SmI_2-Mediated Cyclizations of Derivatized β-Lactams for the Highly Diastereoselective Construction of Functionalized Prolines

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A series of C4-keto-functionalized 1-[(benzoyloxy)(ethoxycarbonyl)methyl]-2-azetidinones were prepared and studied for their tendency to undergo a Reformatsky-type cyclization to fused bicyclic or tricyclic β-lactams with the single-electron reducing agent samarium diiodide. Whereas the azetidinone **21a** underwent reductive cyclization, affording the potent antibiotic sanfetrinem's tricyclic [4.5.6] core structure as the major component, all other examples tested resulted in cyclization followed by an N to O acyl migration involving cleavage of the β-lactam ring as the favored pathway. Highly functionalized proline derivatives were therefore accessed as single diastereomers through the reductive cyclization of benzoates **21b**, **22**, **23a,b**, **24b**, and **25**−**28**. Pertinent for the success of these cyclizations was the addition of 1 equiv of *tert*-butyl alcohol, allowing for the protonation of the basic amide derivative obtained after the acyl migration step. The diastereoselectivities of these reactions deviate from those of similar cyclizations involving the corresponding lithium enolate. This divergence could be rationalized by the coordination of the metal ion of the samarium(III) enolate intermediate to the β-lactam amide functionality in the cyclization step, which may not be possible for lithium enolates.

Introduction

The one-electron reducing agent samarium diiodide has shown a remarkable versatility in promoting numerous synthetic transformations for the construction of complex organic compounds.[1] Many properties of this reagent have contributed to its immense success. Because of its moderate oxidation potential and high oxophilicity, the divalent lanthanide reagent displays in general functional group selectivity in the reduction step and, when relevant, leads to the formation of products with high diastereoselectivities. In addition, the creation of C−C bonds, otherwise difficult to form by other means, may be realized with this reagent. For example, in recent work, we have demonstrated the possibility of performing SmI_2-mediated Reformatsky-type reactions involving derivatized glycine residues in peptides and carbonyl compounds.[2] These room-temperature reactions permit the direct introduction of carbinol side chains at the α-carbon of the glycine unit without the need for protection or deprotonation of the amide functionalities. In a further exploitation of this reaction, we became interested in examining an intramolecular version for the construction of heterocycles, such as the polycyclic β-lactam compounds.

In recent years, the trinem class of β-lactams, as exemplified with Glaxo-Wellcome's sanfetrinem (GV104326), has displayed much popularity due to its significant broad spectrum of antibacterial activity, while still possessing high stability toward relevant β-lactamase (Scheme 1).[3−6] Examination of the trinem structure indicates that the C2−C3 double bond could be created by an intramolecular condensation of a glycine enolate unit in the presence of a suitably modified cyclohexanone moiety, followed by a dehydration step. Precisely, such an approach to several fused bi- and tricyclic β-lactams has previously been reported by Alcaide et al., noting that

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(1) For recent reviews on the application of SmI_2 in organic synthesis: (a) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (d) Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345. (e) Molander G. A. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley: New York, 1994; Vol. 46, p 211. (f) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: London, 1994. (g) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (h) Curran, D. P.; Fevig, T. L.; Jaspersen, C. P.; Totleben, M. L. *Synlett* **1992**, 943.

(2) (a) Ricci, M.; Madariaga, L.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 242. (b) Ricci, M.; Blakskjær, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2000**, *122*, 12413.

(3) (a) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Gaviraghi, G.; Tarzia, G. In *Recent Advances in the Chemistry of Anti-Infective Agents*; Bentley, P. H., Ponsford, R., Eds.; Royal Society of Chemistry: Cambridge, 1992; p 21. (b) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333.

(4) For references on the synthesis of sanfetrinem and analogues thereof from the Glaxo-Wellcome group, see: (a) Rossi, T.; Marchioro, C.; Paio, A.; Thomas, R. J.; Zarantonello, P. *J. Org. Chem.* **1997**, *62*, 1653. (b) Marchioro, C.; Pentassuglia, G.; Perboni, A.; Donati, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 463. (c) Kennedy, G.; Rossi, T.; Tamburini, B. *Tetrahedron Lett.* **1996**, *37*, 7441. (d) Panunzio, M.; Camerini, R.; Pachera, R.; Donati, D.; Marchioro, C.; Perboni, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2929. (e) Chiron, C.; Piga, E.; Rossi, T.; Tamburini, B.; Thomas, R. J. *Tetrahedron Lett.* **1996**, *37*, 3891. (f) Rossi, T.; Biondi, S.; Contini, S.; Thomas, R. J.; Marchioro, C. *J. Am. Chem. Soc.* **1995**, *117*, 9604. (g) Di Fabio, R.; Andreotti, D.; Biondi. S.; Gaviraghi, G.; Rossi, T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2025. (g) Andreotti, D.; Biondi. S.; Di Fabio, R.; Donati, D.; Piga, E.; Rossi, T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2019. (h) Padova, A.; Roberts, S. M.; Donati, D.; Marchioro, C.; Perboni, A. *Tetrahedron* **1996**, *52*, 263. (i) Tranquillini, M. E.; Araldi, G. L.; Donati, D.; Pentassuglia, G.; Pezzoli, A.; Ursini, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1683. (j) Biondi. S.; Gaviraghi, G.; Rossi, T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 525. (k) Chiron, C.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1997**, *38*, 3569. (l) Bismara, C.; Di Fabio, R.; Donati, D.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1995**, *36*, 4283. (m) Di Fabio, R.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1997**, *38*, 3587. (n) Camerini, R.; Panunzio, M.; Bonanomi, G.; Donati, D.; Perboni. A. *Tetrahedron Lett.* **1996**, *37*, 2467. (o) Panunzio, M.; Camerini, R.; Mazzoni, A.; Donati, D.; Marchioro, C.; Pachera, R. *Tetrahedron: Asymmetry* **1997**, *8*, 15. (p) Jackson, M. P.; Roberts, S. M.; Davalli, S.; Donati, D.; Marchioro, C.; Perboni, A.; Proviera, S.; Rossi, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2029.

(5) For another total synthesis of sanfetrinem, see: Hanessian, S.; Rozema, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 9884.

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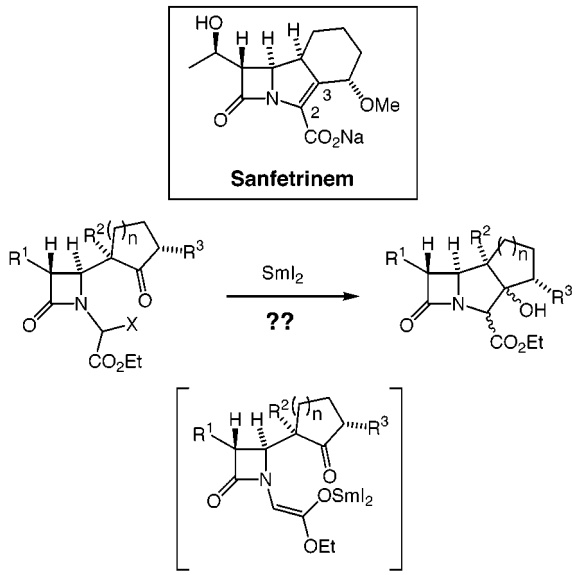
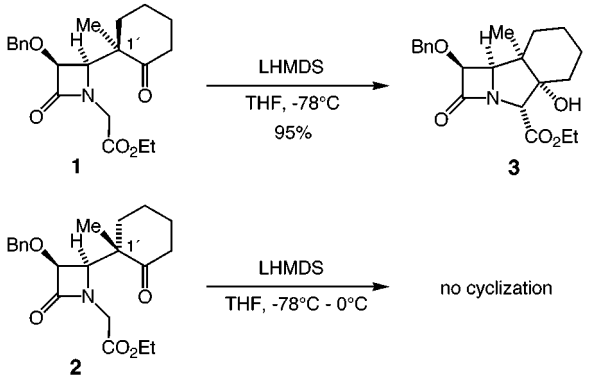
Scheme 1



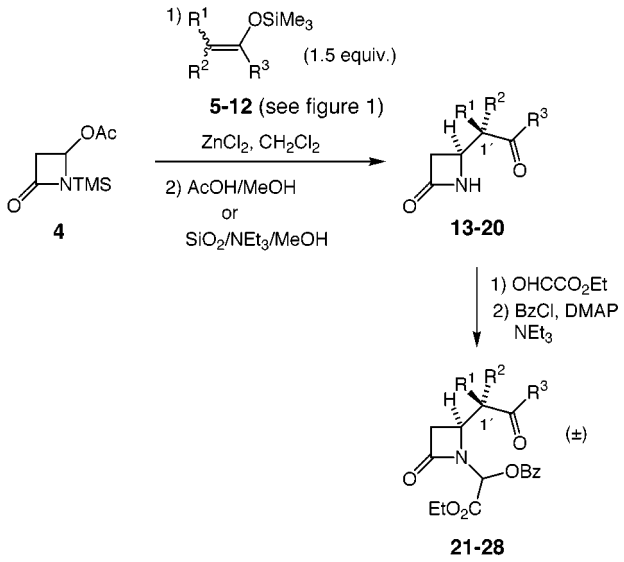
Scheme 2



successful cyclization to the latter is heavily dependent on the structure and stereochemistry of the tricyclic precursors.[7,8] As illustrated with the stereoisomeric β-lactam derivatives **1** and **2** (Scheme 2), only in the former case does the low-temperature-promoted aldol condensation work admirably, affording the tricyclic β-lactam **3** as a single diastereomer. On the other hand, with its C1′-stereoisomer **2**, no cyclization was noted even at higher temperatures. In all the substrates examined though, the carbon C1′ is fully substituted to avoid possible competitive enolization under the conditions used with strong base.

Considering that the precursors to these ring-closing events simply portray an N-substituted glycine derivative, the chemistry described for the selective side chain introduction onto small peptides involving in situ generated glycine enolates[2] represented to us an alternative for constructing the trinem core structure compared to the traditional aldol reaction. The low basic conditions characteristic of reactions promoted by SmI_2[1] likewise suggested that similar structural restrictions of the fused cyclic precursors imparted by the use of strong bases would not come into play.

Scheme 3



Hence, in this paper we provide full details of our attempts to promote this cyclization event with samarium diiodide, for the construction of fused bicyclic and tricyclic β-lactam derivatives. Contrary to our expectations, in all but two cases examined, cyclization is immediately followed by a transacylation step involving the cleavage of the β-lactam ring and resulting in the formation of highly functionalized proline derivatives. The stereochemistry of the products obtained reveals that the transition states in these condensation steps deviate from those encompassing the corresponding lithium enolates.[7,8]

Results and Discussion

Initial efforts to study the SmI_2-promoted cyclization event envisaged was performed on the precursor to the tricyclic [4.5.6] system characteristic of the trinem antibiotics, which in turn required the synthesis of a suitably derivatized glycine moiety. The conventional methodology described by Rossi and co-workers in their synthetic work on sanfetrinem and analogues thereof was therefore adapted.[4,9] Reaction of the TMS-protected 4-acetoxyazetidinone **4**[10] with 1.5 equiv of the trimethylsilyl enol ether of cyclohexanone (**5**) in the presence of zinc chloride afforded an 89% yield of the C4-alkylated azetidinone **13** as an inseparable 1.2:1 mixture of diastereomers at C1′ of the cyclohexyl ring after removal of the silyl protecting group with acetic acid in methanol (Scheme 3). Performing the reaction instead with $SnCl_4$ led to a slightly lower yield of **13**, but the diastereoselectivity was improved to 1:2.3. Next, introduction of the glycine unit was ef-

(6) For other syntheses of the trinem class, see: (a) Martel, S. R.; Wisedale, R.; Gallagher, T.; Hall, L. D.; Mahon, F. M.; Bradbury, R. H.; Hales, N. J. *J. Am. Chem. Soc.* **1997**, *119*, 2309. (b) Planchenault, D.; Wisedale, R.; Gallagher, T.; Hales, N. J. *J. Org. Chem.* **1997**, *62*, 3438. (c) Sakya, S. M.; Strohmeyer, W.; Lang, S. A.; Yang-I, L. *Tetrahedron Lett.* **1997**, *38*, 5913. (d) Hanessian, S.; Griffin, A. M.; Rozema, M. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1857. (e) Hanessian, S.; Reddy, B. *Tetrahedron* **1999**, *55*, 3427. (f) Alcaide, B.; Almendros, P.; Salgado, N. R. *J. Org. Chem.* **2000**, *65*, 3310.

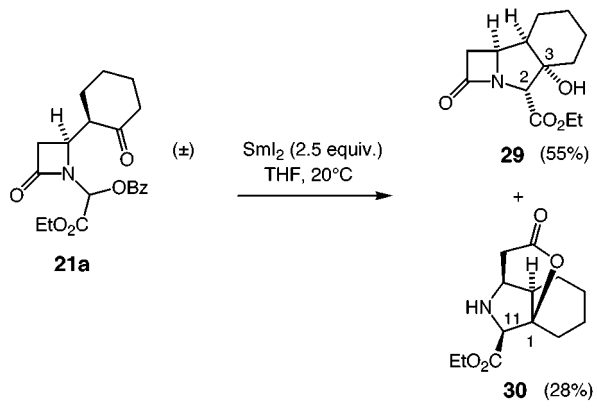
(7) (a) Alcaide, B.; Polanco, C.; Sáez, E.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 7125.

(8) For examples of other aldol cyclizations for the creation of bicyclic fused β-lactams, see: (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.; Karlsson-Andreasson, U.; Lotz, B. T.; Miller, M. J. *Heterocycles* **1995**, *40*, 691.

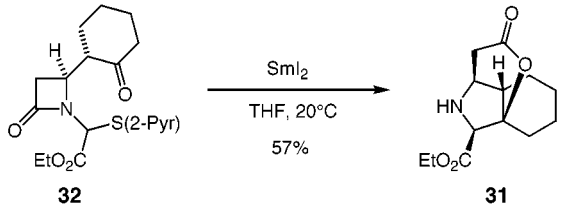
(9) Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 379.

(10) Atrill, R. P.; Barrett, A. G. M.; Quayle, P.; van der Westhuizen, J.; Betts, M. J. *J. Org. Chem.* **1984**, *49*, 1679.

Scheme 4



Scheme 5



fectively achieved with ethyl glyoxylate, and the secondary alcohol obtained was subsequently benzoylated with benzoyl chloride, affording **21**. Separation of the two C1′-diastereomers by column chromatography proved feasible at this stage, the structural assignments of which were later determined from the products obtained in the reductive samariation studies.

The choice of the benzoyloxy substituent was made on the basis of our previous observations that a benzoyloxy-derivatized glycine unit in a dipeptide undergoes fast reductive samariation and coupling with cyclohexanone. Although the yield of this intermolecular condensation was not optimal, the simplicity of the starting compound and its synthesis, in addition to our expectations for a more effective C−C-bond-forming reaction in the intramolecular version, motivated our choice for this precursor.[11]

Addition of the C1′-isomer **21a** (Scheme 4), possessing the pertinent stereochemistry for the sanfetrinem ring structure, to approximately 2.5 equiv of SmI_2 in THF led to its immediate consumption and the formation of two components by TLC analysis. The less polar component proved crystalline (mp 85−87 °C), and single-crystal X-ray analysis (see the Supporting Information) unambiguously confirmed its structure as the fused tricyclic β-lactam **29** obtained as a sole isomer in 55% yield. On the other hand, the more polar component, being an isomer to **29** according to electrospray MS, clearly lacked the β-lactam ring as revealed by the upfield shift of the C4 proton in the ^{1}H NMR spectrum at approximately 4.1 ppm in the β-lactam to 3.54 ppm. Instead, this compound was identified as the proline derivative **30** obtained in 28% yield, whereby the expected intramolecular cyclization was succeeded by an N to O acyl migration involving opening of the β-lactam ring. Clearly, this migration is only possible if C1 in **30** possesses the opposite stereochemistry of C3 in **29**. Conversely, the assignment at C11 was only tentatively designated as shown in Scheme 4 in agreement with structural assignments made for similar compounds (see the discussion below).

The combined yields of **29** and **30** therefore implied that cyclization was indeed quite effective, though leading to two diastereomers compared to only one observed by Alcaide in a similar lithium hexamethyldisilazide-promoted cyclization of **1** (Scheme 1).[7] The SmI_2-induced reaction nevertheless proved quite sensitive to the conditions used as reverse addition of SmI_2 to the benzoate led to only to the debenzoylated product without cyclization, while attempted cyclization at lower temperatures afforded reduced yields of **29** and **30**.

More surprising was the observation that the diastereomer **21b** when treated with SmI_2 led only to the crystalline proline derivative as a single diastereomer, **31**, in a 56% yield, mp 70−72 °C (Table 1, entry 1). Confirmation of the relative stereochemistry was provided by the single-crystal X-ray structure of **31**. Again, lowering the temperature only led to reduced cyclization yields (entry 2). None of the β-lactam could be detected in these cases. In our previous work on peptide alkylations, we noted that the glycine units containing a thiopyridine group led to the best alkylation results.[2,12] Repetition of the above reductive cyclization was therefore attempted with the corresponding thiopyridine derivative **32** (Scheme 5), prepared from azetidinone **13** by successive condensation with ethyl glyoxylate and treatment with first thionyl chloride and then 2-mercaptopyridine in the presence of Hünig's base. However, subjection of compound **32** to cyclization conditions identical to those which **21b** was subjected to did not lead to a notable change in the yield of the proline compound **31**.

The modest yield obtained for the generation of the proline **31** was somewhat of a concern considering that TLC analysis of the worked-up reaction mixtures only revealed one migrating component. We suspected that the low yield could be the result of the formation of the strongly basic amide derivative after cyclization and acyl migration, with concomitant polymerization via intermolecular amide formation with the cyclic esters. Hence, it was pleasing to observe that the addition of 1 equiv of *tert*-butyl alcohol to the benzoate prior to its subjection to SmI_2 significantly increased the cyclization yield, now providing **31** in 74% yield (entry 3). On the other hand, substituting *tert*-butyl alcohol with methanol led to significant yields of the noncyclized product resulting from simple reductive debenzoylation, which may be explained by methanol's lower pK_a value compared to that of *tert*-butyl alcohol.

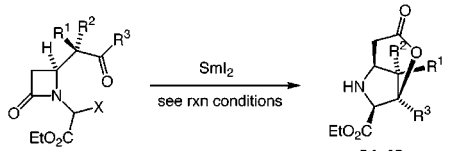
The formation of the tricyclic proline derivatives proved to be general, with other ring-containing β-lactam substrates, **22**,[13] **23a,b**, and **24b** (Table 1, entries 4−7), easily prepared as above (Scheme 3 and Figure 1). All cycliza-

(11) For other examples of SmI_2-promoted reduction of benzoates to generate samarium(III) enolates which though require the presence of HMPA for effective reduction, see: (a) Enholm, E. J.; Jiang, S. *Heterocycles* **1992**, *34*, 2247. (b) Enholm, E. J.; Jiang, S. *Tetrahedron Lett.* **1992**, *33*, 6069. (c) Enholm, E. J.; Jiang, S.; Abboud, K. *J. Org. Chem.* **1993**, *58*, 4061.

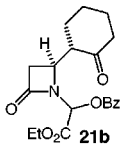
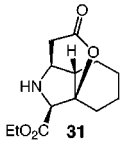
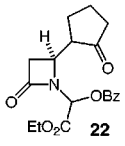
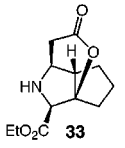
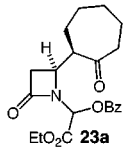
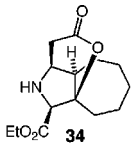
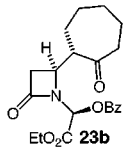
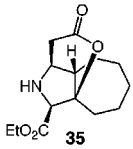
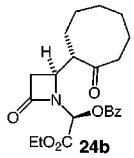
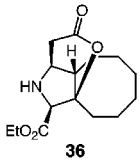
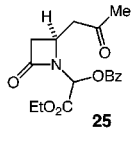
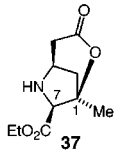
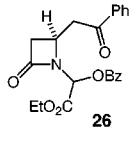
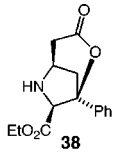
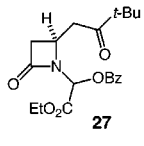
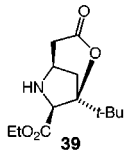
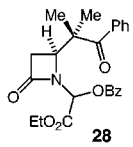
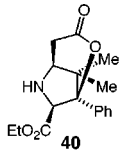
(12) For examples on the use of the pyridyl sulfide and sulfone groups in reductive samariation reactions, see: Skrydstrup, T.; Beau, J.-M. In *Advances in Free Radical Chemistry*; Zard, S. Z., Ed.; JAI Press: Stamford, CT, 1999; Vol. 2, p 89. See also: Mikkelsen, L. M.; Krintel, S. L.; Jiménez-Barbero, J.; Skrydstrup, T. *Chem. Commun.* **2000**, 2319 and references therein.

(13) With this compound a 14% isolated yield of tricyclic [4.5.5] β-lactam was also obtained (corrected yield 38%). The stereochemistry is assumed to be identical to that of compound **29**.

Table 1. SmI_2-Mediated Cyclization of the β-Lactams 4−12



21b-28 31-40

Entry	β-Lactam	Rxn Conditions[a]	Functionalized Proline	Yield[b]
1		THF, 20°C		56%
2		THF, 0°C		38%
3		THF, 20°C *t*-BuOH (1 equiv.)		74%
	21b		**31**	
4		THF, 20°C *t*-BuOH (1 equiv.)		62%[c]
	22		**33**	
5		THF, 20°C *t*-BuOH (1 equiv.)		86%
	23a		**34**	
6		THF, 20°C *t*-BuOH (1 equiv.)		85%
	23b		**35**	
7		THF, 20°C *t*-BuOH (1 equiv.)		85%
	24b		**36**	
8		THF, 20°C *t*-BuOH (1 equiv.)		58%
	25		**37**	
9		THF, 20°C *t*-BuOH (1 equiv.)		66%
	26		**38**	
10		THF, 20°C *t*-BuOH (1 equiv.)		42%
	27		**39**	
11		THF, 20°C *t*-BuOH (1 equiv.)		77%
	28		**40**	

[a] For the exact reaction conditions see the Experimental Procedure. [b] Isolated yields after chromatography on silica gel. [c] The two diastereomers at C1′ of **22** could not be separated by chromatography. Besides the proline compound, the [4.5.5] tricyclic fused β-lactam was also isolated in 38% yield. The yields are therefore corrected on the basis of the diastereomeric ratio of the starting material.

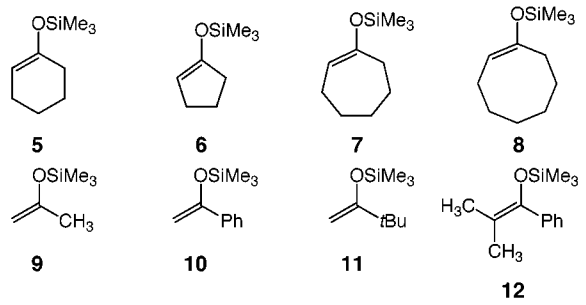


Figure 1.

tion reactions were performed at room temperature and were basically complete after the addition of the benzoates to the ethereal solution of SmI_2. Yields of the functionalized prolines **33**−**36** ranged from 62% for the cyclopentanone derivative to ≥85% for the corresponding seven- and eight-membered cyclic compounds. It is noteworthy that in the case of the cycloheptane derivatives **23a** and **23b** (entries 5 and 6), both C1′-diastereomers result in the formation of the proline derivatives **34** and **35**, respectively This divergence compared with the corresponding six-membered ring compounds **21a** and **21b** may be the result of the greater flexibility of the seven-membered ring, allowing both compounds **23a** and **23b** to pass through similar transition states in the cyclization step.

With the acyclic ketones **25**−**28**, the bicyclic proline compounds **37**−**40** could be isolated in 42−77% yield (Table 1, entries 8−11). The influence of the proton source was more prominent in these latter cases, as for example with **27**, where no cyclization product could be isolated in the absence of *t*-BuOH. Proof for the correct assignment of the relative configuration of these derivatized proline compounds from the acyclic ketones as compared to the cyclic ketones was partially fulfilled by performing nuclear Overhauser experiments on compound **37**. In this case, a positive NOE was observed at the C7-proton upon irradiation of the C1-methyl group, corresponding to the relative configuration as shown for **31**.

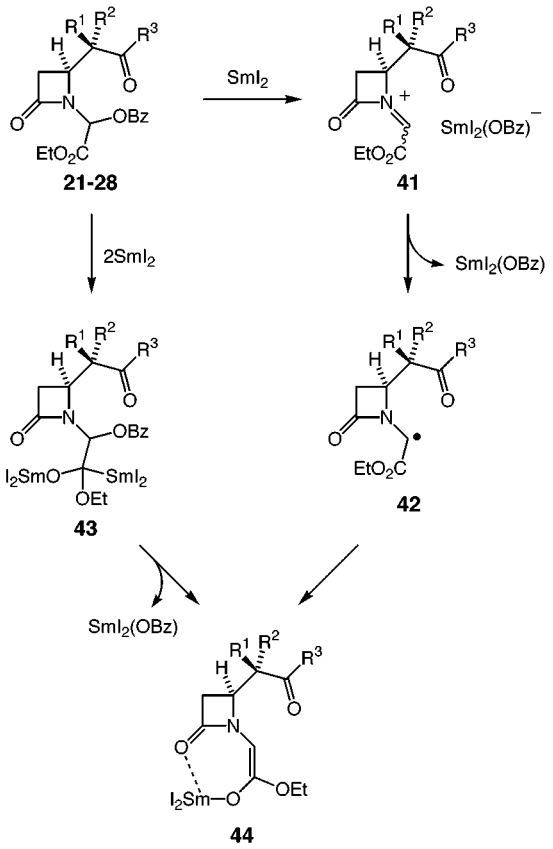
The diastereoselectivities observed in these C−C-bond-forming reactions deviate from previous reactions involving cyclizations with the corresponding lithium enolates obtained by deprotonation.[7,8] Schemes 6 and 7 provide a rational explanation for these observations. Reductive samariation of the benzoyloxy-containing glycine results in the formation of a samarium(III) enolate, **44**. Two pathways may lead to this enolate (Scheme 6), as previously suggested in our work on the reductive coupling of derivatized glycine units in small peptides.[2] Complexation of the Lewis acidic divalent samarium diiodide to the benzoate group could lead to the rapid formation of an iminium ion intermediate, **41**,[14] the high reactivity of which results in an immediate reduction step to the stabile glycyl radical **42**.[15,16] Further reduction with

(14) For examples of reductive samariations involving an intermediate iminium ion, see: Aurrecoechea, J. M.; Fernández, A.; Gorgojo, J. M.; Saornil, C. *Tetrahedron* **1999**, *55*, 7345 and references therein.

(15) (a) Jonsson, M.; Wayner, D. D. M.; Armstrong, D. A.; Yu, D.; Rauk, A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1967. (b) Bordwell, F. G.; Gallagher, T.; Zhang, X. *J. Am. Chem. Soc.* **1991**, *113*, 3495. (c) Clark, K. B.; Wayner, D. D. M.; Demirjdji, S. H.; Koch, T. H. *J. Am. Chem. Soc.* **1993**, *115*, 2447. (d) Rauk, A.; Yu, D.; Taylor, J.; Shustov, G. V.; Block, D. A.; Armstrong, D. A. *Biochemistry* **1999**, *38*, 9089.

(16) For a recent review discussing the reactivity of glycyl radicals, see: Easton, C. J. *Chem. Rev.* **1997**, *97*, 53.

Scheme 6



a second equivalent of SmI_2 then generates the enolate **44**, the geometry of which we tentatively assign the *Z*-stereochemistry. The high oxophilicity of the Sm(III) ion, including its known propensity to complex strongly with amides, suggests the formation of a cyclic enolate structure with β-lactam amide functionality.[17] Another possibility for the transformation of the benzoates **21**−**28** to the enolate **44** involves the known capacity of SmI_2 to reduce α-heterosubstituted amides, resulting in the formation of the dianion **43** followed by a subsequent β-elimination step.[18]

Three possible pathways resulting in ring closure may then be followed from the enolate **44** involving the three cyclic transition structures (TSs) **45**−**47**, as illustrated in Scheme 7. For the β-lactam **21a**, the SmI_2-promoted cyclization via the chair TS **45** is preferred as with the corresponding lithium enolates.[7,8] In the tricyclic product **29** obtained the C3−OH is positioned *trans* to the β-lactam amide group, and hence acyl migration cannot occur. It should be noted that in this transition structure the metal ion must dissociate from the β-lactam amide group prior to complexation with the ketone carbonyl group. On the other hand, to explain the formation of products **30**, **31**, and **33**−**40**, the other sterically more demanding chair TS **46** may be invoked, whereby the resulting C3-alcohol and β-lactam amide of the cyclized product are placed on the same side. Thereafter, the Lewis acidic samarium(III) metal ion promotes the subsequent *trans*-acylation step. However, in this TS there is no likely justification for the initial cyclization to pass through this higher energy TS compared with **45**.

A more plausible explanation for the formation of the proline derivatives involves the sterically less favored boat conformation **47**, whereby the metal counterion is continuously coordinated to the amide group throughout the cyclization and acyl migration step. We can only speculate that with the larger lanthanide metal ion compared to lithium favorable coordination to both the β-lactam and ketone carbonyl groups becomes possible, overriding the sterical interactions that may arise from this conformation. This additional coordination also provides the driving force for the subsequent *trans*-acylation step.[19]

In conclusion, a novel and simple route to highly functionalized proline derivatives employing a SmI_2-promoted cyclization has been presented. The interesting feature of these reactions lies in the ability for simple benzoyloxy-containing glycine derivatives to undergo facile reductive samariation with concomitant C−C bond formation under room-temperature conditions.

As proline plays an important role in protein folding and signal transduction, as well as being a constituent of biologically active and pharmaceutically interesting peptides, considerable interest has been devoted to the preparation of proline surrogates with the intention to study their conformational effects on peptide/protein structure.[20,21] On the synthetic side, proline has been found to be a useful and inexpensive catalyst for promoting both asymmetric aldol and aldol-type reactions.[22,23] Hence, further work is now under way to develop procedures for preparing the cyclic precursors of enantiomeric purity for the SmI_2-induced cyclizations, such that the synthesized proline derivatives may be examined for their ability to influence peptide conformations, as well as their ability to promote enantioselective C−C-bond-forming reactions.

(17) (a) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (b) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265. (c) Urban, D.; Skrydstrup, T.; Beau, J.-M. *J. Org. Chem.* **1998**, *63*, 2507. (d) Andersen, L.; Mikkelsen, L. M.; Beau, J.-M.; Skrydstrup, T. *Synlett* **1998**, 1393. (e) Urban, D.; Skrydstrup, T.; Beau, J.-M. *Chem. Commun.* **1998**, 955.

(18) (a) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887. (b) Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2773. (c) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702.

(19) One reviewer has pointed out the possibility that the tricyclic β-lactam products obtained for compounds **21a** and **22** could be the result of kinetic rather than thermodynamic control. In support of this hypothesis, we observed the formation of the corresponding bicyclic β-lactam product in 19% yield along with the proline derivative **39** (17%) when the starting benzoate **27** was treated with SmI_2 at 0 °C. At 20°, only the proline derivative **39** was observed (Table 1, entry 10).

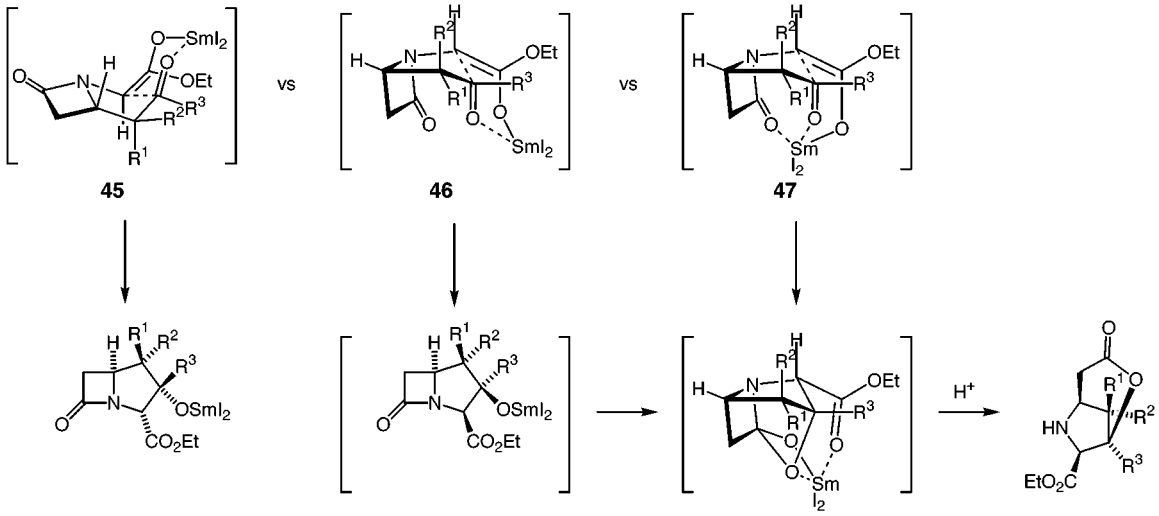
(20) (a) Fisk, J. D.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 5443. (b) Miao, S.; Tam, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4254. (c) An, S. S.A.; Lester, C. C.; Peng, J.-L.; Li, Y.-J.; Rotharf, D. M.; Welker, E.; Thannhauser, T. W.; Zhang, L. S.; Tam, J. P.; Scheraga, H. A. *J. Am. Chem. Soc.* **1999**, *121*, 11558 and references therein.

(21) For some recent references on proline surrogates, see: (a) Keller, M.; Sager, C.; Dumy, P.; Schutkowski, M.; Fischer, G. S.; Mutter, M. *J. Am. Chem. Soc.* **1998**, *120*, 2714. (b) Kern, D.; Schutkowski, M.; Drakenberg, T. *J. Am. Chem. Soc.* **1997**, *119*, 8403. (c) Mamai, A.; Zhang, R.; Natarajan, A.; Madalengoitia, J. S. *J. Org. Chem.* **2001**, *66*, 455. (d) Konopelski, J. P.; Wei, Y.; Olmstead, M. M. *J. Org. Chem.* **1999**, *64*, 5148. (e) Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759. (e) Han, W.; Pelletier, J. C.; Mersinger, L. J.; Kettner, C. A.; Hodge, C. N. *Org. Lett.* **1999**, *1*, 1875. (g) Curran, T. P.; Marcaurelle, L. A.; O'Sullivan, K. M. *Org. Lett.* **1999**, *1*, 1225. (h) Vivet, B.; Cavelier, F.; Martinez, J. *Eur. J. Org. Chem.* **2000**, 807 and references therein.

(22) For some recent examples, see: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (c) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386 and references therein.

(23) For a review, see: Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529.

Scheme 7



Experimental Procedure

General Considerations. Unless otherwise stated, all reactions were carried out under argon. THF was dried and freshly distilled over sodium/benzophenone. Dichloromethane and acetonitrile were freshly distilled over P_2O_5 and CaH_2, respectively. Reactions were monitored by thin-layer chromatography (TLC) analysis. Melting points are uncorrected. All compounds are racemic. The following compounds were prepared according to literature procedures: **4**,[10] **5**−**12**,[24] and **18**.[10] Samarium diiodide was prepared according to a literature procedure.[25]

3-Hydroxy-2-(methoxycarbonyl)-1-azatricyclo[4.5.6]-undecane (29) and 9-Oxo-10-oxa-12-azatricyclo[5.3.2.0^{1,6}]-dodecane-11-carboxylic Acid Ethyl Ester (30). To a 0.1 M solution of SmI_2 in THF (3.2 mL, 0.32 mmol) was added dropwise at 20 °C a solution of the benzoates **21a** (50 mg, 0.134 mmol) in THF (1.5 mL) over a period of 2 min. The reaction mixture was stirred for 15 min and then quenched with saturated aqueous NH_4Cl, after which the THF was removed in vacuo. The residue obtained was mixed with CH_2Cl_2 and then filtered through cotton wool. The aqueous phase was extracted several times with EtOAc and CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash chromatography (EtOAc and then MeOH/CH_2Cl_2, 1:20). This afforded 18.6 mg (55%) of **29** as colorless needles, followed by 9.6 mg (28%) of **30** as a light yellow syrup. Data for **29**: mp 85−87 °C (pentanes/Et_2O); TLC R_f 0.66 (acetone/pentanes, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78−0.89 (m, 1H), 1.25−1.33 (m, 2H), 1.31 (t, 3H, J = 7.0 Hz), 1.55−1.63 (m, 1H), 1.68−1.73 (m, 1H), 1.80−1.83 (m, 2H), 2.10 (dt, 1H, J = 5.2, 13.2 Hz), 2.36−2.39 (m, 1H), 2.60 (br s, 1H), 2.71 (dd, 1H, J = 2.2, 15.8 Hz), 3.11 (dd, 1H, J = 5.4, 15.8 Hz), 4.22−4.26 (m, 1H), 4.24 (dq, 1H, J = 7.0, 11.0 Hz), 4.26 (dq, 1H, J = 7.0, 11.0 Hz), 4.29 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 23.3, 24.0, 24.6, 34.2, 36.3, 48.1, 55.0, 62.0, 62.5, 88.1, 169.8, 175.9; MS (electrospray) m/z 276 (M + Na); HRMS m/e calcd for $C_{13}H_{19}NNaO_4$ (M + Na) 276.1212, found 276.1195.

Data for **30**: TLC R_f 0.36 (acetone/pentanes, 1:4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26−1.38 (m, 1H), 1.31 (t, 3H, J = 7.2 Hz), 1.52−1.90 (m, 6H), 2.05 (dt, 1H, J = 4.8, 12.4 Hz), 2.26 (br s, 1H), 2.28−2.37 (m, 1H), 2.62 (dd, 1H, J = 2.6, 19.0 Hz), 3.54 (dt, 1H, J = 2.6, 5.2 Hz), 3.79 (s, 1H), 4.23 (dq, 1H, J = 7.2, 11.0 Hz), 4.30 (dq, 1H, J = 7.2, 11.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 20.7, 21.9, 24.4, 32.1, 37.8, 45.1, 53.6, 62.2, 69.0, 87.3, 169.7, 212.4; MS (electrospray) m/z 276 (M + Na); HRMS m/e calcd for $C_{13}H_{19}NNaO_4$ (M + Na) 276.1212, found 276.1214.

9-Oxo-10-oxa-12-azatricyclo[5.3.2.0^{1,6}]dodecane-11-carboxylic Acid Ethyl Ester (31). General Procedure for the Cyclization Reactions with SmI_2. To a 0.1 M solution of SmI_2 in THF (6.3 mL, 0.32 mmol) was added dropwise at 20 °C a solution of the benzoates **21b** (93.4 mg, 0.25 mmol) and *t*-BuOH (24 μL, 0.25 mmol) in THF (2.5 mL) over a period of 2 min. The reaction mixture was quenched after 1 min with saturated aqueous NH_4Cl. Workup was performed as above. Flash chromatography (EtOAc/CH_2Cl_2, 1:4) afforded 46.7 mg (74%) of **31** as a white solid: mp 70−72 °C (CH_2Cl_2/pentanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (t, 3H, J = 7.2 Hz), 1.23−1.44 (m, 3H), 1.60 (dt, 1H, J = 4.4, 13.2 Hz), 1.65−1.77 (m, 3H), 1.96 (dd, 1H, J = 5.2, 11.6 Hz), 2.18−2.22 (m, 1H), 2.65 (dd, 1H, J = 3.2, 18.4 Hz), 2.67 (dd, 1H, J = 3.2, 18.4 Hz), 3.15−3.17 (m, 1H), 4.08 (dq, 1H, J = 7.2, 10.6 Hz), 4.14 (dq, 1H, J = 7.2, 10.6 Hz). 4.09 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 22.7, 24.2, 26.7, 29.8, 42.8, 49.0, 56.0, 62.2, 64.0, 89.3, 169.4, 171.7; MS (electrospray) m/z 276 (M + Na); HRMS m/e calcd for $C_{13}H_{19}NNaO_4$ (M + Na) 276.1212, found 276.1212.

8-Oxo-9-oxa-11-azatricyclo[4.3.2.0^{1,5}]undecane-10-carboxylic Acid Ethyl Ester (33). The proline **33** was prepared from the benzoates **22** according to the general procedure outlined for **31**, with the following quantities: 65.4 mg (0.182 mmol) of benzoates **22** and 17 μL (0.182 mmol) of *t*-BuOH in 1.8 mL of THF and SmI_2 in 5.0 mL (0.50 mmol) of THF. Flash chromatography (EtOAc/CH_2Cl_2 and then acetone/CH_2Cl_2, gradient elution) afforded first 3-hydroxy-2-(methoxycarbonyl)-1-azatricyclo[4.5.5]decane (5.9 mg, 14%) and then reduced starting material (7.1 mg, 16%) followed by **33** (16.9 mg, 39%) as clear oils. Data for the tricyclic [4.5.5] β-lactam: TLC R_f 0.41 (EtOAc/CH_2Cl_2, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 1.41−1.52 (m, 1H), 1.80−2.19 (m, 5H), 2.56 (br s, 1H), 2.56−2.68 (m, 1H), 2.76 (dd, 1H, J = 2.2, 16.0 Hz), 3.19 (dd, 1H, J = 5.4, 16.0 Hz), 4.18 (ddd, 1H, J = 2.2, 5.4, 6.8 Hz), 4.25 (q, 2H, J = 7.2 Hz), 4.32 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 24.6, 25.8, 39.3, 40.1, 53.0, 53.8, 61.8, 67.3, 98.9, 169.7, 174.9; MS (electrospray) m/z 262 (M + Na); HRMS m/e calcd for $C_{12}H_{17}NNaO_4$ (M + Na) 262.1055, found 262.1050.

Data for **33**: TLC R_f 0.13 (acetone/CH_2Cl_2, 1:10); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.62−1.82 (m, 2H), 1.89−2.15 (m, 4H), 2.30−2.46 (m, 2H), 2.72 (dd, 1H, J = 3.2, 18.6 Hz), 2.81 (dd, 1H, J = 2.2, 18.6 Hz), 3.59 (m, 1H), 3.92 (s, 1H), 4.24 (dq, 1H, J = 7.2, 10.6 Hz), 4.30 (dq, 1H, J = 7.2, 10.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 21.7, 23.9, 30.8, 42.3, 53.1, 54.2, 62.2, 67.1, 95.5, 169.9, 171.9; MS (electrospray) m/z 262 (M + Na); HRMS m/e calcd for $C_{12}H_{17}NNaO_4$ (M + Na) 262.1055, found 262.1054.

(24) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.

(25) Namy, J. L.; Girard, P.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

10-Oxo-11-oxa-13-azatricyclo[6.3.2.0^{1,7}]tridecane-12-carboxylic Acid Ethyl Ester (34). The proline **34** was prepared from the benzoates **23a** according to the general procedure outlined for **31**, with the following quantities: 96.9 mg (0.250 mmol) of benzoates **23a** and 24 μL (0.250 mmol) of *t*-BuOH in 2.5 mL of THF and SmI_2 in 6.3 mL (0.63 mmol) of THF. Flash chromatography (EtOAc/CH_2Cl_2, gradient elution) afforded **34** (57.8 mg, 86%) as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.51−1.90 (m, 9H), 2.27−2.40 (m, 3H), 2.61 (dd, 1H, J = 2.2, 19.0 Hz), 2.70 (dd, 1H, J = 2.8, 19.0 Hz), 3.45−3.50 (m, 1H), 3.86 (s, 1H), 4.22 (dq, 1H, J = 7.2, 10.6 Hz), 4.30 (dq, 1H, J = 7.2, 10.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 21.0, 21.9, 25.4, 27.3, 36.2, 37.5, 46.8, 55.8, 62.1, 70.7, 90.2, 170.0, 171.4; MS (electrospray) *m*/*z* 290 (M + Na); HRMS *m*/*e* calcd for $C_{14}H_{21}NNaO_4$ (M + Na) 290.1368, found 290.1367.

10-Oxo-11-oxa-13-azatricyclo[6.3.2.0^{1,7}]tridecane-12-carboxylic Acid Ethyl Ester (35). The proline **35** was prepared from the benzoate **23b** according to the general procedure outlined for **31**, with the following quantities: 96.9 mg (0.250 mmol) of benzoate **23b** and 24 μL (0.250 mmol) of *t*-BuOH in 2.5 mL of THF and SmI_2 in 6.3 mL (0.63 mmol) of THF. Flash chromatography (EtOAc/CH_2Cl_2, gradient elution) afforded **35** (56.9 mg, 85%) as a crystalline solid: mp 80−82 °C (CH_2Cl_2/pentanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.40−2.14 (m, 10H), 2.34 (dd, 1H, J = 7.7, 15.7 Hz), 2.39 (br s, 1H), 2.76 (dd, 1H, J = 2.2, 18.6 Hz), 2.79 (dd, 1H, J = 3.0, 18.6 Hz), 3.38−3.40 (m, 1H), 4.01 (s, 1H), 4.22 (dq, 1H, J = 7.2, 10.6 Hz), 4.31 (dq, 1H, J = 7.2, 10.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 23.2, 29.5, 29.6, 30.9, 36.5, 43.1, 53.2, 58.4, 62.1, 69.8, 93.5, 170.1, 171.8; MS (electrospray) *m*/*z* 290 (M + Na); HRMS *m*/*e* calcd for $C_{14}H_{21}NNaO_4$ (M + Na) 290.1368, found 290.1367.

11-Oxo-12-oxa-14-azatricyclo[7.3.2.0^{1,8}]tetradecane-13-carboxylic Acid Ethyl Ester (36). The proline **36** was prepared from the benzoate **24b** according to the general procedure outlined for **31**, with the following quantities: 100 mg (0.250 mmol) of benzoate **24b** and 24 μL (0.250 mmol)of *t*-BuOH in 2.5 mL of THF and SmI_2 in 6.3 mL (0.63 mmol) of THF. Flash chromatography (EtOAc/CH_2Cl_2, gradient elution) afforded **36** (60.0 mg, 85%) as a crystalline solid: mp 110−112 °C (CH_2Cl_2/pentanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.1 Hz), 1.49−2.01 (m, 10H), 2.21−2.35 (m, 3H), 2.78 (dd, 1H, J = 2.4, 10.2 Hz), 2.79 (dd, 1H, J = 3.0, 10.2 Hz), 3.33−3.35 (m, 1H), 3.88 (s, 1H), 4.23 (dq, 1H, J = 7.1, 9.2 Hz), 4.29 (dq, 1H, J = 7.1, 9.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 21.9, 24.7, 26.1, 28.6, 29.5, 30.2, 42.2, 49.2, 59.7, 62.2, 68.7, 92.3, 170.0, 171.8; MS (electrospray) *m*/*z* 304 (M + Na); HRMS *m*/*e* calcd for $C_{15}H_{23}NNaO_4$ (M + Na) 304.1525, found 304.1525.

1-Methyl-3-oxo-2-oxa-6-azabicyclo[3.2.1]octane-7-carboxylic Acid Ethyl Ester (37). The proline **37** was prepared from the benzoates **25** according to the general procedure outlined for **31**, with the following quantities: 80 mg (0.240 mmol) of benzoates **25** and 23 μL (0.240 mmol) of *t*-BuOH in 2.4 mL of THF and SmI_2 in 6.0 mL (0.60 mmol) of THF. Flash chromatography (acetone/CH_2Cl_2, gradient elution) afforded **37** (29.9 mg, 58%) as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7.0 Hz), 1.69 (s, 3H), 1.96 (d, 1H, J = 12.8 Hz), 2.23 (dd, 1H, J = 1.4, 12.8 Hz), 2.50 (br s, 1H), 2.73 (dd, 1H, J = 3.0, 18.6 Hz), 2.76 (dd, 1H, J = 2.2, 18.6 Hz), 3.72−3.77 (m, 1H), 3.86 (s, 1H), 4.25 (dq, 1H, J = 7.0, 10.6 Hz), 4.33 (dq, 1H, J = 7.0, 10.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 21.7, 41.1, 41.4, 51.5, 62.4, 69.1, 87.2, 169.1, 171.0; MS (electrospray) *m*/*z* 236 (M + Na); HRMS *m*/*e* calcd for $C_{10}H_{15}NNaO_4$ (M + Na) 236.0899, found 236.0901.

1-Phenyl-3-oxo-2-oxa-6-azabicyclo[3.2.1]octane-7-carboxylic Acid Ethyl Ester (38). The proline **38** was prepared from the benzoates **26** according to the general procedure outlined for **31**, with the following quantities: 89 mg (0.225 mmol) of benzoates **26** and 22 μL (0.225 mmol) of *t*-BuOH in 2.3 mL of THF and SmI_2 in 5.6 mL (0.56 mmol) of THF. Flash chromatography (acetone/CH_2Cl_2, gradient elution) afforded **38** (40.7 mg, 66%) as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, 3H, J = 7.0 Hz), 2.14 (d, 1H, J = 12.8 Hz), 2.49 (br s, 1H), 2.73 (ddd, 1H, J = 1.6, 5.6, 12.8 Hz), 2.84−2.87 (m, 2H), 3.89 (dt, 1H, J = 2.6, 5.6 Hz), 4.02 (dq, 1H, J = 7.0, 11.0 Hz), 4.23 (dq, 1H, J = 7.0, 11.0 Hz), 4.27 (s, 1H), 7.30−7.46 (m, 3H), 7.52−7.58 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 41.3, 43.1, 51.9, 62.1, 71.4, 89.5, 125.0 (2C), 128.2, 128.5 (2C), 137.3, 168.5, 170.9; MS (electrospray) *m*/*z* 298 (M + Na); HRMS *m*/*e* calcd for $C_{15}H_{17}NNaO_4$ (M + Na) 298.1055, found 298.1061.

1-*tert*-Butyl-3-oxo-2-oxa-6-azabicyclo[3.2.1]octane-7-carboxylic Acid Ethyl Ester (39). The proline **39** was prepared from the benzoates **27** according to the general procedure outlined for **31**, with the following quantities: 93.9 mg (0.250 mmol) of benzoates **27** and 24 μL (0.250 mmol) of *t*-BuOH in 2.5 mL of THF and SmI_2 in 6.3 mL (0.63 mmol) of THF. Flash chromatography (acetone/CH_2Cl_2, gradient elution) afforded first reduced starting material (27.5 mg, 43%) followed by **39** (26.6 mg, 42%) as oils.

Data for the reduced starting material: TLC R_f 0.42 (acetone/CH_2Cl_2, 1:15); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.27 (t, 3H, J = 7.2 Hz), 2.65 (dd, 1H, J = 2.2, 14.6 Hz), 2.94 (dd, 1H, J = 2.6, 18.4 Hz), 3.03 (dd, J = 7.8, 18.4 Hz), 3.20 (dd, 1H, J = 5.2, 14.6 Hz), 4.01 (s, 2H), 4.16 (q, 2H, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 26.5, 41.4, 42.8, 43.1, 44.0, 48.7, 61.3, 167.4, 168.9, 214.8.

Data for **39**: TLC R_f 0.20 (acetone/CH_2Cl_2, 1:4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.29 (t, 3H, J = 7.4 Hz), 1.86 (d, 1H, J = 12.4 Hz), 2.28 (ddd, 1H, J = 2.0, 5.6, 12.6 Hz), 2.70 (dd, 1H, J = 3.6, 18.6 Hz), 2.81−2.90 (m, 1H), 3.68−3.73 (m, 1H), 4.16 (s, 1H), 4.23 (q, 2H, J = 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 26.2, 35.9, 36.9, 41.1, 51.1, 62.2, 64.7, 95.2, 170.1, 173.2; MS (electrospray) *m*/*z* 278 (M + Na); HRMS *m*/*e* calcd for $C_{13}H_{21}NNaO_4$ (M + Na) 278.1368, found 278.1368.

8,8-Dimethyl-1-phenyl-3-oxo-2-oxa-6-azabicyclo[3.2.1]-octane-7-carboxylic Acid Ethyl Ester (40). The proline **40** was prepared from the benzoates **28** according to the general procedure outlined for **31**, with the following quantities: 84.7 mg (0.200 mmol) of benzoates **28** and 19 μL (0.200 mmol) of *t*-BuOH in 2.0 mL of THF and SmI_2 in 5.0 mL (0.50 mmol) of THF. Flash chromatography (acetone/CH_2Cl_2, gradient elution) afforded **40** (46.5 mg, 77%) as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.95 (t, 3H, J = 7.2 Hz), 1.16 (s, 3H), 2.37 (br s, 1H), 2.82 (dd, 1H, J = 2.2, 19.0 Hz), 2.93 (dd, 1H, J = 3.0, 19.0 Hz), 3.35−3.38 (m, 1H), 3.97 (dq, 1H, J = 7.2, 10.6 Hz), 4.13 (dq, 1H, J = 7.2, 10.6 Hz), 4.79 (s, 1H), 7.34−7.46 (m, 3H), 7.47−7.53 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 16.9, 24.0, 40.0, 46.3, 61.2, 61.9, 66.9, 94.3, 127.0, 127.7, 128.1, 133.8, 169.6, 171.6; MS (electrospray) *m*/*z* 326 (M + Na); HRMS *m*/*e* calcd for $C_{17}H_{21}NNaO_4$ (M + Na) 326.1368, found 326.1367.

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Supporting Information Available: Single-crystal X-ray structures and crystallographic data for the tricyclic β-lactam **29**, the proline derivative **31**, the intermediate in the synthesis of **23b**, and the β-lactam **24b**, experimental procedures and characterization of compounds **13**−**17**, **19**−**23**, **24b**, and **25**−**28**, and ^{1}H and ^{13}C NMR spectra for compounds **31** and **33**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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