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Conformationally Constrained β-Amino Acid Derivatives by Intramolecular [2 + 2]-Photocycloaddition of a Tetronic Acid Amide and Subsequent Lactone Ring Opening

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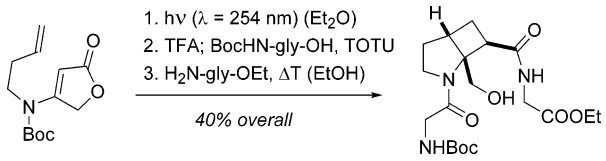

The *N*-Boc-protected *N*-3-alkenyltetronic acid amides **9** and **12** were prepared from tetronic acid bromide (**7**) and the corresponding amines **6** and **10** by nucleophilic substitution and subsequent acylation in 71% and 39% overall yield. They underwent an intramolecular [2 + 2]-photocycloaddition upon direct irradiation ($\lambda = 254$ nm) to yield diastereoselectively the strained lactones **15** (76%) and **16** (91%) with a 2-azabicyclo[3.2.0]heptane core. In attempts to defunctionalize the 1-hydroxymethyl substituent of the 2-azabicyclo[3.2.0]heptane skeleton, lactone **15** was converted into mesylate **18** (74% overall yield). Intermolecular substitution reactions on this mesylate, however, proceeded sluggishly or failed completely. Lactone **15** could be opened reductively (Dibal-H) or by substitution with benzylamine to the *N*-Boc-protected 2-azabicyclo[3.2.0]heptanes **21** (71%) and **22** (81%). Conformationally constrained β-amino acid derivatives were obtained by quantitative *N*-Boc deprotection of photocycloaddition product **15**, followed by *N*-functionalization and subsequent lactone ring opening. The *N*-functionalization was conducted by acylation (to **24**−**26**), alkylation (to **27**), tosylation (to **28**), and isocyanate addition (to **30**). The reactions proceeded in yields of 70−84%. Lactone ring opening reactions were conducted with amines to establish the suitability of this process for library synthesis. As an example, the tripeptide **38** was obtained from photocycloaddition product **15** in an overall yield of 51%.

Introduction

Conformationally constrained compounds adopt a lower number of conformations than their unconstrained analogues.[1] In these compounds, functional groups and other substituents are spatially arranged in a conformationally restricted environment. While there are acyclic compounds, which are restricted in the number of conformations they adopt,[2] it is mostly cyclic skeletons that are being used to position substitutents in a defined fashion. In this respect, cyclobutane β-amino acids represent an interesting class of conformationally restricted β-amino acid derivatives, which can for example mimic or induce reverse-turn motifs of peptides and proteins. Increasing interest in β-amino acids[3] has been stimulated by the seminal studies of Seebach et al.[4] and Gellman et al.[5] on the folding and biological activity of β-peptides.[6]

The synthesis of cyclobutane β-amino acids[7] relies to a large extent on the photochemical [2 + 2]-cycloaddition[8] of two alkenes. A few selected examples are depicted in Figure 1. The parent *cis*-2-amino-1-cyclobutanecarboxylic

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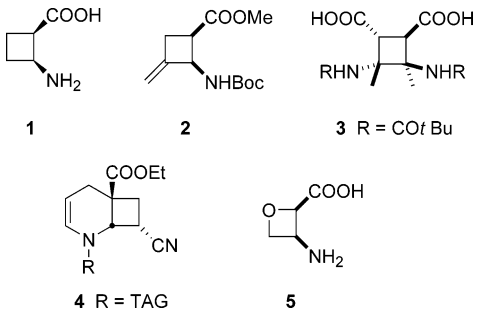


FIGURE 1. Molecular formula of previously reported, conformationally restrained β-amino acids **1**−**5**.

acid (**1**) was prepared photochemically from uracil and ethylene.[9] Enantiomerically pure product **1** was available upon using a chiral uracil derivative with phenylalaninol as source of chirality.[10] The [2 + 2]-photocycloaddition of allene to maleimide was the key step in the synthesis of the potentially antifungal β-amino acid **2**.[11] Steglich et al. employed the sensitized photodimerization of 2-*tert*-butyl-4-methyl-1,3-oxazin-6-one for the preparation of the interesting bis(acylamino)dicarboxylic acid **3**.[12,13] Bicyclic amino acid derivatives such as **4** [TAG = 1-(tetraacetyl-β-D-glucopyranosyl)] were obtained from the [2 + 2]-photocycloaddition of dihydropyridines with acrylonitrile.[14] The oxygen analogue of **1**, oxetin (**5**), is a natural product, which was prepared synthetically by a [2 + 2]-photocycloaddition (Paternò−Büchi reaction).[15]

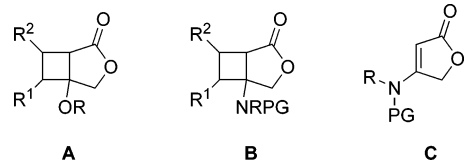
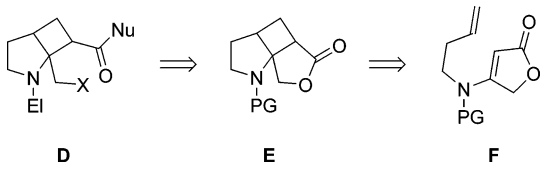


FIGURE 2. General structure of [2 + 2]-photocycloaddition products **A** and **B** derived from tetronates and tetronic acid amides (**C**).

SCHEME 1



Recent studies in our group have revealed that derivatives **A** of cyclobutane β-hydroxycarboxylic acid (Figure 2) can be nicely generated from tetronic acid esters by inter- or intramolecular [2 + 2]-photocycloaddition.[16] The reactions proceed best by direct irradiation of the corresponding tetronates at $\lambda = 254$ nm. A similar access to conformationally restricted β-amino acid derivatives **B** (PG = protecting group) appeared feasible upon irradiation of tetronic acid amides **C**.

We were specifically interested in the synthesis of β-proline derivatives such as **D** (Scheme 1) which occurred to us as potential pharmacophores.[17] It was speculated that decoration of the amino group with an electrophile (El) would be possible from intermediate **E**. In addition, we expected to be able to attach nucleophiles (Nu) to the lactone carbonyl group. By this method, a variety of compounds would be accessible from a single scaffold. It was open in the planning stage whether X would be left as an OH group or whether it was to be converted into a methyl (X = H) or alkyl group (X = R). Compounds of type **D** are characterized by their rigid 2-azabicyclo[3.2.0]heptane skeleton which allows positioning of the carbonyl group and the amino group in a given angle. Tetronic acid amides of general structure **F**

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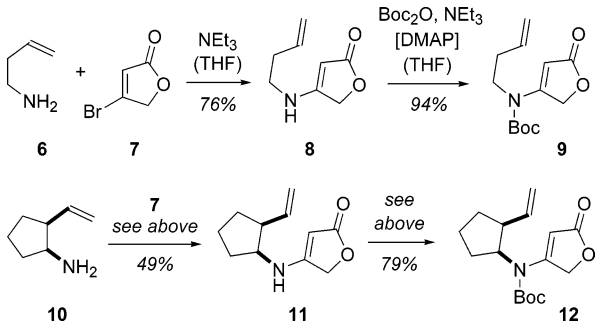
SCHEME 2



appeared to be suitable precursors for the intramolecular [2 + 2]-photocycloaddition.

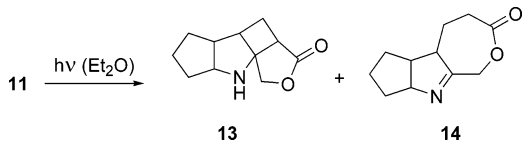
In this paper, we describe our synthetic results in this field. We report the first [2 + 2]-photocycloaddition reactions of tetronic acid amides proceeding in good yields and with high diastereoselectivity. Ring opening reactions of the photocycloaddition products were studied and the primary products were further converted into 2-azabicyclo[3.2.0]heptanes of general structure **D**.

Results and Discussion

Preparation of Starting Materials and [2 + 2]-Photocycloaddition Experiments. The unprotected amides **8** and **11** (Scheme 2) were prepared by a nucleophilic substitution reaction at the vinylogous acid bromide **7,** which in turn was readily obtained from tetronic acid.[18,19] The homoallylic amines **6**[20] and **10**[21] were employed as nitrogen nucleophiles. Alternative attempts to obtain the amides by aminodemethoxylation[22] from the corresponding methyl tetronate[23] or aminodehydroxylation from the parent tetronic acid[24] were less successful. The former reactions failed completely, while the latter reactions provided the desired products in low yields (**8**, 24%; **11**, 26%).

The choice of protecting group at the nitrogen atom was guided by previous experience in our group. In studies directed toward the photochemical synthesis of 3-azabicyclo[3.2.0]heptanes and of 1-aza-3-oxatricyclo-[5.3.0.0^{6,9}]decan-2-ones, we had previously used alkoxycarbonyl protecting groups at an irradiation wavelength λ = 254 nm.[17] In Paternò−Büchi reactions of carbonyl compounds and enamines, the *N-tert*-butyloxycarbonyl protection had turned out to be an excellent choice to allow for the otherwise impossible [2 + 2]-photocycloaddition reaction of enamines (λ = 300−350 nm).[25] In general, a *N*-acylation of amines is required in many photochemical reactions to avoid electron transfer from the amine to the photoexcited substrate. Having said this, the question arises why the intramolecular photocycloaddition we planned was not conducted with the unprotected amides **8** and **11**. Due to conjugation in the vinylogous π-system they should not be susceptible to an electron transfer. Indeed, there was no hint for side reactions arising from electron transfer in the irradiation of amide **11**. However, the irradiation product **13** proved to be unstable under the reaction conditions. Its isolation was impossible, and careful analysis revealed that the ring-opened imine **14** was a major side product, which apparently reacts further in an undefined fashion. Apparently, the ring strain in the primary cyclobutane lactone **13** is so high that a retro-Mannich reaction[26] is readily induced (Scheme 3).

SCHEME 3



This observation is important to understand our further strategy. Being afraid of the retro-Mannich cleavage, we planned the ring opening of the lactone (e.g., in compounds of type **E**) with a nucleophile prior to the introduction of the electrophile at the amine nitrogen atom (cf. Scheme 1).

Upon direct irradiation (λ = 254 nm, light source: Rayonet RPR-2537 Å) of the *N*-Boc-protected amides **9** and **12**, no side reactions were observed and the [2 + 2]-photocycloaddition products **15** and **16** were obtained in good yields (Scheme 4). Cyclobutane **15** was obtained as a single diastereoisomer. The depicted configuration was deduced from two-dimensional NMR experiments and from ^{1}H NMR NOE studies on consecutive products (vide infra). The configuration assignment is in line with our previous results obtained with the corresponding tetronate.[16] The tetracyclic product **16** showed impurities of a minor diastereoisomer which could not be separated by flash chromatography. Again, the relative configura-

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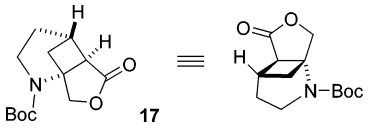
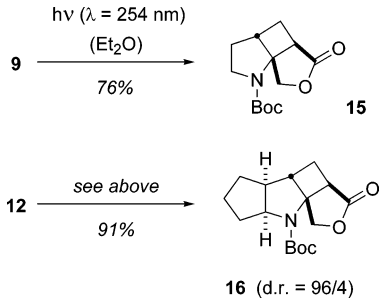


FIGURE 3. Structure of the strained photocycloaddition product **17**.

SCHEME 4



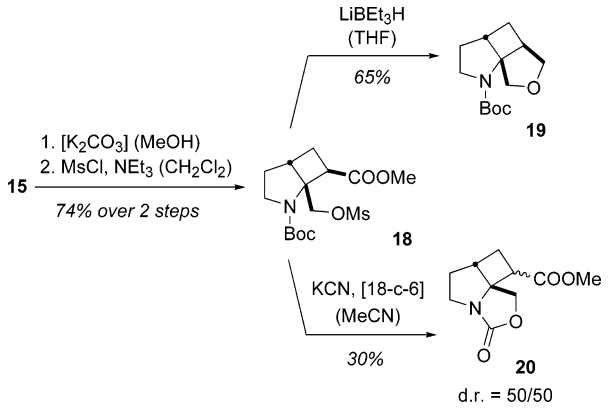
tion of the major diastereoisomer deduced from ^{1}H NMR NOE studies is in accord with our previous findings in the tetronate series[16] and can be explained similarly based on the preferred substrate conformation.

In contrast to the intramolecular tetronate [2 + 2]-photocycloaddition reactions which had to be conducted in highly dilute solutions, the tetronic acid amide cycloaddition proceeded well even at concentrations as high as 4×10^{-2} M. Due to the high yields obtained there was no need for further optimization, e.g., by attempting a sensitized irradiation. In addition, sensitization had not been proven beneficial in our previous tetronate work.[16] While conducting large-scale irradiations, we noted an enrichment of a side product in batches of recovered starting material, which exhibited an R_f value similar to that of **9** on TLC. Its isolation was successful, and its structure was elucidated by single-crystal X-ray crystallography (see the Supporting Information). It turned out to be the crossed [2 + 2]-photocycloaddition product **17** (Figure 3). Having identified this side product, it was possible to determine the regioselectivity of the photocycloaddition of tetronic acid amide **9** by GC as 91/9.

As anticipated, the corresponding *N*-tosyl derivative obtained from **8** by *N*-tosylation[27] (1.5 equiv of NaH, 1.5 equiv of TsCl, THF, reflux, 62%) was less suited for the photocycloaddition, and significant decomposition was observed.

Lactone Ring Opening and Further Transformations. As mentioned above, our further experiments aimed at the conversion of photocycloaddition product **15** to compounds of type **D** were guided by the notion that a nucleophilic lactone ring opening had to occur prior to *N*-functionalization. The high ring strain in cyclobutane lactone **15** manifested itself by the ease with which the solvolytic cleavage occurred. Stirring of the lactone at 0 °C in a methanolic K_2CO_3 solution[28] sufficed to induce a smooth epimerization-free ring opening to the corresponding γ-hydroxy ester (Scheme 5). Aiming at a removal of the polar hydroxyl group, we converted the

SCHEME 5



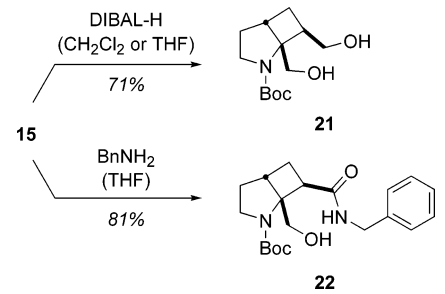
free alcohol to mesylate **18**. An intermolecular nucleophilic attack at the primary methylene group of this compound proved much more difficult than anticipated at first sight. Attempts to reduce the mesylate by hydride nucleophiles worked only with $LiBEt_3H$.[29] The reduction led to a single, defined product, which, however, turned out to be tetrahydrofuran **19**, rather than the S_N2 product.

Intensive efforts to achieve an alkyl substitution with cuprates remained disappointing. The best result was recorded in a methyldemesylation with 2 equiv of Me_2CuLi at 0 °C in THF. The corresponding *N*-Boc-protected 1-ethyl-2-azabicyclo[3.2.0]heptane was isolated in 30% yield as a 3/2 mixture of diastereoisomers. The epimerization of the *exo*-cyclobutanecarboxylate to the *endo*-product is facile and was observed in other reactions as well. It took place, for example, upon treatment of mesylate with KCN and [18-c-6] in refluxing acetonitrile,[30] and the diastereomeric products *exo*-**20a** and *endo*-**20b** were isolated in roughly equal amounts. The oxazolidinone clearly arose from thermally induced nucleophilic substitution of the mesylate by the carbonyl oxygen atom of the carbamate protecting group. The cyclization was incomplete after 6 h of reflux, and starting material was reisolated (37%). The same ring closure was feasible in the absence of KCN by refluxing substrate **18** in acetonitrile. In this case, the epimerization was suppressed and the *exo*-diastereoisomer **20a** was the exclusive product (51% yield). Configuration assignments were again based on ^{1}H NMR NOESY experiments.

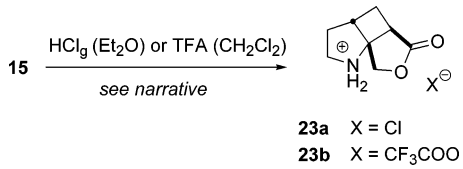
The above-mentioned first set of experiments on lactone **15** impressively testified to the difficulty for attack at the exocyclic methylene group in mesylate **18**. Inspection of molecular models confirmed that there is no reasonable trajectory for the approach of an intermolecular nucleophile due to the steric bias provided by the *N*-Boc-protected 2-azabicyclo[3.2.0]heptane. A second set of experiments corroborated the high ring strain of the lactone ring in compound **15** (Scheme 6). Attempted reduction of the lactone to the corresponding lactol was not feasible under standard conditions with Dibal-H.[31] A complete reduction was observed, indicating that the

(27) Fujita, R.; Watanabe, K.; Ikeura, W.; Ohtake, Y.; Hongo, H.; Harigaya, Y.; Matsuzaki, H. *Tetrahedron* **2001**, *57*, 8841−8850.
(28) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1993**, *58*, 6229−6234.
(29) (a) Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166−2168. (b) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1598−1611.
(30) Malpass, J. R.; Patel, A. B.; Davies, J. W.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 9348−9355.

SCHEME 6



SCHEME 7



primary hemiacetal is in this specific case unstable and that the aldehyde is readily reduced. 1,4-Diol **21** was the only detectable product. The ring opening of lactone **15** with *N*-benzylamine occurred readily at ambient temperature furnishing the corresponding amide **22** in 81% yield.

Since the attempts to remove the hydroxyl group in lactone ring-opening products of compound **15** had failed, we decided to leave the hydroxyl group unprotected and to aim at compounds with the general structure **D** (X = OH). Nucleophilic ring opening of the lactone was facile and a functionalization of the pyrrolidine nitrogen atom with electrophiles appeared sensible as the next step. Attempts to deprotect the *N*-Boc group in intermediates such as amide **22** were in progress when we discovered that the *N*-Boc deprotection could also be conducted on the primary photocycloaddition product **15**. Upon treatment of this compound with HCl or even more favorably with trifluoroacetic acid (TFA), the ammonium salts **23** were obtained without the formation of retro-Mannich products (Scheme 7). Our suspicion that an excess of acid would facilitate the cyclobutane opening was not confirmed. In fact, a large excess of TFA (20 equiv), which was required to guarantee a complete *N*-Boc deprotection, did not cause any cyclobutane ring opening. The ammonium salts could not be stored for long nor could they be characterized, but it was tempting to see whether they could be used for an intermolecular electrophilic attack at the nitrogen atom.

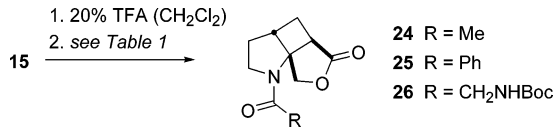
***N*-Functionalization of the Pyrrolidine Ring and Additional Lactone Ring Opening Reactions.** Initial experiments with trifluoroacetate **23b** were conducted with various acylating agents (Scheme 8). To this end, the pyrrolidine **15** was deprotected with TFA and subsequently treated with the reagent combinations indicated in Table 1. Acylations with acetyl and benzoyl chloride proceeded smoothly under standard conditions (entries 1, 2) to yield *N*-acylpyrrolidines **24** and **25**. More importantly, the acylation was also feasible under typical peptide coupling conditions. Coupling reagent *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) in the presence of 1-hydroxy-7-azabenzotriazole (HOAt) and Hünig base (*i*Pr$_2$NEt) was similarly well suited as was *O*-[(ethoxycarbonyl)cyanomethenamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TOTU) in the presence of *N*-ethylmorpholine (entries 3, 4). Under the latter conditions, dipeptide **26** was obtained from **15** and *N*-Boc-glycine in good yields (entry 5).

TABLE 1. *N*-Deprotection and Subsequent Acylation of the Pyrrolidine Ring in [2 + 2]-Photocycloaddition Product 15 (See Scheme 8)

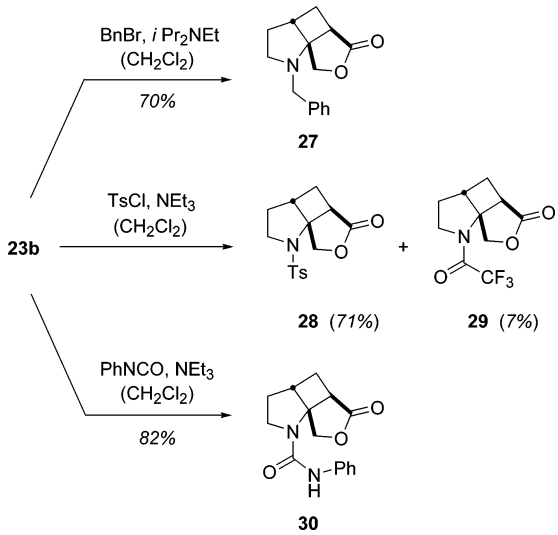
entry	conditions[a]	product	yield[b] (%)
1	2 equiv of CH_3COCl, 5 equiv of NEt_3 (CH_2Cl_2)	**24**	82
2	2 equiv of PhCOCl, 5 equiv of NEt_3 (CH_2Cl_2)	**25**	84
3	1.2 equiv of PhCOOH, 1.2 equiv of HATU, 1.2 equiv of HOAt, 6 equiv of *i*-Pr$_2$NEt (DMF)	**25**	70
4	1.2 equiv of PhCOOH, 1.2 equiv of TOTU, 6 equiv of *N*-ethylmorpholine (DMF)	**25**	72
5	1.2 equiv of *N*-Boc-glycine, 1.2 equiv of TOTU, 6 equiv of *N*-ethylmorpholine (DMF)	**26**	74

[a] After deprotection (TFA in CH_2Cl_2, rt, 1 h), excess TFA and CH_2Cl_2 were removed and the residue was dissolved in the given solvent. The acylation reactions were conducted at rt until the starting material was consumed (6−16 h). [b] Yield of isolated product.

SCHEME 8



SCHEME 9



The straightforward attack by sp^2-electrophiles at the nitrogen atom of the pyrrolidine, derived from ammonium salt **23b**, encouraged us to study the reaction of **23b** with other electrophiles under basic conditions (Scheme 9). The *N*-benzylation proceeded smoothly with benzyl bromide in the presence of *i*-Pr$_2$NEt to yield the *N*-benzyl

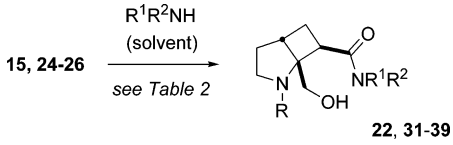
(31) Examples of similar reductions with Dibal-H yielding the lactol: (a) Bergmeier, S. C.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019−5022. (b) Sugiyama, H.; Shiori, T.; Yokokawa, F. *Tetrahedron Lett.* **2002**, *43*, 3489−3492.

TABLE 2. Synthesis of the 2-Azabicyclo[3.2.0]heptanes 22 and 31−39 by Nucleophilic Ring Opening of the Strained Lactone 15 and 24−26 by Various Amines

entry	substrate	R	R^1	R^2	equiv of amine	*T* (°C)/time	solvent	product	yield[a] (%)
1	**15**	Boc	H	$CH_2C_6H_5$	2	rt/15 h	THF	**22**	81
2	**25**	Bz	H	$CH_2C_6H_5$	2	rt/15 h	THF	**31**	65
3	**24**	Ac	H	$CH_2C_6H_5$	2	rt/7 h	THF	**32**	79
4	**15**	Boc	H	*i*-C_3H_7	5	0 °C → rt/7 d	THF	**33**	76
5	**15**	Boc	H	*cyclo*-C_6H_{11}	1.5	rt/70 h + reflux/21 h	THF	**34**	74
6	**15**	Boc	H	*cyclo*-C_6H_{11}	1.5	rt/18 h	EtOH	**34**	67
7	**15**	Boc	H	*n*-C_4H_9	1.5	60°C/15 h	THF	**35**	79
8	**15**	Boc	H	*n*-C_4H_9	1.5	rt/15 h	EtOH	**35**	90
9	**15**	Boc	−$(CH_2)_4$−		1.5	reflux/17 h	*i*-PrOH	**36**	63
10	**15**	Boc	H	CH_2COOEt[b]	1.5[c]	rt/15 h	EtOH	**37**	53[d]
11	**15**	Boc	H	CH_2COOEt[b]	1.5[c]	reflux/20 h	EtOH	**37**	74
12	**26**	$COCH_2NHBoc$	H	CH_2COOEt[b]	1.5[c]	reflux/20 h	EtOH	**38**	69
13	**15**	Boc	H	C_6H_5	1.5	rt/17 h + reflux/24 h	THF	**39**	*e*
14	**15**	Boc	H	C_6H_5	1.5	rt/3 d + reflux/27 h	*i*-PrOH	**39**	*e*

[a] Yield of isolated product. [b] Employed as its hydrochloride salt. [c] 2 equiv of NEt_3 was added as auxiliary base. [d] The reaction was incomplete. 26% of starting material was recovered. [e] No product formation was observed.

SCHEME 10



pyrrolidine **27**. In the *N*-tosylation reaction, the major product was the expected pyrrolidine **28** but an additional product was isolated, which was identified as the *N*-trifluoroacetyl pyrrolidine **29**. Its formation can be explained by a mixed anhydride $TsOC(O)CF_3$ generated via substitution of the chloride ion in TsCl by trifluoroacetate. The anhydride is an ambident electrophile which can be attacked at the sulfur atom or at the carbonyl group. The latter attack accounts for the *N*-trifluoroacetylation. In a final experiment, phenyl isocyanate was employed as the electrophile. Its reaction with ammonium salt **23b** in the presence of NEt_3 led to the urea **30** in very good yield.

With these results, we returned to the previously discussed lactone ring-opening reaction with amines (Scheme 6). Optimized conditions for these reactions were sought, which would allow the reaction of a given amine with strained lactones to the corresponding amide. The plan was to establish—in collaboration with an industrial partner—a library of compounds which possess the general structure **D** (Scheme 1, X = OH) and which can be decorated at the N- and at the C-terminal position. The general reaction studied in these experiments is depicted in Scheme 10, and a selection of results is summarized in Table 2. Entries 1−3 in Table 2 illustrate that the conditions suited for a ring opening of the *N*-Boc derivative **15** are equally applicable to the reaction of other pyrrolidines, such as **24** and **25**. This observation was also corroborated in the library synthesis using other electrophiles similar to compounds **24**−**30**. Since it was conveniently prepared, further experiments were conducted with the strained photocycloaddition product **15**. Yields for the reaction with simple primary amines (entries 4−8) varied between 67 and 90%. In general, 1.5−2 equiv of the amine was sufficient to allow for a complete conversion. The volatile 2-propylamine (bp 33−34 °C) was used in larger excess and was stirred at room temperature to keep the amine concentration in the solution sufficiently high (entry 4). The reaction of other less volatile α-branched amines, such as cyclohexylamine, could be driven to completion by refluxing in THF (entry 5). Even more favorably, the reaction was conducted in EtOH as the solvent (entry 6), which facilitated a complete conversion after 18 h at room temperature. The same trend was observed for butylamine. While the reaction in THF required 15 h at 60 °C, the reaction in EtOH was complete at room temperature after the same period of time (entries 7, 8). Secondary amines, such as pyrrolidine, required harsher conditions. The reaction in refluxing 2-propanol eventually led to the formation of the desired amide **36** in 63% yield (entry 9). Amino acids, such as glycine, were also employed for the lactone ring opening. In the optimization reactions glycine ethyl ester hydrochloride was used in the presence of triethylamine as base. The reaction at room temperature in EtOH remained incomplete after 15 h (entry 10), whereas under reflux the corresponding peptide bond was formed more rapidly (entry 11). The very same conditions employed for the conversion of **15** were applied to the dipeptide **26** which could by this means be converted into tripeptide **38** (entry 12). Less nucleophilic aromatic amines, such as aniline, could not be brought to reaction even under forceful conditions (entries 13, 14).

As mentioned above, the reaction conditions established in the model studies with *N*-Boc protected pyrrolidine **15** could be transferred to other substrates as well as to other amines. The formation of tripeptides such as **38** appears to be a feature that reaches further than simple library synthesis and might be applicable to a de novo construction of conformationally restricted peptides. A crystal structure was obtained for the ring opening product **31** (see the Supporting Information).

Conclusion

In summary, two complex *N*-Boc-protected 2-aza-9-oxatricyclo[5.3.0.$0^{1,5}$]decan-8-ones **15** and **16** were synthesized photochemically by irradiation of the readily available tetronic acid amides **9** and **12**. Further reactions of compound **15** were studied. Attempts to replace the hydroxyl group after lactone ring opening and mesylation failed. An electrophilic attack at the pyrrolidine nitrogen atom was possible after removal of the Boc group. The intermediate tricylic ammonium salts **23** were sufficiently stable toward a retro-Mannich fragmentation to

allow for *N*-functionalization. Several substitution products **24**−**30** were obtained in very good yields. The subsequent lactone ring opening by amines led to a host of conformationally restricted β-proline analogues a few of which were described in more detail. It was also demonstrated that the 2-azabicyclo[3.2.0]heptane core can be used as a building block in peptide synthesis.

Experimental Section

Preparation of Starting Materials. But-3-enylamine (**6**),[20] *cis*-2-vinylcyclopentylamine (**10**),[21] and 4-bromo-2,5-dihydro-2-oxofuran (**7**)[19] were synthesized according to reported procedures.

4-(3-Butenylamino)-5*H*-furan-2-one (8). 4-Bromo-2,5-dihydro-2-oxofuran (**7**) (8.15 g, 50.0 mmol) was dissolved in dry THF (150 mL), and 3.91 g (55.0 mmol) but-3-enylamine (**6**) and 15.2 g (20.8 mL, 150 mmol) anhydrous NEt_3 were added. The mixture was refluxed overnight, cooled to rt, and filtered. The filtrate was evaporated to dryness, and the crude product was purified by column chromatography (P/EA = 1:4 as eluent) to give 5.78 g (37.8 mmol, 76%) of the desired product as a bay-colored oil: R_f = 0.24 (P/EA = 1/3); ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.33−2.41 (m, 2 H), 3.19 (virt. q, $^3J \cong 6.6$ Hz, 2 H), 4.64 (s, 1 H), 4.65 (s, 2 H), 5.10−5.16 (m, 2 H), 5.61 (br. s, 1 H), 5.77 (ddt, ^3J = 17.0, ^3J = 10.2, ^3J = 6.6 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 32.8 (CH_2), 44.1 (CH_2), 67.6 (CH_2), 80.9 (CH), 117.8 (CH_2), 134.3 (CH), 168.1 (C), 176.1 (C). Anal. Calcd for $C_8H_{11}NO_2$ (153.08): C, 62.73; H, 7.24; N, 9.14. Found: C, 62.60; H, 7.22; N, 9.31.

4-(*N*-*tert*-Butoxycarbonyl-3-butenylamino)-5*H*-furan-2-one (9). 4-(3-Butenylamino)-5*H*-furan-2-one (**8**) (5.51 g, 36.0 mmol) was dissolved in dry THF (100 mL). At 0 °C, a solution of 8.25 g (37.8 mmol) of di-*tert*-butyl dicarbonate in THF (50 mL) was added dropwise. After addition of 6.00 mL (4.37 g, 43.2 mmol) of NEt_3 and 0.88 g (7.20 mmol) of DMAP, the solution was stirred for another 30 min at 0 °C and then at rt overnight. The solvent was evaporated at reduced pressure, and the resulting crude product was purified by column chromatography (P/EA = 3:1→ 2:1 as eluent) to give 8.61 g (34.0 mmol, 94%) of the desired product as a colorless oil: R_f = 0.25 (P/EA = 3:1); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.53 (s, 9 H), 2.37 (virt. q, $^3J \cong 7.4$ Hz, 2 H), 3.67 (t, ^3J = 7.4 Hz, 2 H), 5.05−5.13 (m, 2 H), 5.20 (s, 2 H), 5.22 (s, 1 H), 5.70−5.81 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 28.0 (CH_3), 31.2 (CH_2), 47.8 (CH_2), 70.7 (CH_2), 84.3 (C), 94.6 (CH), 117.9 (CH_2), 133.6 (CH), 151.2 (C), 163.6 (C), 173.2 (C). Anal. Calcd for $C_{13}H_{19}NO_4$ (253.13): C, 61.64; H, 7.56; N, 5.53. Found: C, 61.73; H, 7.49; N, 5.65.

4-(*cis*-2-Vinylcyclopentylamino)-5*H*-furan-2-one (11). According to the aforementioned procedure, tetronic acid amide **11** was prepared from 4-bromo-2,5-dihydro-2-oxofuran (**7**) (489 mg, 3.00 mmol), 334 mg (3.00 mmol) of *cis*-2-vinylcyclopentylamine (**10**), and NEt_3 (876 mg, 1.20 mL, 8.70 mmol) in THF (25 mL). Column chromatography (P/EA = 1:2 as eluent) yielded 285 mg (1.47 mmol, 49%) of the desired product as colorless crystals: R_f = 0.26 (P/EA = 1/2); mp 106 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.57−2.10 (m, 6 H), 2.71−2.79 (m, 1 H), 3.61−3.69 (m, 1 H), 4.63 (s, 2 H), 4.65 (s, 1 H), 5.09−5.14 (m, 2 H), 5.23 (br. d, ^3J = 5.7 Hz, 1 H), 5.73−5.83 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.6 (CH_2), 28.6 (CH_2), 31.0 (CH_2), 46.7 (CH), 58.6 (CH), 67.6 (CH_2), 81.7 (CH), 117.4 (CH_2), 136.6 (CH), 167.2 (C), 176.0 (C); HRMS (EI) calcd for $C_{11}H_{15}NO_2$ 193.1103, found 193.1105.

4-(*N*-*tert*-Butoxycarbonyl-(*cis*-2-vinylcyclopentylamino)-5*H*-furan-2-one (12). According to the aforementioned procedure, Boc-protected tetronic acid amide **12** was prepared from tetronic acid amide **11** (284 mg, 1.47 mmol), 321 mg (1.47 mmol) of di-*tert*-butyl dicarbonate, 0.20 mL (149 mg, 1.47 mmol) of NEt_3, and 36.0 mg (0.29 mmol) of DMAP in THF (15 mL). Column chromatography (P/EA = 3:1→ 1:3 as eluent) gave 124 mg (0.64 mmol, 44%) of the starting material **11** and 192 mg (0.65 mmol, 44%, 79% brsm) of the desired product **12** as a pale yellow oil: R_f = 0.32 (P/EA = 3:1); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.46−1.56 (m, 1 H), 1.53 (s, 9 H), 1.80−2.04 (m, 4 H), 2.34−2.45 (m, 1 H), 2.89 (virt quint, $^3J \cong 8.5$ Hz, 1 H), 4.22−4.29 (m, 1 H), 4.95−5.03 (m, 2 H), 5.07−5.19 (m, 2 H), 5.30 (s, 1 H), 5.68 (ddt, ^3J = 17.1, 10.3, 8.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 24.6 (CH_2), 28.1 (CH_3), 29.0 (CH_2), 32.0 (CH_2), 45.9 (CH), 63.8 (CH), 71.2 (CH_2), 84.5 (C), 96.2 (CH), 116.8 (CH_2), 137.4 (CH), 151.6 (C), 165.6 (C), 173.3 (C); HRMS (EI) calcd for $C_{16}H_{23}NO_4$ 293.1627, found 293.1628; HRMS (EI) calcd for $C_{16}H_{23}NO_4 - C_4H_8$ 237.1001, found 237.0999.

General Procedure for the [2 + 2] Photocycloaddition of Tetronic Acid Amides. In a quartz vessel, a solution of the respective tetronic acid amide in anhydrous Et_2O was irradiated at rt and 254 nm until GC and TLC analysis indicated complete conversion (light source: Rayonet RPR-2537 Å). The solvent was then evaporated under reduced pressure, and the remaining residue was purified by column chromatography to give the desired product.

***N*-*tert*-Butoxycarbonyl-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]-decan-8-one (15).** The compound was prepared from tetronic acid amide **9** (198 mg, 0.78 mmol) in Et_2O (20 mL) by irradiation for 4 h. Column chromatography (P/EA = 3:1 as eluent) yielded 150 mg (0.59 mmol, 76%) of the desired product as colorless crystals: R_f = 0.34 (P/EA = 2:1); mp 119 °C; ^{1}H NMR (360 MHz, DMSO-d_6, 327 K) δ 1.40 (s, 9 H), 1.74−1.83 (m, 1 H), 2.06−2.20 (m, 3 H), 2.94−2.98 (m, 2 H), 3.39−3.46 (m, 1 H), 3.64−3.71 (m, 1 H), 4.29 (d, ^2J = 9.1 Hz, 1 H), 4.50 (d, ^2J = 9.1 Hz, 1 H); ^{13}C NMR (90 MHz, DMSO-d_6, 327 K) δ 25.2 (CH_2), 27.7 (CH_3), 29.0 (CH_2), 37.7 (CH), 41.8 (CH), 48.3 (CH_2), 65.9 (C), 72.8 (CH_2), 79.5 (C), 152.9 (C), 177.3 (C); HRMS (EI) calcd for $C_{13}H_{19}NO_4 - C_4H_8$ 197.0688, found 197.0685. Anal. Calcd for $C_{13}H_{19}NO_4$ (253.13): C, 61.64; H, 7.56; N, 5.53. Found: C, 61.38; H, 7.57; N, 5.43.

***N*-*tert*-Butoxycarbonyl-7-aza-4-oxatricyclo[4.3.1.0^{2,6}]-decan-3-one (crossed-isomer: 17):** R_f = 0.4 (P/EA = 2:1); mp 94 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 353 K) δ 1.42 (s, 9 H), 1.50 (dd, ^2J = 10.4 Hz, ^3J = 7.8 Hz, 1 H), 2.04−2.15 (m, 2 H), 2.34 (dd, ^2J = 10.4 Hz, ^3J = 5.7 Hz, 1 H), 2.67−2.69 (m, 1 H), 3.15 (d, ^3J = 7.7 Hz, 1 H), 3.47−3.53 (m, 1 H), 3.93 (dd, ^2J = 12.8 Hz, ^3J = 8.4 Hz, 1 H), 4.27 (d, ^2J = 9.4 Hz, 1 H), 4.38 (d, ^2J = 9.4 Hz, 1 H); ^{13}C NMR (90 MHz, DMSO-d_6, 353 K) δ 27.7 (CH_3), 29.1 (CH_2), 32.4 (CH), 39.0 (CH_2), 40.1 (CH_2), 45.0 (CH), 65.1 (C), 72.2 (CH_2), 79.6 (C), 153.8 (C), 175.1 (C); HRMS (EI) calcd for $C_{13}H_{19}NO_4$ 253.1314, found 253.1313.

***N*-*tert*-Butoxycarbonyl-2-aza-12-oxatetracyclo[6.5.0.0^{1,10}.0^{3,7}]tridecan-11-one (16).** The compound was prepared from tetronic acid amide **12** (66.0 mg, 0.22 mmol) in Et_2O (10 mL) by irradiation for 2 h. Column chromatography (P/EA = 3:1 as eluent) yielded 59.0 mg (0.20 mmol, 91%) of the desired product as a colorless oil (dr = 96/4, HPLC): R_f = 0.43 (P/EE = 3:1); ^{1}H NMR (360 MHz, DMSO-d_6, 327 K) δ 1.35−1.74 (m, 6 H), 1.40 (s, 9 H), 2.17−2.26 (m, 2 H), 2.52−2.60 (m, 1 H), 2.67−2.75 (m, 1 H), 2.91 (ddd, ^3J = 9.1, 4.7, 1.2 Hz, 1 H), 4.22 (d, ^3J = 8.7 Hz, 1 H), 4.38−4.49 (m, 2 H); ^{13}C NMR (90 MHz, DMSO-d_6, 327 K) δ = 24.1 (CH_2), 26.7 (CH_2), 27.7 (CH_3), 32.7 (CH_2), 34.4 (CH_2), 36.6 (CH), 47.7 (CH), 48.1 (CH), 66.8 (CH), 68.4 (C), 72.7 (CH_2), 79.4 (C), 152.6 (C), 177.3 (C); HRMS (EI) calcd for $C_{16}H_{23}NO_4$ 293.1627, found 293.1627.

***cis*-1-Methanesulfonyloxymethyl-2-azabicyclo[3.2.0]-heptane-2,7-dicarboxylic Acid 2-*tert*-Butyl Ester 7-Methyl Ester (18).** The methanolysis was conducted as previously described by Marshall et al.[28] Lactone **15** (2.05 g, 8.09 mmol) was dissolved in MeOH (30 mL) and cooled to 0 °C. After addition of K_2CO_3 (0.57 g, 4.10 mmol), the mixture was stirred for 1.5 h at this temperature. Saturated aqueous NH_4Cl solution (50 mL) was added, and MeOH was evaporated under reduced pressure. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2-

SO_4), filtered, and concentrated to dryness. The residue was dissolved again in CH_2Cl_2 (40 mL) and cooled to 0 °C. After addition of NEt_3 (2.25 mL, 1.64 g, 16.2 mmol), a solution of methanesulfonic acid chloride (0.76 mL, 1.11 g, 9.72 mmol) in 5 mL of CH_2Cl_2 was added dropwise. After the mixture was warmed to rt overnight, saturated aqueous NH_4Cl solution (25 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was subjected to column chromatography (P/EA = 2:1 → 3:2 as eluent) to give 2.36 g of a crystalline substance consisting of 2.18 g (6.00 mmol, 74%) of the desired product and 0.18 g (0.7 mmol, 9%) of the starting material **15**. An analytical sample of the desired product was obtained by repeated column chromatography in form of colorless crystals: R_f = 0.21 (P/EA = 2:1); mp 107 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 1.62−1.82 (m, 1 H), 1.88 (ddd, ^2J = 12.6, ^3J = 9.2, 7.0 Hz, 1 H), 1.95−2.06 (m, 1 H), 2.47 (ddd, ^2J = 12.6, ^3J = 9.4, 4.9 Hz, 1 H), 2.96 (s, 3 H), 3.04−3.21 (m, 2 H), 3.60−3.82 (m, 2 H), 3.71 (s, 3 H), 4.40 (d, ^2J = 10.2 Hz, 1 H), 4.52−4.93 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.5 (CH_2), 28.0 (CH_2), 28.3 (CH_3), 37.4 (CH_3), 40.5 (CH), 44.3 (CH), 48.1 (CH_2), 52.0 (CH_3), 66.4 (C), 69.1 (CH_2), 81.0 (C), 153.5 (C), 172.4 (C); HRMS (EI) calcd for $C_{15}H_{25}NO_7S - OC_4H_9$ 290.0698, found 290.0696. Anal. Calcd for $C_{15}H_{25}NO_7S$ (363.43): C, 49.57; H, 6.93; N, 3.85. Found: C, 49.70; H, 6.83; N, 3.72.

***N*-*tert*-Butoxycarbonyl-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]-decane (19).** The reduction was performed after a modified procedure of Rosen et al.[29b] Mesylate **18** (0.73 g, 2.00 mmol) was dissolved in dry THF (3 mL) and cooled to 0 °C. At this temperature, 2.30 mL (2.30 mmol) of a solution of $LiBEt_3H$ (1 M in THF) was slowly added, and stirring was continued for 10 min. Then the reaction mixture was warmed to rt and stirred for 90 min. After the mixture was cooled to 0 °C, an additional 2.30 mL (2.30 mmol) of a solution of $LiBEt_3H$ (1 M in THF) was added. The reaction mixture was warmed to rt, and after being stirred for 3.5 h, it was quenched by addition of H_2O (0.5 mL). The mixture was diluted with EA (20 mL) and consecutively washed with H_2O (20 mL), 1 M aqueous H_3PO_4 (20 mL), saturated aqueous K_2CO_3 solution (20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crystalline substance was purified by column chromatography (P/Et_2O = 3:1 as eluent) to yield 0.31 g (1.30 mmol, 65%) of tetrahydrofuran **19** as colorless crystals: R_f = 0.22 (P/Et_2O = 3:1); mp 62 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.67−1.88 (m, 3 H), 2.06−2.16 (m, 1 H), 2.63−2.71 (m, 2 H), 3.36−3.43 (m, 1 H), 3.55 (d, ^2J = 8.4 Hz, 1 H), 3.77−3.83 (m, 2 H), 3.91−3.97 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 27.7 (CH_2), 28.6 (CH_3), 31.2 (CH_2), 39.6 (CH), 41.5 (CH), 49.2 (CH_2), 71.9 (CH_2), 72.1 (C), 74.4 (CH_2), 79.9 (C), 154.0 (C); HRMS (EI) calcd for $C_{13}H_{21}NO_3$ 239.1522, found 239.1521. Anal. Calcd for $C_{13}H_{21}NO_3$ (239.31): C, 65.25; H, 8.84; N, 5.85. Found: C, 64.94; H, 8.99; N, 5.63.

7-Methoxycarbonyl-1-aza-9-oxatricyclo[5.3.0.0^{4,7}]decan-10-one (20a, 20b). The reaction conditions applied correspond to those previously described by Malpass et al.[30] KCN (0.43 g, 6.56 mmol) and 18-c-6 (43.0 mg, 0.16 mmol) were added to a solution of mesylate **18** (0.60 g, 1.64 mmol) in 10 mL of MeCN. The resulting mixture was refluxed for 6 h and was then allowed to cool to rt. Et_2O (20 mL) was added, and the resulting white precipitate was filtered off. The filtrate was concentrated to dryness. Column chromatography (P/EA = 2:1 as eluent) gave 0.22 g of mesylate **18** (0.61 mmol, 37%), 55.0 mg of *cis*-substituted proline **20a** (0.26 mmol, 16%, 25% brsm) as a colorless oil, and 64.0 mg of the *trans*-diastereomer **20b** (0.30 mmol, 18%, 29% brsm) as colorless crystals. *cis*-Diastereomer **20a**: R_f = 0.20 (P/EA = 2:1); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.67−1.80 (m, 3 H), 2.34 (ddd, ^2J = 13.1, ^3J = 9.9, 6.2 Hz, 1 H), 3.07−3.13 (m, 1 H), 3.26 (dd, ^3J = 10.1, 6.2 Hz, 1 H), 3.32 (dd, ^2J = 12.5, ^3J = 6.7 Hz, 1 H), 3.74 (s, 3 H), 4.09 (dd, ^2J = 12.5, ^3J = 6.9 Hz, 1 H), 4.29 (d, ^2J = 10.4 Hz, 1 H), 4.37 (d, ^2J = 10.4 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.0 (CH_2), 31.4 (CH_2), 44.2 (CH), 46.3 (CH_2), 47.1 (CH), 52.0 (CH_3), 69.4 (CH_2), 70.7 (C), 160.2 (C), 173.0 (C); HRMS (EI) calcd for $C_{10}H_{13}NO_4$ 211.0845, found 211.0847. *trans*-Diastereomer **20b**: R_f = 0.16 (P/EA = 2:1); mp 130 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.59−1.76 (m, 2 H), 2.01 (ddd, ^2J = 13.2, ^3J = 8.9, 6.8 Hz, 1 H), 2.14 (ddd, ^2J = 13.2, ^3J = 10.1, 9.2 Hz, 1 H), 2.94−3.00 (m, 1 H), 3.30−3.39 (m, 2 H), 3.70 (s, 3 H), 4.00 (dd, ^2J = 12.3, ^3J = 7.5 Hz, 1 H), 4.40−4.46 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.6 (CH_2), 31.0 (CH_2), 43.2 (CH), 45.7 (CH), 47.5 (CH_2), 52.0 (CH_3), 71.4 (C), 72.3 (CH_2), 160.7 (C), 170.5 (C); HRMS (EI) calcd for $C_{10}H_{13}NO_4$ 211.0845, found 211.0839.

1,7-Bis-hydroxymethyl-2-azabicyclo[3.2.0]heptane-2-carboxylic Acid *tert*-Butyl Ester (21). A solution of lactone **15** (939 mg, 3.70 mmol) in 5 mL of CH_2Cl_2 was cooled to −78 °C, and 9.27 mL (9.27 mmol) of a DIBAL-H solution (1 M in CH_2Cl_2) was slowly added. Stirring at −78 °C was continued for 3 h. Then the reaction was quenched by addition of 180 μL of H_2O. The reaction mixture was allowed to warm to rt, and 180 μL of 1 M NaOH and 540 μL of H_2O were added. After being stirred for 1 h, the resulting precipitate was filtered (Celite) and washed with CH_2Cl_2. The filtrate was concentrated to dryness. Column chromatography (P/EA = 1:2 as eluent) gave 671 mg of the desired product (2.61 mmol, 71%) as a colorless oil: R_f = 0.25 (P/EA = 1/2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 1.61−1.70 (m, 2 H), 1.72−1.83 (m, 1 H), 1.83−1.94 (m, 1 H), 2.48−2.73 (m, 2 H), 3.59−3.74 (m, 4 H), 3.82 (dd, ^2J = 12.0, ^3J = 10.7 Hz, 1 H), 3.98 (d, ^2J = 12.3 Hz, 1 H), 4.15 (br. s, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 22.6 (CH_2), 28.4 (CH_3), 28.7 (CH_2), 40.0 (CH), 43.5 (CH), 49.0 (CH_2), 64.1 (CH_2), 65.6 (CH_2), 69.7 (C), 81.2 (C); HRMS (EI) calcd for $C_{13}H_{23}NO_4 - C_4H_8$ 201.1001, found 201.1005; HRMS (EI) calcd for $C_{13}H_{23}NO_4 - C_3H_6O$ 199.1209, found 199.1207.

7-Benzylcarbamoyl-1-hydroxymethyl-2-azabicyclo[3.2.0]-heptane-2-carboxylic Acid *tert*-Butyl Ester (22). Lactone **15** (127 mg, 0.50 mmol) was dissolved in THF (3 mL). After addition of benzylamine (109 μL, 107 mg, 1.00 mmol), stirring was continued for 15 h at rt. Evaporation to dryness followed by column chromatography (P/EA = 1:1 → 1:2 as eluent) gave 146 mg (0.41 mmol, 81%) of the desired product as colorless crystals: R_f = 0.31 (P/EA = 1:3); mp 115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9 H), 1.73−1.80 (m, 2 H), 2.06−2.13 (m, 1 H), 2.22−2.57 (br. s, 1 H), 2.58−2.74 (m, 1 H), 2.75−2.96 (m, 1 H), 3.07 (virt. t, $^3J \cong$ 7.7 Hz, 1 H), 3.46 (virt. dt, ^2J = 10.9, $^3J \cong$ 7.1 Hz, 1 H), 3.58−3.77 (m, 2 H), 3.80−3.97 (m, 1 H), 4.43 (dd, ^2J = 14.9, ^3J = 5.1 Hz, 1 H), 4.52 (dd, ^2J = 14.9, ^3J = 5.1 Hz, 1 H), 7.22−7.37 (m, 5 H), 7.73 (br s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 22.3 (CH_2), 28.4 (CH_3), 30.4 (CH_2), 37.9 (CH), 43.5 (CH_2), 45.4 (CH), 49.4 (CH_2), 62.9 (CH_2), 69.7 (C), 80.5 (C), 127.1 (CH), 127.6 (CH), 128.4 (CH), 138.6 (C), 155.2 (C), 171.4 (C); HRMS (EI) calcd for $C_{20}H_{28}N_2O_4 - H_2O$ 342.1943, found 342.1949. Anal. Calcd for $C_{20}H_{28}N_2O_4$ (360.45): C, 66.64; H, 7.83; N, 7.77. Found: C, 66.33; H, 7.95; N, 7.74.

2-Azonia-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one Trifluoroacetate (23b). A solution of Boc-protected pyrrolidine **15** (253 mg, 1.00 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0 °C, and 1.5 mL of TFA (2.30 g, 20.2 mmol) was slowly added. The solution was allowed to warm to rt and was stirred at this temperature for 1 h. Then CH_2Cl_2 and excess TFA were evaporated in vacuo. The obtained crude pyrrolidinium trifluoroacetate **23b** was directly subjected to subsequent transformations.

***N*-Acetyl-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (24).** Pyrrolidinium trifluoroacetate **23b** (1.00 mmol) prepared according to the aforementioned procedure was dissolved in CH_2Cl_2 (7 mL). At 0 °C, 143 mL of AcCl (157 mg, 2.00 mmol) and 693 mL of NEt_3 (506 mg, 5.00 mmol) were added dropwise. The reaction mixture was allowed to warm to rt and was stirred overnight. After addition of 10 mL of H_2O, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and filtered. The filtrate

was evaporated to dryness. Column chromatography (EA/MeOH = 99:1 as eluent) gave 161 mg (0.82 mmol, 82%) of the desired product as colorless crystals: $R_f = 0.18$ (EA/MeOH = 99:1); mp 74 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.87−1.95 (m, 1 H), 2.11 (s, 3 H), 2.13−2−28 (m, 2 H), 2.36 (ddd, ^2J = 12.8, ^3J = 8.3, 3.6 Hz, 1 H), 2.98−3.05 (m, 1 H), 3.12 (ddd, ^3J = 9.7, 3.6, ^4J = 1.0 Hz, 1 H), 3.70−3.83 (m, 2 H), 4.04 (d, ^2J = 8.6 Hz, 1 H), 4.86 (d, ^2J = 8.6 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.6 (CH_3), 26.8 (CH_2), 29.4 (CH_2), 37.4 (CH), 42.0 (CH), 49.7 (CH_2), 68.2 (C), 71.4 (CH_2), 170.7 (C), 178.3 (C); HRMS (EI) calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0896.

***N*-Benzoyl-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (25).** HATU (456 mg, 1.20 mmol), HOAt (163 mg, 1.20 mmol), and benzoic acid (147 mg, 1.20 mmol) were dissolved in DMF (3 mL). After addition of 1.05 mL of *i*-Pr_2NEt (776 mg, 6.00 mmol), stirring at rt was continued for 30 min. Pyrrolidinium trifluoroacetate **23b** (1.00 mmol) prepared according to the aforementioned procedure was dissolved in DMF (1 mL) and added dropwise to the solution of the activated ester. Stirring at rt was continued overnight. After addition of H_2O (20 mL), the mixture was extracted with EA (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and filtered. Evaporation to dryness followed by column chromatography (P/EA = 1:1 as eluent) gave 179 mg (0.70 mmol, 70%) of the desired product as colorless crystals: R_f = 0.30 (P/EE = 1:1); mp 114 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 185−1.95 (m, 1 H), 2.22 (ddd, ^2J = 13.1, ^3J = 9.9, ^3J = 4.9 Hz, 1 H), 2.31−2.44 (m, 2 H), 2.96−3.04 (m, 1 H), 3.37 (dd, ^3J = 9.9, ^3J = 5.1 Hz, 1 H), 3.67−3.82 (m, 2 H), 4.34 (d, ^2J = 9.1 Hz, 1 H), 4.81 (d, ^2J = 9.1 Hz, 1 H), 7.39−7.55 (m, 5 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 27.2 (CH_2), 32.3 (CH_2), 38.5 (CH), 41.6 (CH), 51.9 (CH_2), 68.1 (C), 72.8 (CH_2), 127.5 (CH), 128.4 (CH), 130.8 (CH), 135.7 (C), 170.5 (C), 177.9 (C); HRMS (EI) calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1051. Anal. Calcd for $C_{15}H_{15}NO_3$ (257.28): C, 70.02; H, 5.88; N, 5.44. Found: C, 69.77; H, 5.73; N, 5.44.

***N*-(*N*-*tert*-Butoxycarbonylaminoacetyl)-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (26).** A solution of *N*-*tert*-butoxycarbonylglycine (210 mg, 1.20 mmol) in DMF (2 mL) was cooled to 0 °C. After addition of TOTU (394 mg, 1.20 mmol) and *N*-ethylmorpholine (770 mL, 691 mg, 6.00 mmol), stirring was continued for 10 min at 0 °C and then for an additional 20 min at rt. Pyrrolidinium trifluoroacetate **23b** (1.00 mmol) prepared according to the aforementioned procedure was dissolved in DMF (1 mL), and the solution of activated ester was added dropwise. After the mixture was stirred at rt for 7 h, saturated aqueous $NaHCO_3$ solution (30 mL) was added. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were subsequently washed with saturated aqueous $NaHCO_3$ solution (3 × 30 mL), H_2O (30 mL), and brine (2 × 30 mL), dried (Na_2SO_4), and filtered. Evaporation to dryness and column chromatography (P/EA = 1:4 as eluent) gave 230 mg (0.74 mmol, 74%) of the desired product as a pale yellow oil: R_f = 0.24 (P/EA = 1/4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 1.91−1.99 (m, 1 H), 2.14−2.32 (m, 2 H), 2.39 (ddd, ^2J = 12.9, ^3J = 8.2, ^3J = 3.7 Hz, 1 H), 2.99−3.05 (m, 1 H), 3.10 (dd, ^3J = 9.8, ^3J = 3.7 Hz, 1 H), 3.65−3.80 (m, 2 H), 3.88−4.01 (m, 2 H), 4.08 (d, ^2J = 8.9 Hz, 1 H), 4.84 (d, ^2J = 8.9 Hz, 1 H), 5.36 (br. s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 26.9 (CH_2), 28.3 (CH_3), 29.7 (CH_2), 37.5 (CH), 41.7 (CH), 43.6 (CH_2), 47.8 (CH_2), 68.8 (C), 71.2 (CH_2), 79.9 (C), 155.8 (C), 168.6 (C), 177.7 (C); HRMS (EI) calcd for $C_{15}H_{22}N_2O_5$ 310.1529, found 310.1527.

***N*-Benzyl-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (27).** Pyrrolidinium trifluoroacetate **23b** (0.40 mmol) prepared according to the aforementioned procedure was dissolved in dry CH_2Cl_2 (4 mL) and was cooled to 0 °C. After addition of benzyl bromide (71.0 mL, 103 mg, 0.60 mmol) and *i*-Pr_2NEt (420 mL, 310 mg, 2.40 mmol), stirring was continued overnight and the reaction mixture was allowed to warm to rt. Then CH_2Cl_2 (15 mL) and H_2O (15 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and filtered. Evaporation to dryness followed by column chromatography (P/EA = 3:1 as eluent) yielded 68.0 mg (0.28 mmol, 70%) of the desired product as colorless crystals: R_f = 0.27 (P/EA = 3:1); mp 77 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.59 (dd, ^2J = 12.8, ^3J = 5.8 Hz, 1 H), 1.87−2.02 (m, 2 H), 2.31 (ddd, ^2J = 12.9, ^3J = 8.9, ^3J = 3.9 Hz, 1 H), 2.65 (ddd, ^2J = 11.3, ^3J = 9.7, ^3J = 5.8 Hz, 1 H), 2.98 (virt. q, $^3J \cong$ 7.4 Hz, 1 H), 3.10−3.15 (m, 2 H), 3.40 (d, ^2J = 13.4 Hz, 1 H), 3.87 (d, ^2J = 13.4 Hz, 1 H), 4.18 (d, ^2J = 10.0 Hz, 1 H), 4.25 (d, ^2J = 10.0 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 26.2 (CH_2), 28.9 (CH_2), 32.6 (CH), 42.8 (CH), 52.4 (CH_2), 53.3 (CH_2), 71.3 (C), 72.6 (CH_2), 127.3 (CH), 128.3 (CH), 128.5 (CH), 138.6 (C), 179.2 (C); HRMS (EI) calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1261.

***N*-*p*-Toluenesulfonyl-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (28).** Pyrrolidinium trifluoroacetate **23b** (1.00 mmol) prepared according to the aforementioned procedure was dissolved in dry CH_2Cl_2 (8 mL) and cooled to 0 °C. A solution of *p*-toluenesulfonic acid chloride (229 mg, 1.20 mmol) in CH_2Cl_2 (5 mL) and NEt_3 (0.83 mL, 607 mg, 6.00 mmol) were added simultaneously at this temperature. Stirring was continued overnight, and the reaction mixture was allowed to warm to rt. Then CH_2Cl_2 (30 mL) and H_2O (30 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and filtered. Evaporation to dryness followed by column chromatography (P/EA = 2:1 → P/EA = 1:1 as eluent) yielded 236 mg of a crystalline substance consisting of 218 mg (0.71 mmol, 71%) of the desired tosylate **28** and 18.0 mg (0.07 mmol, 7%) of trifluoroacetate **29**. An analytical sample of tosylate **28** was prepared by repeated column chromatography giving the desired product as colorless crystals: R_f = 0.21 (P/EA = 2:1); mp 113 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.75 (dd, ^2J = 13.2, ^3J = 6.1 Hz, 1 H), 1.95−2.06 (m, 2 H), 2.22 (ddd, ^2J = 12.9, ^3J = 8.5, ^3J = 3.2 Hz, 1 H), 2.45 (s, 3 H), 2.94 (ddd, ^3J = 10.0, ^3J = 3.2, ^4J = 1.1 Hz, 1 H), 3.10 (virt. q, $^3J \cong$ 7.8 Hz, 1 H), 3.56−3.69 (m, 2 H), 4.19 (d, ^2J = 9.4 Hz, 1 H), 5.05 (d, ^2J = 9.4 Hz, 1 H), 7.35 (d, ^3J = 8.3 Hz, 2 H), 7.73 (d, ^3J = 8.3 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.6 (CH_3), 25.7 (CH_2), 27.7 (CH_2), 37.3 (CH), 45.0 (CH), 50.0 (CH_2), 69.3 (C), 72.9 (CH_2), 127.5 (CH), 130.1 (CH), 135.8 (C), 144.6 (C), 177.5 (C); HRMS (EI) calcd for $C_{15}H_{17}NO_4S$ 307.0878, found 307.0875. ***N*-Trifluoroacetyl-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (29)**: R_f = 0.23 (P/EA = 2:1); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.98−2.07 (m, 1 H), 2.26 (ddd, ^2J = 13.1, ^3J = 9.9, ^3J = 6.1 Hz, 1 H), 2.35−2.49 (m, 2 H), 3.02−3.09 (m, 1 H), 3.21 (ddd, ^3J = 9.9, ^3J = 4.2, ^4J = 1.1 Hz, 1 H), 3.82−3.89 (m, 1 H), 4.02−4.09 (m, 1 H), 4.21 (d, ^2J = 9.1 Hz, 1 H), 4.76 (d, ^2J = 9.1 Hz, 1 H).

***N*-Phenylcarbamoyl-2-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (30).** Pyrrolidinium trifluoroacetate **23b** (0.40 mmol) prepared according to the aforementioned procedure was dissolved in dry CH_2Cl_2 (4 mL) and was cooled to 0 °C. After addition of phenyl isocyanate (65.0 mL, 71.0 mg, 0.60 mmol) and NEt_3 (333 mL, 243 mg, 2.40 mmol), stirring was continued overnight and the reaction mixture was allowed to warm to rt. Then CH_2Cl_2 (15 mL) and H_2O (15 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and filtered. Evaporation to dryness followed by column chromatography (P/EA = 1:1 as eluent) yielded 89.0 mg (0.33 mmol, 82%) of the desired product as colorless crystals: R_f = 0.25 (P/EA = 1:1); mp 164 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.94−2.02 (m, 1 H), 2.15−2.33 (m, 2 H), 2.39 (ddd, ^2J = 12.8, ^3J = 8.4, ^3J = 3.3 Hz, 1 H), 3.07 (virt q, $^3J \cong$ 7.9 Hz, 1 H), 3.22 (ddd, ^3J = 9.8, ^3J = 3.3, ^4J = 1.2 Hz, 1 H), 3.73−3.84 (m, 2 H), 4.10 (d, ^2J = 8.6 Hz, 1 H), 4.92 (d, ^2J = 8.6 Hz, 1 H), 6.41 (br s, 1 H), 7.07 (virt t, $^3J \cong$ 7.3 Hz, 1 H), 7.28−7.39 (m, 4 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 26.5 (CH_2), 28.9 (CH_2), 37.6 (CH), 42.2 (CH), 48.3 (CH_2), 69.3 (C), 72.3 (CH_2), 120.0 (CH), 123.8 (CH), 129.0

(CH), 138.0 (C), 154.1 (C), 178.2 (C); HRMS (EI) calcd for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1155.

***N*-Benzoyl-1-hydroxymethyl-2-azabicyclo[3.2.0]heptane-7-carboxylic Acid Benzyl Amide (31).** Lactone **25** (179 mg, 0.70 mmol) was dissolved in dry THF (4 mL). After addition of benzylamine (153 μL, 150 mg, 1.40 mmol), stirring was continued for 15 h at rt. Evaporation to dryness followed by column chromatography (P/EA = 1:8 as eluent) gave 166 mg (0.46 mmol, 65%) of the desired product as colorless crystals: R_f = 0.25 (P/EA = 1:8); mp 175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (br s, 1 H), 1.77−1.89 (m, 2 H), 2.26−2.32 (m, 1 H), 2.72−2.78 (m, 1 H), 2.89 (virt. q, $^3J \cong$ 8.4 Hz, 1 H), 3.42 (virt t, $^3J \cong$ 9.2 Hz, 1 H), 3.63 (virt. td, $^2J \cong {}^3J \cong$ 11.2, $^3J \cong$ 6.0 Hz, 1 H), 3.69−3.72 (m, 1 H), 3.83 (d, ^2J = 11.7 Hz, 1 H), 4.02 (d, ^2J = 11.7 Hz, 1 H), 4.47 (dd, ^2J = 14.8, ^3J = 5.8 Hz, 1 H), 4.54 (dd, ^2J = 14.8, ^3J = 6.1 Hz, 1 H), 7.22−7.53 (m, 10 H), 8.69 (br s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 22.6 (CH_2), 32.9 (CH_2), 36.6 (CH), 43.5 (CH_2), 45.3 (CH), 54.0 (CH_2), 61.1 (CH_2), 71.1 (C), 127.0 (CH), 127.4 (CH), 127.8 (CH), 128.3 (CH), 128.5 (CH), 130.6 (CH), 136.3 (C), 139.1 (C), 169.9 (C), 171.1 (C); HRMS (EI) calcd for $C_{22}H_{24}N_2O_3 - H_2O$ 346.1681, found 346.1686.

***N*-Acetyl-1-hydroxymethyl-2-azabicyclo[3.2.0]heptane-7-carboxylic Acid Benzylamide (32).** Lactone **24** (178 mg, 0.91 mmol) was dissolved in THF (5 mL). After addition of benzylamine (199 μL, 195 mg, 1.82 mmol), stirring was continued for 7 h at rt. Evaporation to dryness followed by column chromatography (CH_2Cl_2/MeOH = 95:5 as eluent) gave 218 mg (0.72 mmol, 79%) of the desired product as a colorless oil: R_f = 0.28 (CH_2Cl_2/MeOH = 90/10); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.76 (ddd, ^2J = 12.7, ^3J = 9.3, 3.6 Hz, 1 H), 1.84−1.94 (m, 1 H), 2.11 (s, 3 H), 2.22−2.31 (m, 1 H), 2.64−2.72 (m, 1 H), 2.80−2.88 (m, 1 H), 3.16 (virt. t, $^3J \cong$ 8.7 Hz, 1 H), 3.53−3.60 (m, 1 H), 3.67 (d, ^2J = 11.6 Hz, 1 H), 3.78 (ddd, ^2J = 10.8, ^3J = 7.8, 3.5 Hz, 1 H), 3.95 (d, ^2J = 11.6 Hz, 1 H), 4.40−4.50 (m, 2 H), 7.21−7.35 (m, 5 H), 8.10 (br. s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 22.6 (CH_2), 23.5 (CH_3), 31.5 (CH_2), 37.2 (CH), 43.5 (CH_2), 45.2 (CH), 51.3 (CH_2), 62.0 (CH_2), 70.7 (C), 127.1 (CH), 127.8 (CH), 128.5 (CH), 138.9 (C), 170.2 (C), 171.0 (C); HRMS (EI) calcd for $C_{17}H_{22}N_2O_3$ 302.1631, found 302.1631.

1-Hydroxymethyl-7-isopropylcarbamoyl-2-azabicyclo-[3.2.0]heptane-2-carboxylic Acid *tert*-Butyl Ester (33). Lactone **15** (127 mg, 0.50 mmol) was dissolved in THF (4 mL) and was cooled to 0 °C. After addition of isopropylamine (214 μL, 148 mg, 2.50 mmol), stirring was continued for 7 d and the reaction mixture was slowly warmed to rt. Evaporation to dryness followed by column chromatography (P/EA = 1:1 → 1:2 as eluent) gave 118 mg (0.38 mmol, 76%) of the desired product as colorless crystals: R_f = 0.29 (P/EA = 1:2); mp 133−135 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.14 (d, ^3J = 6.7 Hz, 3 H), 1.18 (d, ^3J = 6.6 Hz, 3 H), 1.48 (s, 9 H), 1.65−1.79 (m, 2 H), 2.02−2.12 (m, 1 H), 2.21−2.72 (br. s, 1 H), 2.56−2.64 (m, 1 H), 2.74−2.91 (m, 1 H), 2.97 (virt. t, $^3J \cong$ 8.3 Hz, 1 H), 3.44−3.51 (m, 1 H), 3.60−3.80 (m, 2 H), 3.80−3.98 (m, 1 H), 4.03 (q, ^3J = 6.6 Hz, 0.5 H), 4.07 (q, ^3J = 6.7 Hz, 0.5 H), 7.08 (br. s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 22.1 (CH_2), 22.5/22.6 (CH_3), 28.4 (CH_3), 30.2 (CH_2), 38.1 (CH), 41.4 (CH), 45.6 (CH), 49.4 (CH_2), 63.1 (CH_2), 69.6 (C), 80.5 (C), 155.3 (C), 170.3/170.5 (C); HRMS (EI) calcd for $C_{16}H_{28}N_2O_4 - H_2O$ 294.1943, found 294.1947. Anal. Calcd for $C_{16}H_{28}N_2O_4$ (312.40): C, 61.51; H, 9.03; N, 8.97. Found: C, 61.26; H, 9.17; N, 8.93.

7-Cyclohexylcarbamoyl-1-hydroxymethyl-2-azabicyclo-[3.2.0]heptane-2-carboxylic Acid *tert*-Butyl Ester (34). Lactone **15** (70.9 mg, 0.28 mmol) was dissolved in EtOH (3 mL). After addition of cyclohexylamine (48.0 μL, 41.7 mg, 0.42 mmol), stirring was continued for 18 h at rt. Evaporation to dryness followed by column chromatography (P/EA = 1:1 as eluent) gave 66.0 mg (0.19 mmol, 67%) of the desired product as colorless crystals: R_f = 0.25 (P/EA = 1:1); mp 158−160 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.12−1.42 (m, 5 H), 1.47 (s, 9 H), 1.51−1.62 (m, 1 H), 1.62−1.97 (m, 6 H), 2.03−2.12 (m, 1 H), 2.49−2.68 (m, 1 H), 2.72−2.91 (m, 1 H), 2.98 (virt. t, $^3J \cong$ 8.3 Hz, 1 H), 3.42−3.49 (m, 1 H), 3.57−3.82 (m, 3 H), 3.83−4.00 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 22.2 (CH_2), 24.5 (CH_2), 25.6 (CH_2), 28.5 (CH_3), 30.3 (CH_2), 32.8 (CH_2), 38.1 (CH), 45.7 (CH), 48.1 (CH), 49.4 (CH_2), 63.1 (CH_2), 69.7 (C), 80.5 (C), 155.2 (C), 170.2 (C); HRMS (EI) calcd for $C_{19}H_{32}N_2O_4 - H_2O$ 334.2257, found 334.2255. Anal. Calcd for $C_{19}H_{32}N_2O_4$ (352.47): C, 64.74; H, 9.15; N, 7.95. Found: C, 64.64; H, 9.40; N, 7.95.

7-Butylcarbamoyl-1-hydroxymethyl-2-azabicyclo[3.2.0]-heptane-2-carboxylic Acid *tert*-Butyl Ester (35). Lactone **15** (70.9 mg, 0.28 mmol) was dissolved in EtOH (3 mL). After addition of butylamine (41.5 μL, 30.7 mg, 0.42 mmol), stirring was continued for 15 h at rt. Evaporation to dryness followed by column chromatography (P/EA = 1:1 as eluent) gave 82.0 mg (0.25 mmol, 90%) of the desired product as colorless crystals: R_f = 0.24 (P/EA = 1:1); mp 68 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.91 (t, ^3J = 7.4 Hz, 3 H), 1.35 (virt hext, $^3J \cong$ 7.4 Hz, 2 H), 1.41−1.54 (m, 11 H), 1.63−1.77 (m, 2 H), 2.05−2.12 (m, 1 H), 2.48−2.69 (m, 1 H), 2.70−2.92 (m, 1 H), 2.99 (virt t, $^3J \cong$ 8.3 Hz, 1 H), 3.15−3.32 (m, 2 H), 3.41−3.47 (m, 1 H), 3.56−3.79 (m, 2 H), 3.80−4.03 (m, 1 H), 7.32 (br. s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.7 (CH_3), 20.1 (CH_2), 22.3 (CH_2), 28.4 (CH_3), 30.4 (CH_2), 31.5 (CH_2), 38.0 (CH), 39.3 (CH_2), 45.5 (CH), 49.5 (CH_2), 63.0 (CH_2), 69.6 (C), 80.5 (C), 155.2 (C), 171.2 (C); HRMS (EI) calcd for $C_{17}H_{30}N_2O_4 - H_2O$ 308.2100, found 308.2101. Anal. Calcd for $C_{17}H_{30}N_2O_4$ (326.43): C, 62.55; H, 9.26; N, 8.58. Found: C, 62.56; H, 9.39; N, 8.47.

1-Hydroxymethyl-7-(pyrrolidine-1-carbonyl)-2-azabicyclo[3.2.0]heptane-2-carboxylic Acid *tert*-Butyl Ester (36). Lactone **15** (127 mg, 0.50 mmol) was dissolved in 2-propanol (5 mL). After addition of pyrrolidine (62.6 μL, 53.3 mg, 0.75 mmol), the reaction mixture was refluxed for 17 h. Evaporation to dryness followed by column chromatography (P/EA = 1:3 as eluent) gave 103 mg (0.32 mmol, 63%) of the desired product as colorless crystals: R_f = 0.21 (P/EA = 1:3); mp 103 °C; ^{1}H NMR (360 MHz, DMSO-d_6, T = 280 K, 298 K, 353 K) no data interpretation possible due to signal broadening by rotamers; ^{13}C NMR (90 MHz, DMSO-d_6, 353 K) δ 23.3 (CH_2), 23.5 (CH_2), 25.2 (CH_2), 27.9 (CH_3), 28.1 (CH_2), 43.1 (CH), 45.0 (CH_2), 45.6 (CH_2), 48.0 (CH_2), 60.5 (CH_2), 69.7 (C), 78.3 (C), 152.8 (C), 169.7 (C); HRMS (EI) calcd for $C_{17}H_{28}N_2O_4$ 324.2049, found 324.2039. Anal. Calcd for $C_{17}H_{28}N_2O_4$ (324.42): C, 62.94; H, 8.70; N, 8.64. Found: C, 62.65; H, 8.83; N, 8.46.

7-(Ethoxycarbonylmethylcarbamoyl)-1-hydroxymethyl-2-azabicyclo[3.2.0]heptane-2-carboxylic Acid *tert*-Butyl Ester (37). Lactone **15** (127 mg, 0.50 mmol) was dissolved in EtOH (5 mL). After addition of glycine ethyl ester hydrochloride (105 mg, 0.75 mmol) and NEt_3 (139 μL, 101 mg, 1.00 mmol), the reaction mixture was refluxed for 20 h. Evaporation to dryness followed by column chromatography (P/EA = 2:1 → 1:1 as eluent) gave 131 mg (0.37 mmol, 74%) of the desired product as a colorless oil: R_f = 0.22 (P/EA = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, ^3J = 7.2 Hz, 3 H), 1.46 (s, 9 H), 1.61−1.74 (m, 1 H), 1.76−1.82 (m, 1 H), 2.09−2.20 (m, 1 H), 2.64−2.70 (m, 1 H), 2.87−3.02 (m, 1 H), 3.08 (virt. t, $^3J \cong$ 8.9 Hz, 1 H), 3.33−3.44 (m, 2 H), 3.72−3.83 (m, 2 H), 4.22 (q, ^3J = 7.2 Hz, 2 H), 4.27 (d, ^2J = 11.8 Hz, 1 H), 4.34 (dd, ^2J = 17.7 Hz, ^3J = 6.4 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.8 (CH_2), 28.5 (CH_3), 31.0 (CH_2), 37.8 (CH), 41.2 (CH_2), 44.5 (CH), 49.3 (CH_2), 61.7 (CH_2), 62.5 (CH_2), 70.1 (C), 80.5 (C), 155.1 (C), 171.6 (C), 172.4 (C); HRMS (EI) calcd for $C_{17}H_{28}N_2O_6 - H_2O$ 338.1842, found 338.1837.

{[*N*-(*N*-*tert*-Butoxycarbonylaminoacetyl)-1-hydroxymethyl-2-azabicyclo[3.2.0]heptane-7-carbonyl]amino}-acetic Acid Ethyl Ester (38). Lactone **26** (49.7 mg, 0.16 mmol) was dissolved in EtOH (4 mL). After addition of glycine ethyl ester hydrochloride (33.4 mg, 0.24 mmol) and NEt_3 (44.4 μL, 32.4 mg, 0.32 mmol), the reaction mixture was refluxed for 20 h. Evaporation to dryness followed by column chromatography (EE → EE/MeOH = 95:5 as eluent) gave 46.0 mg (0.11 mmol, 69%) of the desired product as colorless oil: R_f = 0.29 (EE/MeOH = 95:5); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.28 (t, ^3J = 7.0 Hz, 3 H), 1.44 (s, 9 H), 1.70−1.77 (m, 1 H), 1.84−2.00

(m, 1 H), 2.29−2.43 (m, 1 H), 2.66−2.75 (m, 1 H), 2.87−3.00 (m, 1 H), 3.16 (virt t, $^3J \cong 9.1$ Hz, 1 H), 3.41−3.49 (m, 1 H), 3.53 (d, $^2J = 11.8$ Hz, 1 H), 3.68−3.82 (m, 2 H), 3.87 (dd, $^2J = 17.3$, $^3J = 4.2$ Hz, 1 H), 3.99 (dd, $^2J = 17.3$, $^3J = 3.9$ Hz, 1 H), 4.18−4.26 (m, 3 H), 4.36 (dd, $^2J = 17.9$, $^3J = 6.8$ Hz, 1 H), 5.33 (br. s, 1 H), 8.37 (br. s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.1 (CH_3), 23.2 (CH_2), 28.3 (CH_3), 32.1 (CH_2), 36.8 (CH), 41.2 (CH_2), 43.6 (CH_2), 44.3 (CH), 48.9 (CH_2), 61.3 (CH_2), 61.7 (CH_2), 71.6 (C), 80.0 (C), 155.7 (C), 167.8 (C), 171.6 (C), 171.9 (C); HRMS (EI) calcd for $C_{19}H_{31}N_3O_7$ 413.2162, found 413.2155.

X-ray Crystallography. General Remarks. Crystals suitable for diffraction experiments were selected in F06206R oil and used for intensity data collection on a Nonius DIP2020 diffractometer with sealed-tube anode, employing graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods and refined with standard difference Fourier techniques.[32] All non-hydrogen atoms of the asymmetric unit were refined with anisotropic thermal displacement parameters. All hydrogen atoms were found in the difference Fourier map and refined freely with individual isotropic thermal displacement parameters. Full-matrix least-squares refinements were carried out by minimizing $\Sigma w(F_o^2 - F_c^2)^2$ with SHELXL-97 weighting scheme. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-282838 (**17**) and -282837 (**31**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

Compound 17: $C_{13}H_{19}NO_4$, $M_r = 253.3$ g mol^{-1}, colorless fragment, size 0.50 mm × 0.20 mm × 0.10 mm, monoclinic, space group *C*2/*c*, $a = 20.4347(16)$ Å, $b = 6.6251(6)$ Å, $c = 19.3921(14)$ Å, $\alpha = 90°$, $\beta = 96.979(7)°$, $\gamma = 90°$, $V = 2605.9(4)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.291$ g cm^{-3}, μ(Mo Kα) = 0.083 mm^{-1}, $F(000) = 1088$, $T = 173$ K. The final model parameters were refined to wR2 = 0.1266 based on all data, R1 = 0.0426 based on data with $I \geq 2\sigma(I)$, GOF = 1.146, and min/max residual electron density −0.182/−0.194 e Å^{-3}.

Compound 31: $C_{22.5}H_{25}ClN_2O_3$, $M_r = 406.9$ g mol^{-1}, colorless fragment, size 0.40 mm × 0.40 mm × 0.35 mm, orthorhombic, space group *Pbcn*, $a = 32.3497(6)$ Å, $b = 9.91170(10)$ Å, $c = 12.2514(2)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 3928.30(10)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.376$ g cm^{-3}, μ(Mo Kα) = 0.083 mm^{-1}, $F(000) = 1720$, $T = 173$ K. The compound crystallizes with half a dichloromethane molecule in the unit cell. The final model parameters were refined to *wR2* = 0.0948 based on all data, R1 = 0.0371 based on data with $I \geq 2\sigma(I)$, GOF = 1.028, and min/max residual electron density −0.256/0.193 e Å^{-3}.

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Supporting Information Available: General experimental methods, IR and MS data of all compounds, NOESY NMR data for selected compounds, and ^{13}C NMR spectra of all compounds. X-ray crystallographic files and ORTEP figures for compounds **17** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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