett.* **2002**, *4*, 3663.
[38] The assignment of relative stereochemistry on the basis of the observed coupling constant for the methine protons 3-H and 4-H is a very well established criterion in β-lactam chemistry. See, for example: a) B. Alcaide, P. Almendros, N. Rodríguez-Salgado, A. Rodríguez-Vicente, *J. Org. Chem.* **2000**, *65*, 4453; b) X. F. Ren, E. Turos, C. H. Lake, M. R. Churchill, *J. Org. Chem.* **1995**, *60*, 6468; c) B. Alcaide, G. Domínguez, G. Escobar, U. Parreño, J. Plumet, *Heterocycles* **1986**, *24*, 1579.
[39] For clarity through this work, tricyclic systems have been numbered according to the numeration used for trinems. Thus, the four-membered ring nitrogen atom has been assigned the locator 1, and the remaining positions have been numbered to place the higher number on the lactam carbonyl group.
[40] These values are in good agreement with those reported for related compounds. See, for example: a) A. Collins, M. S. Ashwood, H. Eder, S. H. B. Wright, D. J. Kennedy, *Tetrahedron Lett.* **1990**, *31*, 2055; b) T. K. M. Shinh, W.-C. Fung, C.-H. Wong, *J. Chem. Soc., Chem. Commun.* **1994**, 449.
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[42] Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

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