JOC The Journal of Organic Chemistry

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An Intramolecular [2 + 2] Photocycloaddition Approach to Conformationally Restricted Bis-Pyrrolidines

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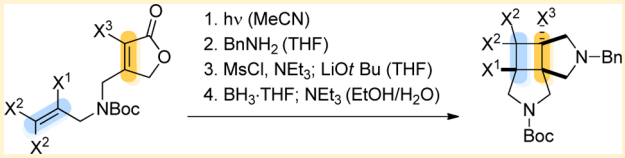
Supporting Information

ABSTRACT: With *N*-Boc-protected 4-(allylaminomethyl)-2-(5*H*)furanones as starting materials, a photochemical approach is presented to give 3,9-diazatricyclo[5.3.0.0^{1,5}]decanes as conformationally restricted bis-pyrrolidines. The products are orthogonally protected at the two nitrogen atoms and exhibit, depending on the substitution pattern at positions C5, C6, and C7, latent C_2 symmetry. When the furanones had a phenyl group at the 3-position (X^3), alternative photochemical pathways were observed.



INTRODUCTION

Four-membered alicyclics, most notably cyclobutanes[1] and oxetanes,[2] combine the rigidity of a small-ring compound with—in comparison to three-membered rings—a remarkable stability toward ring-opening reactions. In searches for kinetically stable, conformationally restricted analogues of known scaffolds, the introduction of a four-membered ring is frequently considered.[3] In this context, photochemical [2 + 2] photocycloaddition reactions play a crucial role in the construction of conformationally restricted molecules, as they allow for the formation of cyclobutanes and oxetanes in a single reaction step. Cyclic α,β-unsaturated carbonyl compounds are key components in the most important [2 + 2] photocycloaddition approach toward cyclobutane products.[4] They can be readily excited at long wavelength and undergo rapid intersystem crossing (ISC) to relatively long-lived triplet states,[5] which can be intercepted inter- or intramolecularly by another olefin to provide the desired cyclobutane products. When considering potential conformationally restricted variants[6] of the pharmacologically relevant[7] bis-pyrrolidines **1** and **2**, we noted that a cyclobutane backbone connecting the 4,9-position of the spiro skeleton would result in the 3,9-diazatricyclo[5.3.0.0^{1,5}]decane skeleton **A**, as depicted in Figure 1, which in turn would position the basic nitrogen atoms in a defined spatial relationship.[8]

If the substituents X^1 and X^3 are identical, the molecules will exhibit latent C_2 symmetry, readily manifested by deprotection of the nitrogen atoms. Although there have been a few scattered reports on the synthesis of molecules with the 3,9-diazatricyclo-[5.3.0.0^{1,5}]decane skeleton **A**,[9] a general approach has, to the best of our knowledge, not yet been reported. Since previous studies have shown[10] that lactones of type **B** can be generated by intramolecular [2 + 2] photocycloaddition reactions of appropriately substituted 4-aminomethyl-2(5*H*)-furanones,[11,12] we considered them as potential precursors of the desired

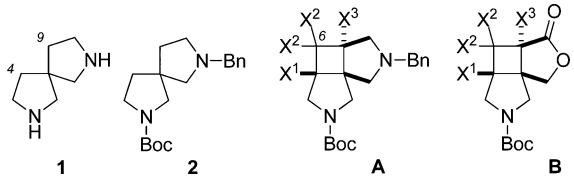


Figure 1. Structures of the parent 2,7-diazaspiro[4.4]nonane (**1**), its protected analogue **2**, and related generic pyrrolidine derivatives **A** and **B**.

products **A**. In this report, we describe the synthesis of both latently symmetric ($X^1 = X^3$) and nonsymmetric ($X^1 \neq X^3$) 3,9-diazatricyclo[5.3.0.0^{1,5}]decanes employing an intramolecular [2 + 2] photocycloaddition as the key step. We discuss possible side reactions and show that the chosen protective groups at the nitrogen atoms allow for orthogonal deprotection in further synthetic transformations.

RESULTS

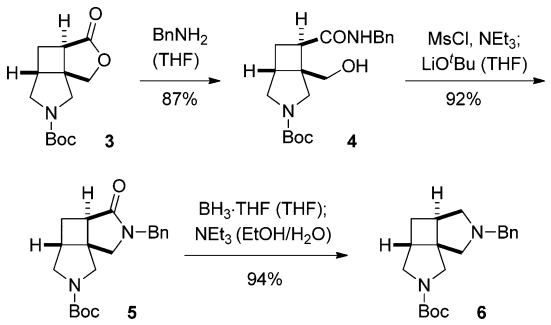
Parent and Nonsymmetric 3,9-Diazatricyclo-[5.3.0.0^{1,5}]decanes. Before performing an extensive study on the [2 + 2] photocycloaddition route to compounds of type **B**, we screened possible reaction conditions to convert compounds of type **B** into the target compounds **A**. Lactone ring opening of the previously reported *tert*-butyloxycarbonyl (Boc) protected 3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (**3**)[10a] was performed with benzylamine. It was found that the ring opening works best in this case upon heating to reflux in THF solution, and it delivered γ-hydroxyamide **4** in 87% yield.[13] The cyclization to lactam **5** was preferably performed in a one-pot procedure by initial mesylation of the free hydroxy

Received: June 11, 2014
Published: July 7, 2014

   dx.doi.org/10.1021/jo501302f | J. Org. Chem. 2014, 79, 7152–7161

group with methanesulfonyl chloride (MsCl) and subsequent treatment with LiO^{t}Bu to induce the nucleophilic substitution.[14] Selective lactam reduction with borane−THF complex delivered after workup the doubly protected 3,9-diazatricyclo-[5.3.0.0^{1,5}]decane as the corresponding ammonium salt, from which the free base **6** was liberated with triethylamine (Scheme 1).[15] It was possible to perform the reduction of amide **4** prior

Scheme 1. Conversion of Photocycloaddition Product 3 into the Orthogonally Protected, Conformationally Restricted Bis-Pyrrolidine 6



to the cyclization, but the attempted conversion of the resulting δ-amino alcohol into product **6** could not be performed in this case (vide infra).

The synthesis of product **6** was readily performed in the lab on a multigram scale (up to 27 g of product). Compound **5** could be easily separated into its enantiomers by chiral preparative chiral HPLC (see the Experimental Section). The crystal structure of the 1*S*,5*S*,7*S* enantiomer, which is dextrorotatory, is depicted in Figure 2. It nicely illustrates the

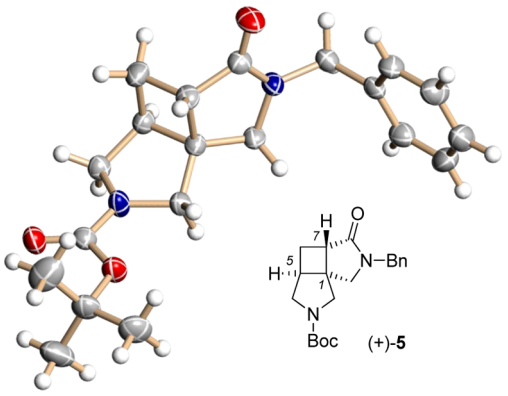
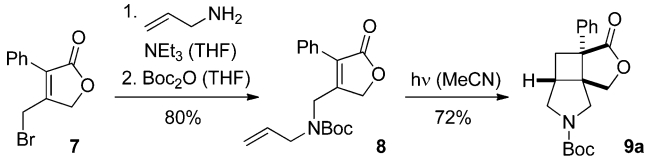


Figure 2. Crystal structure of the enantiomerically pure product (+)-**5**.

rigidity of the molecular skeleton due to the almost planar cyclobutane ring. Bis-pyrrolidine **6** turned out to be slightly less basic than the less restricted compound **2**, most likely because the *N*-benzylpyrrolidine part in **6** adopts an *endo* conformation ("boat shaped") relative to the cyclobutane ring. The pK_a of the corresponding ammonium ion was determined to be 8.2 for **6**, in comparison to 8.4 for **2**.

Alkyl bromide **7** was required as a starting material for the synthesis of 7-phenyl-substituted 3-aza-9-oxatricyclo[5.3.0.0^{1,5}]-decan-8-one (**9a**). Although the compound has been previously prepared by 2-fold Wohl−Ziegler bromination of 3-methyl-2-phenylcrotonic acid and subsequent ring closure by nucleophilic displacement of a bromide leaving group,[16] we found it more convenient to synthesize it from the respective alcohol (see the Supporting Information) by bromodehydroxylation with PBr_3.[10b] With bromide **7** as the starting material, the synthesis of tricyclic lactone was readily accomplished via the *N*-Boc-protected 4-(allylaminomethyl)-2(5*H*)-furanone **8** (Scheme 2). Irradiation of the latter compound at λ 300 nm

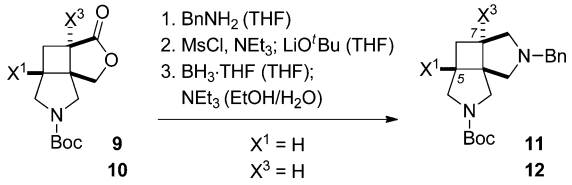
Scheme 2. Synthesis of Lactone 9a by Substitution of Bromide 7 and Subsequent Intramolecular [2 + 2] Photocycloaddition



furnished the desired product **9a** after an extended irradiation period of 5 days. Attempts to perform the reaction at shorter wavelength (λ 254 nm) resulted in complete loss of starting material after 2 h of irradiation time. Despite the fact that the yield of product **9a** was good, a second product was isolated in minor amounts, which could not be fully characterized but was assigned a structure on the basis of X-ray crystallographic evidence (see the Supporting Information for further details).

Other 3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-ones with substituents at the 7-position (X^3 = Ph, Me, F; **9** in Table 1) and at

Table 1. Conversion of Lactones 9 and 10 into Orthogonally Protected, Conformationally Restricted Bis-Pyrrolidines 11 and 12



entry	X^1	X^3	substrate	product	yield[a] (%)
1	H	Ph	**9a**	**11a**	54
2[b]	H	Me	**9b**	**11b**	52
3[b]	H	F	**9c**	**11c**	52
4	Ph	H	**10a**	**12a**	62
5	Me	H	**10b**	**12b**	51

[a]Total yield over three reaction steps. Specific reaction conditions for the individual steps: (1) $BnNH_2$ (1.05 equiv) THF, reflux, 14 h; (2) MsCl (1.4 equiv), NEt_3 (1.7 equiv), THF, −78 → 0 °C, 2 h, then −50 °C, LiO^{t}Bu (1 M in THF, 2.8 equiv), 25 min; (3) BH_3·THF (1 M in THF, 3.3 equiv), 0 °C → room temperature, 14 h, then NEt_3 (5.85 equiv), EtOH, H_2O, reflux, 90 min. [b]The ring opening with benzylamine was performed for 72 h at ambient temperature.

the 5-position (X^1 = Ph, Me; **10** in Table 1) have been previously described.[10] In the present study, it was shown that their conversion to the conformationally restricted bis-pyrrolidines **11** and **12** could be performed in full analogy to the previously described conversion **3** → **6**. However, the intermediate products for the reaction sequence were in these cases not fully characterized but immediately taken into the next reaction step. The yields provided in Table 1 refer to overall yields as recorded for the complete sequence, and they vary between 51% and 62%.

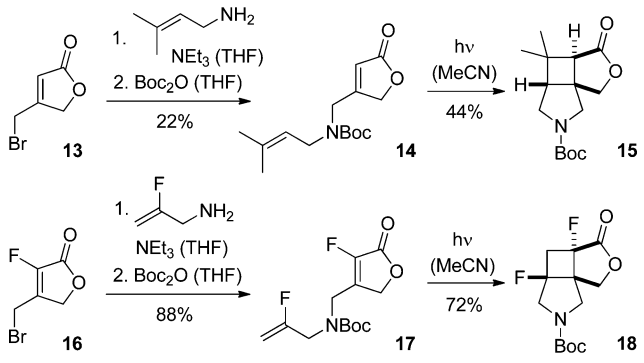
dx.doi.org/10.1021/jo501302f | J. Org. Chem. 2014, 79, 7152−7161

In contrast to the conversion **4** → **6**, for which a reduction/cyclization protocol with 1,1′-carbonylimidazole (CDI) as the reagent had given a product mixture, it was possible for the ring-opening products of lactones **9a,b** to perform the reduction (BH_3·THF, then NEt_3) prior to the cyclization with CDI in CH_2Cl_2. Apparently, the additional substituent at the 7-position favors the nucleophilic displacement of the activated alcohol by the amine and disfavors the formation of the cyclic carbamate. The two-step procedure proceeded in nearly quantitative yield and is a viable alternative to the cyclization/reduction route depicted in Table 1.

Compounds **11** showed a significantly reduced basicity in comparison to the parent compound **6**. The pK_a decrease for the ammonium salts of **11a** (pK_a = 6.7) and **11b** (pK_a = 7.7) is mainly due to the neopentylic character[17] of the amines by introduction of the angular phenyl (**11a**) and methyl (**11b**) substituents at carbon atom C7. The even further reduced basicity of the fluoro compound **11c** (pK_a = 5.7) is testimony to the strongly inductive electron withdrawing power of the fluorine substituent. In addition, the fluorine adopts a gauche position relative to the nitrogen atom N9 in the adjacent boat-shaped pyrrolidine ring, which is ideal for stabilization of the corresponding ammonium ion.[18]

C_2-Symmetric 3,9-Diazatricyclo[5.3.0.0^{1,5}]decanes. Diamines of general structure **B** (Figure 1) with identical substituents X^1 and X^3 exhibit a latent C_2 symmetry, which is only disturbed by the nonsymmetric orthogonal amine protection at nitrogen atoms N3 and N9. Product **6** represents the parent member of this compound class, while other members show substitution at positions C5, C7 (X^1 and X^3) and C6 (X^2). According to our general strategy for the synthesis of 3,9-diazatricyclo[5.3.0.0^{1,5}]decanes, substituents at C6 were introduced via the respective allylic amine. With the known[10b] bromide **13** as the starting material, nucleophilic substitution by 3-methylbut-2-enylamine and subsequent Boc protection delivered the photocycloaddition precursor **14**, which gave upon irradiation (λ 254 nm) in acetonitrile the desired lactone product **15** (Scheme 3).

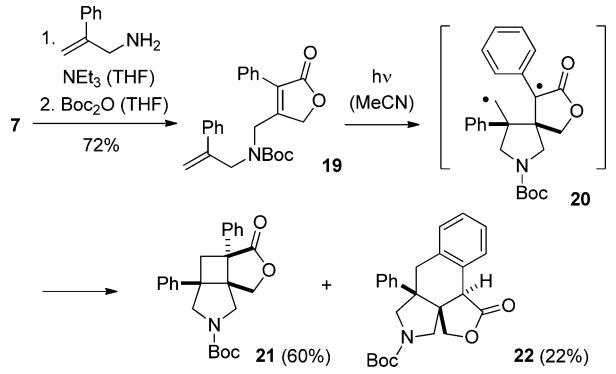
Scheme 3. Synthesis of Lactones 15 and 18 by Intramolecular [2 + 2] Photocycloaddition of Substrates 14 and 17



For the introduction of substituents at C5, C7 in the final target, the 2(5*H*)-furanone component and the tethered olefin must carry an identical substituent, the 2(5*H*)-furanone at the α-position and the olefin at the internal carbon atom. In order to access the difluorosubstituted product **18**, it was therefore necessary to start the synthesis with the known[10b] α-fluoro-2(5*H*)furanone **16**. Nucleophilic displacement with 2-fluoroprop-2-enylamine[10a] was facile and delivered after Boc protection the desired difluorinated substrate **17**, the [2 + 2] photocycloaddition (λ 254 nm) of which generated cleanly the desired product **18** as a single diastereoisomer.

Similar to the synthesis of the difluorinated product **18**, the diphenylated product **21** (Scheme 4) was synthesized from the

Scheme 4. Formation of the [2 + 2] Photocycloaddition Product 21 and of the Byproduct 22 upon Irradiation of Lactone 19 at λ 300 nm

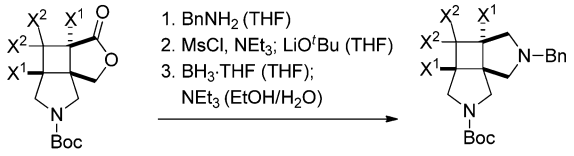


respective α-substituted 2(5*H*)-furanone **7** (Scheme 2). Aminodebromination with 2-phenylprop-2-enylamine gave after Boc protection the desired 2(5*H*)-furanone **19**. As was already observed with the α-phenyl-substituted substrate **8**, the photophysical and photochemical behavior of these compounds was different from that of the other *N*-Boc-4-(allylamino)-2(5*H*)-furanones. They exhibit an intense absorption ($\varepsilon \cong$ 9500 M^{-1} cm^{-1}) at ca. 250 nm, which is weak for the other 2(5*H*)-furanones, and they decomposed upon irradiation in acetonitrile at this wavelength (λ 254 nm). At longer wavelength (λ 300 nm) the desired [2 + 2] photocycloaddition was observed, and it proceeded within 6 h to completion in the case of substrate **19**. Two products could be cleanly isolated from the product mixture, the major product of which was the expected lactone **21**. On the basis of extensive NMR studies structure **22** was assigned to an isomeric byproduct, which was isolated in 22% yield. Mechanistically, the formation of this byproduct is straightforward, on the basis of the likely assumption that the photocycloaddition proceeds in the triplet manifold via 1,4-diradical intermediate **20**. Recombination of the radical centers after ISC leads to cyclobutane ring formation or alternatively attack at the aromatic ortho position to give a nonaromatic cyclohexadiene product, which undergoes rapid tautomerization to **22**. Remarkably, irradiation of substrate **19** generated a third product, which was more difficult to isolate than **21** and **22** and turned out to be unstable (see Supporting Information).

With substrates **15**, **18**, and **21** in hand, the transformation to the desired bis-pyrrolidines with latent C_2 symmetry was pursued. In addition, the previously reported[10] 3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one **23** was included in this series of experiments (Table 2). To our delight, the three-step sequence of lactone ring opening/lactam formation/reduction turned out to be general and could be applied nicely to the synthesis of products **24**–**27**. Yields varied between 43 and 79%. The ammonium salt of product **25** showed an extremely low pK_a value of 4.9, which can be explained by the presence of two electron-withdrawing fluorine substituents, while the basicitiy of product **24** (pK_a = 8.3) was expectedly found to

dx.doi.org/10.1021/jo501302f | J. Org. Chem. 2014, 79, 7152–7161

Table 2. Synthesis of Orthogonally Protected C_2-Symmetric 3,9-Diazatricyclo[5.3.0.0^{1,5}]decanes 24−27 from [2 + 2] Photocycloaddition Products



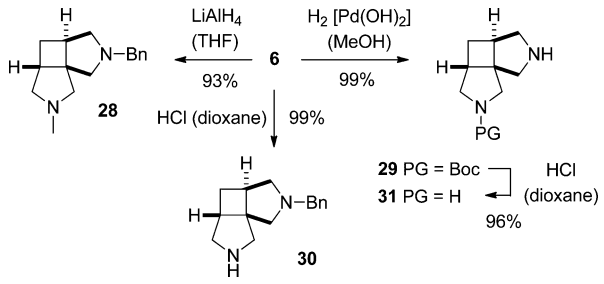
entry	X^1	X^2	substrate	product	yield[a] (%)
1	H	Me	**15**	**24**	43
2[b]	F	H	**18**	**25**	79
3[b]	Ph	H	**21**	**26**	56
4	Me	H	**23**	**27**	48

[a]Total yield over three reaction steps. Specific reaction conditions for the individual steps: (1) $BnNH_2$ (1.05 equiv) THF, reflux, 14 h; (2) MsCl (1.4 equiv), NEt_3 (1.7 equiv), THF, −78 → 0 °C, 2 h, then −50 °C, LiO^{t}Bu (1 M in THF, 2.8 equiv), 25 min; (3) BH_3·THF (1 M in THF, 3.3 equiv), 0 °C → room temperature, 14 h, then NEt_3 (5.85 equiv), EtOH, H_2O, reflux, 90 min. [b]The ring opening with benzylamine was performed for 72 h at ambient temperature.

be almost identical with that of the parent compound **6**. A single-crystal X-ray analysis of compound **25** (see the Supporting Information) confirmed the notion that the fluorine atom at the *N*-benzylpyrrolidine ring is positioned gauche to the basic nitrogen atom N9 (vide supra).

Further Functionalization of 3,9-Diazatricyclo-[5.3.0.0^{1,5}]decane 6. The known orthogonality of benzyl and Boc protecting groups allowed us to address the two amine positions separately. With the parent 3,9-diazatricyclo-[5.3.0.0^{1,5}]decane, i.e. compound **6**, as a model substrate, it was shown that complete reduction of the Boc group with an excess of lithium aluminum hydride led to the *N*-methyl derivative **28** (Scheme 5). With a first pK_a value of 9.2 for the

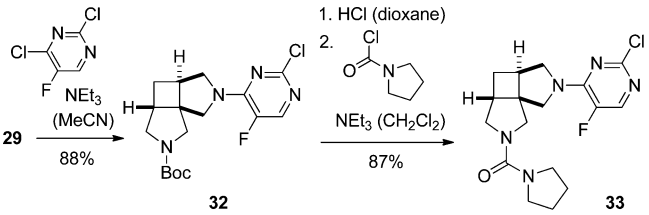
Scheme 5. Further Functionalization of Protected 3,9-Diazatricyclo[5.3.0.0^{1,5}]decane 6 Utilizing the Orthogonality of Its Protecting Groups



ammonium ion of **28**, the basicity of this compound is still significantly lower than that of *N*-methylpyrrolidine (pK_a = 10.5).[19] Selective deprotection of the benzyl group was achieved by hydrogenolysis of substrate **6** in the presence of Pearlman's catalyst to give the mono-Boc-protected diamine **29**. The Boc group was conveniently removed by stirring substrate **6** in a solution of hydrochloric acid in dioxane at room temperature to produce the monobenzylated diamine **30**. Eventually, the C_2-symmetric diamine **31** was available as its dihydrochloride upon deprotection of compound **29** with HCl in dioxane.

An example of an orthogonal disubstitution procedure is depicted in Scheme 6, which shows how the two amino groups

Scheme 6. Decoration of the Nitrogen Atoms in 3,9-Diazatricyclo[5.3.0.0^{1,5}]decane 29 by N-Substitution Reactions



can be selectively addressed and how the conformationally restricted bis-pyrrolidine skeleton can be decorated. For the decoration of the scaffold two pharmacologically relevant heterocyclic units (pyrimidine, pyrrolidine) were arbitrarily chosen. Nucleophilic displacement of the 4-chloro group in 2,4-dichloro-5-fluoropyrimidine was accomplished with mono-protected diamine **29** to give product **32** in high yields. After removal of the Boc group, the second amine nitrogen atom was acylated by a chloroformamide to provide urea **33**.

CONCLUSION

In summary, 10 members of a new class of rigid scaffolds have been prepared. They can be best described as conformationally restricted bis-pyrrolidines but also contain a conformationally restriced 3,7-diazabicyclo[3.3.1]nonane skeleton. Their cyclobutane core is established by an intramolecular 2(5*H*)-furanone [2 + 2] photocycloaddition, and the furanone-derived γ-lactone is transformed into a pyrrolidine by three further reaction steps. Except for 3-phenyl-2(5*H*)-furanones, the [2 + 2] photocycloaddition proceeds rapidly (0.5−18 h) and is amenable to scale-up (>20 g in a single batch). The two nitrogen atoms, which are orthogonally protected, can be addressed sequentially, and the new scaffolds therefore deliver a great number of opportunities for further decoration.

EXPERIMENTAL SECTION

General Methods. All reactions, sensitive to air or moisture, were carried out in flame-dried glassware under a positive pressure of argon using standard techniques. For the photoreactions, the compounds were dissolved in the corresponding solvent, degassed by purging with Ar in an ultrasonicator for 15 min, and irradiated in a merry-go-round reactor, equipped with 16 lamps emitting at λ 254 nm or at λ 300 nm.[20] Unless otherwise stated, the reactions were stopped when the starting material was fully consumed according to thin-layer chromatography (TLC) and/or LC-MS analysis. The solvent was then removed, and the residue was purified by column chromatography. Unless otherwise noted, only one reaction product could be isolated. Flash chromatography was performed on silica gel 60 (230−400 mesh) with the eluent mixtures given for the corresponding procedures. TLC was performed on silica-coated glass plates (silica gel 60 F_{254}). Compounds were detected by UV (λ 254 nm), CAM (cerium ammonium molybdate solution), or $KMnO_4$. ^{1}H and ^{13}C NMR spectra were recorded at 300 K unless otherwise indicated. Chemical shifts are reported relative to the solvent ($CHCl_3$, δ(^{1}H) 7.26 ppm, δ(^{13}C) 77.0 ppm; DMSO, δ(^{1}H) 2.50 ppm, δ(^{13}C) 39.5 ppm) as reference. Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm), peak shape (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal), coupling constant (Hz), and integration. ^{13}C NMR spectra are proton-decoupled. In some cases, two rotamers are detectable by NMR spectroscopy. When possible,

dx.doi.org/10.1021/jo501302f | J. Org. Chem. 2014, 79, 7152−7161

the NMR data of the major rotamer are given. Apparent multiplets which occur as a result of the accidental equality of coupling constants with those of magnetically nonequivalent protons are marked as virtual (virt). The relative configuration of the products and the multiplicity of the ^{13}C NMR signals were determined by two-dimensional NMR spectra (COSY, NOESY, HSQC, HMBC). HRMS data were recorded by electron spray ionization (ESI) on an ion trap mass spectrometer. The pK_a values were all measured by spectrophotometric (UV-metric) titration methods.[21]

***tert*-Butyl 7-(Benzylcarbamoyl)-1-(hydroxymethyl)-3-azabicyclo[3.2.0]heptane-3-carboxylate (4).** A mixture of the *N*-Boc derivative **3** (5.00 g, 19.7 mmol, 1.0 equiv) and benzylamine (2.24 mL, 20.5 mmol, 1.05 equiv) in dry THF (6.0 mL) was refluxed under argon for 14 h. Evaporation to dryness and purification of the crude product by column chromatography (heptane/EtOAc 1/3) afforded the desired product **4** as a white solid (6.17 g, 87%). Mp: 117−119 °C. R_f = 0.34 (heptane/EtOAc 1/3). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3485 (s, C−OH), 3298 (s, NH), 3024 (m), 1676 (vs, NH−C═O), 1645 (w), 1414 (m), 1365 (m), 1254 (s), 1174 (s), 732 (s), 697 (s). ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.28 (br. s, 1 H), 7.34−7.28 (m, 2 H), 7.27−7.18 (m, 3 H), 4.64 (t, J = 5.3 Hz, 1 H), 4.28 (dd, J = 15.1 Hz, J = 5.9 Hz, 1 H), 4.22 (dd, J = 15.1 Hz, J = 5.9 Hz, 1 H), 3.58 (br. s, 1 H), 3.48 (dd, J = 11.0 Hz, J = 4.6 Hz, 1 H), 3.45−3.43 (m, 1 H), 3.41 (dd, J = 11.4 Hz, J = 1.8 Hz, 1 H), 3.25 (br. s, 1 H), 3.16 (br. s, 1 H), 2.90 (t, J = 8.2 Hz, 1 H), 2.53−2.49 (m, 1 H), 2.47−2.42 (m, 1 H), 1.58 (dd, J = 11.3 Hz, J = 2.6 Hz, 1 H), 1.42 (s, 9 H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ (ppm) 171.3, 154.7, 140.1, 128.7, 127.8, 127.2, 78.8, 61.4, 53.3, 52.8, 43.4, 42.7, 40.6, 28.6, 24.3 (*one carbon atom not observed*). MS (EI, 70 eV): m/z (%) 361 (11) [(M + H)$^+$], 306 (100) [(M − C_4H_8)$^+$]. HRMS (ESI): calculated for $C_{20}H_{29}N_2O_4^+$ [(M + H)]$^+$ 361.2122, found 361.2122.

9-Benzyl-3-*tert*-butoxycarbonyl-3,9-diazatricyclo[5.3.0.0^{1,5}]-decan-8-one (5). To a solution of alcohol **4** (9.29 g, 25.3 mmol, 1.0 equiv) in dry THF (333 mL) at −78 °C were added methanesulfonyl chloride (2.76 mL, 35.4 mmol, 1.4 equiv) and then dropwise a solution of triethylamine (5.98 mL, 42.9 mmol, 1.7 equiv) in dry THF (18.5 mL). The cooling bath was removed, and the mixture was warmed to 0 °C within 30 min. After 2 h at 0 °C the mixture was recooled to −50 °C, lithium *tert*-butoxide (1 M in THF) (65.0 mL, 65.0 mmol, 2.8 equiv) was added, and the reaction mixture was stirred at 0 °C for 25 min. The reaction mixture was poured into ice−water and brine and extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and then filtered. Removal of the solvent under vacuum left a light yellow oil which was purified by column chromatography (heptane/EtOAc 1/1) to give the desired product **5** (7.90 g, 92%) as a white solid. Mp: 134−135 °C. R_f = 0.48 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2973 (s, C−H), 2867 (s, C−H), 1680 (vs, C═O), 1673 (vs), 1400 (s), 1474 (w), 1400 (vs), 1145 (m), 1131 (m), 877 (w). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.39−7.37 (m, 2 H), 7.33−7.26 (m, 3 H), 4.55 (d, J = 14.6 Hz, 1 H), 4.39 (d, J = 14.6 Hz, 1 H), 3.83 (d, J = 11.8 Hz, 1 H), 3.50 (d, J = 11.8 Hz, 1 H), 3.35 (d, J = 10.3 Hz, 1 H), 3.30 (d, J = 10.2 Hz, 1 H), 3.25 (dd, J = 12.0 Hz, J = 6.6 Hz, 1 H), 3.02 (d, J = 12.0 Hz, 1 H), 2.73 (dd, J = 9.3 Hz, J = 3.7 Hz, 1 H), 2.69−2.67 (m, 1 H), 2.19 (ddd, J = 12.5 Hz, J = 8.5 Hz, J = 3.7 Hz, 1 H), 2.02 (ddd, J = 12.5 Hz, J = 9.3 Hz, J = 6.2 Hz, 1 H), 1.47 (s, 9 H). $^{13}C\{^1H\}$ NMR (91 MHz, $CDCl_3$): δ (ppm) 179.1, 154.8, 137.3, 129.2, 128.1, 127.8, 79.2, 53.3, 52.3, 47.3, 46.4, 45.9, 42.8, 41.6, 28.6, 28.4. MS (EI, 70 EV): m/z (%) 343 (100) [(M + H)$^+$], 287 (13) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{20}H_{26}N_2O_3^+$ [(M)]$^+$ 342.1943, found 342.1952.

The enantiomer separation of 9-benzyl-3-*tert*-butoxycarbonyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decan-8-one (**5**; 6.97 g, 20.4 mmol) was performed on preparative chiral HPLC (Reprosil Chiral-NR; heptane/EtOH 6/4, flow rate 35 mL/min; (+)-**5** t_R = 37.00 min; (−)-**5** t_R = 45.00 min) in batches of 200 mg each to give (+)-**5** (3.18 g) as a light yellow solid and (−)-**5** (3.10 g) as a light yellow solid. Both compounds were crystallized from hot EtOAc/*n*-heptane and submitted to single-crystal X-ray analysis, which revealed that (+)-**5** is (1*S*,5*S*,7*S*)-9-benzyl-3-*tert*-butoxycarbonyl-3,9-diazatricyclo-[5.3.0.01,5]decan-8-one ((+)-**5**; 3.18 g, 9.29 mmol, 45.6% yield, mp 126−128 °C, 100% ee; $[\alpha]_D^{20}$ = +111.0° (c = 1.00, $CHCl_3$)) and (−)-**5** is (1*R*,5*R*,7*R*)-9-benzyl-3-*tert*-butoxycarbonyl-3,9-diazatricyclo-[5.3.0.0^{1,5}]decan-8-one ((−)-**5**; 3.10 g, 9.05 mmol, 44.5% yield, mp 127−129 °C, 98.8% ee, $[\alpha]_D^{20}$ = −97.7° (c = 1.00, $CHCl_3$)).

9-Benzyl-3-*tert*-butoxycarbonyl-3,9-diazatricyclo[5.3.0.0^{1,5}]-decane (6). To a suspension of the pyrrolidinone **5** (29.8 g, 87.0 mmol, 1.0 equiv) in THF (50 mL) at 0 °C was added cold borane−THF complex (1 M in THF) (287 mL, 287 mmol, 3.3 equiv), and the mixture was stirred at room temperature for 18 h. After the reaction mixture was concentrated under reduced pressure to give a white solid, ethanol (430 mL), triethylamine (71.0 mL, 509 mmol, 5.85 equiv), and water (71 mL) were added at 23 °C (exothermic), and the mixture was heated to reflux (95 °C) for 1.5 h. After the reaction mixture was concentrated under reduced pressure, water (500 mL) and 3 M NaOH (aq) (200 mL) were added, and the mixture was extracted twice with dichloromethane (2 × ca. 250 mL). The combined organic layers were dried over Na_2SO_4 and then filtered. Removal of the solvent under vacuum left a light yellow oil. The crude material was purified by column chromatography (heptane/EtOAc 1/1) to give the pure product **6** (27.0 g, 94%) as a colorless oil which crystallized later to a white solid. Mp: 73−75 °C. R_f = 0.61 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2971 (s, C−H), 2846 (s, C−H), 1676 (vs, C═O), 1392 (s), 1394 (m), 1390 (vs), 1117 (m), 770 (w). ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.38 (d, J = 7.0 Hz, 2 H), 7.30 (virt t, $J \approx$ 7.0 Hz, 2 H), 7.25−7.23 (m, 1 H), 3.70 (d, J = 13.4 Hz, 1 H), 3.68−3.65 (m, 1 H), 3.63 (d, J = 13.4 Hz, 1 H), 3.59−3.54 (m, 1 H), 3.28 (br. s, 1 H), 2.98 (d, J = 11.6 Hz, 1 H), 2.86 (d, J = 9.5 Hz, 1 H), 2.82 (d, J = 9.5 Hz, 1 H), 2.57 (dd, J = 12.5 Hz, J = 7.9 Hz, 1 H), 2.40 (br. s, 1 H), 2.21 (dd, J = 9.5 Hz, J = 6.2 Hz, 1 H), 2.03−2.01 (m, 1 H), 1.99 (ddd, J = 12.4 Hz, J = 8.7 Hz, J = 5.0 Hz, 1 H), 1.77 (br. s, 1 H), 1.48 (s, 9 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 155.2, 136.2, 128.6, 128.2, 126.6, 79.2, 60.3, 60.0, 58.3, 52.2, 50.5, 47.3, 40.1, 39.2, 29.4, 28.6. MS (EI, 70 EV): m/z (%) 329 (100) [(M + H)$^+$], 273 (53) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{20}H_{28}N_2O_2^+$ [(M)]$^+$ 328.2150, found 328.2157.

***tert*-Butyl *N*-Allyl-*N*-[(2-oxo-3-phenyl-5*H*-furan-4-yl)methyl]-carbamate (8).** To a solution of 4-(bromomethyl)-3-phenylfuran-2(5*H*)-one (**7**; 320 mg, 1.26 mmol, 1.0 equiv) in THF (7.5 mL) were added triethylamine (529 μL, 3.79 mmol, 2.0 equiv) and allylamine (100 μL, 1.33 mmol, 1.1 equiv). The resulting solution was stirred at room temperature for 12 h. Water was added, the aqueous layer was extracted with EtOAc, and the extract was dried over Na_2SO_4, filtered, and evaporated to dryness. This product was dissolved in dichloromethane, and the solution was passed through a short pad of silica gel (heptane/EtOAc 1/3), concentrated under reduced pressure, and used in the next step without further purification (250 mg, 87%). To a solution of this amine (250 mg, 1.09 mmol, 1.0 equiv) in dry THF (3.0 mL) was added Boc_2O (238 mg, 1.09 mmol, 1.0 equiv). The resulting solution was heated to 40 °C for 2 h. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (heptane/EtOAc 1/1) to afford the Boc-protected product **8** as a colorless oil (329 mg, 92%). R_f = 0.51 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2968 (w, C−H), 1750 (vs, C═O), 1697 (s, C═O), 1412 (m), 1391 (m), 1365 (m), 1125 (m), 1103 (m). ^1H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.57−7.51 (m, 2 H), 7.50−7.47 (m, 2 H), 7.45−7.42 (m, 1 H), 5.70 (ddt, J = 16.2 Hz, J = 10.5 Hz, J = 5.7 Hz, 1 H), 5.05 (dd, J = 10.5 Hz, J = 1.1 Hz, 1 H), 4.95−4.91 (m, 3 H), 4.35 (s, 2 H), 3.90−3.74 (m, 2 H), 1.35 (s, 9 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 172.9, 161.0, 164.7, 133.9, 130.0, 129.3, 129.0, 128.9, 126.2, 118.0, 86.1, 70.9, 50.5, 43.9, 28.4. MS (EI, 70 EV): m/z (%) 328 (90) [(M − H)$^+$], 274 (100) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{14}H_{16}NO_2$ [(M − $C_5H_9O_2$)$^+$] 230.1191, found 230.1182.

***N*-*tert*-Butoxycarbonyl-7-phenyl-3-aza-9-oxatricyclo-[5.3.0.0^{1,5}]decan-8-one (9a).** The compound was prepared from photoprecursor **8** (40.0 mg, 0.20 mmol) in 25 mL of acetonitrile by irradiation for 5 days (5 mM) at λ 300 nm. Purification of the crude product by column chromatography (heptane/EtOAc 1/1) afforded the photoproduct **9a** as a white solid (28.8 mg, 72%). Mp: 103 °C. R_f = 0.44 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2936 (w), 1765 (s,

dx.doi.org/10.1021/jo501302f | J. Org. Chem. 2014, 79, 7152−7161

C═O), 1687 (vs, C═O), 1165 (s), 1013 (s), 876 (w). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.42−7.35 (m, 2 H), 7.34−7.27 (m, 1 H), 7.14−7.07 (m, 2 H), 4.51 (d, J = 9.8 Hz, 1 H), 4.34 (d, J = 9.8 Hz, 1 H), 3.54 (d, J = 11.6 Hz, 1 H), 3.46 (d, J = 12.6 Hz, 1 H), 3.24 (dd, J = 11.6 Hz, J = 6.4 Hz 1 H), 2.97 (d, J = 12.6 Hz, 1 H), 2.93−2.91 (m, 1 H), 2.56 (dd, J = 12.5 Hz, J = 8.2 Hz, 1 H), 2.38 (dd, J = 12.5 Hz, J = 6.9 Hz, 1 H), 1.27 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 180.4, 154.4, 135.5, 129.1, 127.8, 127.0, 80.0, 71.5, 51.5, 50.9, 49.1, 46.9, 38.1, 31.8, 28.3. MS (EI, 70 EV): m/z (%) 274 (100) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{14}H_{16}NO_2$ [(M − $C_5H_9O_2$)$^+$] 230.1191, found 230.1201.

9-Benzyl-3-*tert*-butoxycarbonyl-7-phenyl-3,9-diazatricyclo-[5.3.0.0^{1,5}]decane (11a). With the photocycloaddition product **9a** (92.0 mg, 0.27 mmol) as the starting material, conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **11a** (61.0 mg, 54%) was finally obtained as a colorless oil. R_f = 0.51 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2972 (w, C−H), 1677 (vs, C═O), 1427 (m), 1389 (m), 1104 (m), 1085 (m), 1028 (m), 876 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.33 (d, J = 7.0 Hz, 2 H), 7.30−7.25 (m, 5 H), 7.14−7.08 (m, 3 H), 3.68 (d, J = 13.2 Hz, 1 H), 3.63 (d, J = 13.2 Hz, 1 H), 3.56 (d, J = 12.2 Hz, 1 H), 3.40−3.25 (m, 1 H), 3.13−3.10 (m, 1 H), 3.07 (d, J = 9.8 Hz, 1 H), 2.92 (d, J = 9.3 Hz, 1 H), 2.76 (d, J = 12.2 Hz, 1 H), 2.66−2.58 (m, 1 H), 2.39−2.37 (m, 2 H), 2.39−2.37 (m, 2 H), 1.07 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 154.0, 142.8, 139.3, 128.6, 128.2, 128.0, 127.5, 126.9, 125.9, 79.1, 71.2, 61.2, 60.1, 59.8, 51.9, 50.1, 47.8, 37.6, 33.8, 28.1. MS (EI, 70 eV): m/z (%) 274 (100) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{26}H_{32}N_2O_2^+$ [M]$^+$ 404.2465, found 404.2474.

9-Benzyl-3-*tert*-butoxycarbonyl-7-methyl-3,9-diazatricyclo-[5.3.0.0^{1,5}]decane (11b). With the photocycloaddition product **9b**[10b] (318 mg, 1.19 mmol) as the starting material, the conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **11b** (212 mg, 52%) was finally obtained as a colorless oil. R_f = 0.55 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2782 (w, C−H), 2782 (s, C−H), 1693 (vs, C═O), 1390 (s), 1364 (m), 1235 (w), 1171 (s), 1117 (s), 877 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.37 (d, J = 7.3 Hz, 2 H), 7.32 (t, J = 7.3 Hz, 1 H), 7.24 (d, J = 7.3 Hz, 2 H), 3.74−3.68 (m, 1 H), 3.65 (d, J = 13.4 Hz, 1 H), 3.60 (d, J = 13.4 Hz, 1 H), 3.46 (d, J = 13.2 Hz, 1 H), 3.26 (d, J = 13.2 Hz, 1 H), 2.87−2.85 (m, 3 H), 2.56−2.49 (m, 1 H), 2.25 (dd, J = 11.9 Hz, J = 9.1 Hz, 1 H), 2.03 (br. s, 1 H), 1.85 (d, J = 8.7 Hz, 1 H), 1.48 (s, 9 H), 1.44−1.37 (m, 1 H), 1.00 (s, 3 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 154.8, 139.4, 128.6, 128.2, 126.8, 79.2, 67.7, 60.4 and 60.3, 59.8, 55.5 and 54.6, 53.2 and 52.6, 48.0 and 47.7, 41.9, 38.4, 37.5 and 37.4, 28.6, 19.6, and 19.3. *Rotamers*. MS (EI, 70 eV): m/z (%) 343 (10) [(M + H)$^+$]. HRMS (ESI): calculated for $C_{21}H_{30}N_2O_2^+$ [M]$^+$ 342.2307, found 342.2309.

9-Benzyl-3-*tert*-butoxycarbonyl-7-fluoro-3,9-diazatricyclo-[5.3.0.0^{1,5}]decane (11c). With the photocycloaddition product **9c**[10b] (408 mg, 1.5 mmol) as the starting material, the conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **11c** (271 mg, 52%) was finally obtained as a colorless oil. R_f = 0.35 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2974 (m, C−H), 2794 (m, C−H), 1694 (vs, C═O), 1390 (s), 1171 (s), 1108 (m), 876 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.40−7.37 (m, 3 H), 7.32−7.26 (m, 2 H), 3.94 (d, J = 12.1 Hz, 1 H), 3.72 (d, J = 13.1 Hz, 1 H), 3.60 (d, J = 13.1 Hz, 1 H), 3.46 (d, J = 10.8 Hz, 1 H), 3.23 (dd, J = 11.5 Hz, J = 6.5 Hz, 1 H), 3.18 (dd, J = 9.5 Hz, J_F = 1.0 Hz, 1 H), 3.00−2.90 (m, 1 H), 2.84 (d, J = 9.7 Hz, 1 H), 2.52 (dd, J = 13.2 Hz, J_F = 8.9 Hz, 1 H), 2.44 (ddd, J_F = 21.6 Hz, J = 9.5 Hz, J = 1.3 Hz, 1 H), 2.37 (virt quin, $J \approx$ 7.3 Hz, 1 H), 2.26−2.24 (m, 1 H), 2.06−2.04 (m, 1 H), 1.48 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 151.7, 138.4, 128.6, 128.3, 127.2, 95.5 (d, J_F = 247.2 Hz), 79.5, 67.7 (d, J_F = 27.2 Hz), 59.4, 58.8, 58.2 (d, J_F = 17.6 Hz), 57.2, 45.9, 36.5 (d, J_F = 24.8 Hz), 34.1 (d, J_F = 8.8 Hz), 28.5. *Rotamers*. MS (EI, 70 eV): m/z (%) 347 (100) [(M + H)$^+$]. HRMS (ESI): calculated for $C_{20}H_{27}FN_2O_2^+$ [M]$^+$ 346.2057, found 346.2057.

9-Benzyl-3-*tert*-butoxycarbonyl-5-phenyl-3,9-diazatricyclo-[5.3.0.0^{1,5}]decane (12a). With the photocycloaddition product **10a**[10b] (352 mg, 1.07 mmol) as the starting material, the conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **12a** (268 mg, 62%) was finally obtained as a colorless oil. R_f = 0.56 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2972 (s, C−H), 2931 (s, C−H), 1677 (vs, C═O), 1602 (w), 1427 (s), 1104 (s), 876 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.35 (d, J = 7.4 Hz, 2 H), 7.27 (t, J = 7.4 Hz, 1 H), 7.18 (d, J = 7.4 Hz, 2 H), 7.11−7.03 (m, 3 H), 6.81−6.74 (m, 2 H), 4.06−3.88 (m, 1 H), 3.85−3.73 (m, 1 H), 3.70 (d, J = 13.9 Hz, 1 H), 3.58−3.44 (m, 1 H), 3.29 (d, J = 10.4 Hz, 1 H), 3.21 (d, J = 13.9 Hz, 1 H), 2.82−2.76 (m, 1 H), 2.75−2.71 (m, 1 H), 2.69 (ddd, J = 12.0 Hz, J = 5.8 Hz, J = 1.1 Hz, 1 H), 2.59−2.45 (m, 1 H), 2.27 (dd, J = 9.5 Hz, J = 5.5 Hz, 1 H), 2.24−2.16 (m, 1 H), 1.82−1.69 (m, 1 H), 1.49 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 154.7, 143.8, 139.5, 128.2, 128.0, 127.5, 127.1, 126.3, 125.9, 79.5, 64.5, 60.1, 59.0, 58.2, 55.3, 52.4, 37.8, 33.0, 30.3, 28.5. MS (EI, 70 EV): m/z (%) 405 (100) [(M + H)$^+$], 349 (17) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{26}H_{32}N_2O_2^+$ [(M)]$^+$ 404.2464, found 404.2467.

9-Benzyl-3-*tert*-butoxycarbonyl-5-methyl-3,9-diazatricyclo-[5.3.0.0^{1,5}]decane (12b). With the photocycloaddition product **10b**[10b] (180 mg, 0.68 mmol) as the starting material, the conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **12b** (118 mg, 51%) was finally obtained as a colorless oil. R_f = 0.51 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2812 (s, C−H), 2782 (s, C−H), 1683 (vs, C═O), 1390 (s), 1171 (s), 1117 (s), 877 (m). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.35−7.33 (m, 3 H), 7.26−7.21 (m, 2 H), 3.68 (d, J = 13.9 Hz, 1 H), 3.56 (d, J = 10.0 Hz, 1 H), 3.52 (d, J = 13.9 Hz, 1 H). 3.51−3.47 (m, 1 H), 2.97−2.94 (m, 1 H), 2.89−2.84 (m, 1 H), 2.78 (d, J = 10.0 Hz, 1 H), 2.69 (d, J = 9.3 Hz, 1 H), 2.22 (ddd, J = 9.0 Hz, J = 5.7 Hz, J = 5.7 Hz, 1 H), 2.13 (dd, J = 9.3 Hz, J = 5.7 Hz, 1 H), 1.91 (dd, J = 11.8 Hz, J = 9 Hz, 1 H), 1.87 (d, J = 10.0 Hz, 1 H), 1.55 (dd, J = 11.8 Hz, J = 5.7 Hz, 1 H), 1.40 (s, 9 H), 1.08 (s, 3 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 155.1, 139.8, 128.4, 128.2, 126.8, 79.2, 61.1, 60.1, 59.6, 55.7, 53.1, 52.6, 38.2, 42.9, 36.9, 28.5, 19.6. MS (EI, 70 EV): m/z (%) 343 (100) [(M + H)$^+$]. HRMS (ESI): calculated for $C_{21}H_{30}N_2O_2^+$ [(M)]$^+$ 342.2307, found 342.2313.

***tert*-Butyl *N*-(3-Methylbut-2-enyl)-*N*-[(5-oxo-2*H*-furan-3-yl)-methyl]carbamate (14).** To a solution of 4-(bromomethyl)furan-2(5*H*)-one (**13**; 1.35 g, 7.63 mmol, 1.0 equiv) in THF (45 mL) were added triethylamine (3.19 mL, 22.9 mmol, 3.0 equiv) and finally the 3,3-dimethylallylamine (650 mg, 7.63 mmol, 1.0 equiv). The resulting solution was stirred at room temperature for 12 h. Water was added, the aqueous layer was extracted with EtOAc, and the extract was dried over Na_2SO_4, filtered, and evaporated to dryness. This product was dissolved in dichloromethane and the solution passed through a short pad of silica gel (heptane/EtOAc 1/3), concentrated under reduced pressure, and used in the next step without further purification (445 mg, 35%). To a solution of the crude amine (445 mg, 2.46 mmol, 1.0 equiv) in dry THF (6.2 mL) was added Boc_2O (536 mg, 2.46 mmol, 1.0 equiv). The resulting solution was heated to 40 °C for 2 h. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (heptane/EtOAc 1/1) to afford the Boc-protected product **14** as a colorless oil (425 mg, 22% from bromide **13**). R_f = 0.57 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2975 (m, C−H), 1779 (s, C═O), 1746 (vs), 1688 (s), 1449 (m), 1366 (m), 1159 (s), 1116 (m), 1028 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.97−4.87 (m, 1 H), 4.83−4.77 (m, 1 H), 4.68 (s, 2 H), 4.23−4.12 (m, 2 H), 3.84−3.65 (m, 2 H), 1.85 (s, 3 H), 1.69 (s, 3 H), 1.47 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 178.1, 156.0, 140.7, 124.9, 113.1, 112.9, 80.8, 71.2, 53.2, 41.8, 28.3, 19.7, 8.6. MS (EI, 70 EV): m/z (%) 226 (100) [(M − C_4H_8)$^+$]. HRMS (ESI): calculated for $C_{10}H_{15}NO_2$ [(M − $C_5H_8O_2$)$^+$] 181.1182, found 181.1177.

dx.doi.org/10.1021/jo501302f | J. Org. Chem. 2014, 79, 7152−7161

***N-tert*-Butoxycarbonyl-6,6-dimethyl-3-aza-9-oxatricyclo-[5.3.0.0^{1,5}]decan-8-one (15).** The compound was prepared from photoprecursor **14** (400 mg, 1.42 mmol) in 284 mL of acetonitrile by irradiation for 12 h (5 mM) at λ 254 nm. Purification of the crude product by column chromatography (heptane/EtOAc 1/1) afforded the photoproduct **15** as a white solid (173 mg, 44%). Mp: 151 °C. R_f = 0.51 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2965 (m), 2869 (w), 1753 (m, C═O), 1696 (s, C═O), 1476 (w), 1417 (s), 1365 (s), 1170 (s), 1134 (s), 1013 (w). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.44 (d, J = 9.8 Hz, 1 H), 4.19 (d, J = 9.8 Hz, 1 H), 3.94−3.84 (m, 1 H), 3.83−3.74 (m, 1 H), 3.23 (dd, J = 12.6 Hz, J = 7.5 Hz, 1 H), 3.03 (d, J = 12.1 Hz, 1 H), 2.60 (s, 1 H), 2.44 (d, J = 7.5 Hz, 1 H), 1.48 (s, 9 H), 1.18 (s, 3 H), 1.17 (s, 3 H). ^{13}C{^{1}H} NMR (91 MHz, $CDCl_3$): δ (ppm) 176.6, 154.3, 80.1, 73.6, 52.7, 51.6, 51.4, 47.4, 35.7, 28.5, 26.4, 23.5. (*one carbon atom not observed*). MS (EI, 70 EV): m/z (%) 226 (100) [(M − C_4H_8)$^+$]. HRMS (ESI): calculated for $C_{10}H_{15}NO_2$ [(M − $C_5H_8O_2$)$^+$] 181.1182, found 181.1187.

***tert*-Butyl 2-Fluoroallyl[(3-fluoro-2-oxo-5*H*-furan-4-yl)-methyl]carbamate (17).** To a solution of 4-(bromomethyl)-3-fluorofuran-2(5*H*)-one (**16**; 1.5 g, 7.69 mmol, 1.0 equiv) in THF (45 mL) were added triethylamine (3.22 mL, 23.1 mmol, 3.0 equiv) and then 2-fluoroallylamine (866 mg, 11.5 mmol, 1.5 equiv). The resulting solution was stirred at room temperature for 14 h. Water was added, the aqueous layer was extracted with EtOAc, and the extract was dried over Na_2SO_4, filtered, and evaporated to dryness. This product was dissolved in dichloromethane and the solution passed through a short pad of silica gel (heptane/EtOAc 1/3), concentrated under reduced pressure, and used in the next step without further purification (1.30 g, 89%). To a solution of the crude amine (1.11 g, 5.87 μmol, 1.0 equiv) in dry THF (14.7 mL) was added Boc_2O (1.34 g, 6.16 mmol, 1.1 equiv). The resulting solution was heated to 40 °C for 2 h. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (heptane/EtOAc 1/1) to afford the Boc-protected product **17** as a colorless oil (1.68 g, 88% from bromide **16**). R_f = 0.41 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2979 (m, C−H), 1778 (s, C═O), 1693 (s, C═O), 1454 (m), 1408 (m), 1368 (m), 1155 (vs), 1104 (s), 874 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.82−4.70 (m, 3 H), 4.55−4.39 (m, 1 H), 4.26 (s, 2 H), 4.07−3.88 (m, 2 H), 1.48 (s, 9 H). ^{19}F NMR (235 MHz, DMSO-d_6): δ (ppm) −103.7 (m), −148.4 (m). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 164.7 (d, J_F = 31.1 Hz), 160.7 (d, ^1J_F = 260.2 Hz), 155.2, 144.3 (d, ^1J_F = 273.4 Hz), 134.8 (d, ^2J_F = 31.1 Hz), 93.3 (d, J_F = 5.0 Hz), 81.8, 67.5, 48.5 (d, J_F = 31.4 Hz), 40.8, 28.2. MS (EI, 70 eV): m/z (%) 234 (100) [(M − C_4H_7)$^+$]. HRMS (ESI, 70 eV): calculated for $C_{13}H_{17}F_2NO_4$ [M$^+$] 289.1125, found 289.1119.

***N-tert*-Butoxycarbonyl-5,7-difluoro-3-aza-9-oxatricyclo-[5.3.0.0^{1,5}]decan-8-one (18).** The compound was prepared from photoprecursor **17** (1.50 g, 5.19 mmol) in 1.04 L of acetonitrile by irradiation for 1 h (5 mM) at λ 254 nm. Purification of the crude by column chromatography (heptane/EtOAc 1/1) afforded the photoproduct **18** as a white solid (1.08 g, 72%). Mp: 110−112 °C. R_f = 0.37 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2978 (w, C−H), 1768 (vs, C═O), 1683 (s, C═O), 1403 (s), 1171 (s), 1098 (s, C−F), 868 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.67 (dd, J = 10.4 Hz, J_F = 3.2 Hz, 1 H), 4.26−4.05 (m, 3 H), 3.50−3.46 (m, 1 H), 3.26 (dd, J = 12.6 Hz, J_F = 1.0 Hz, 1 H), 3.02 (dddd, J_F = 15.2 Hz, J_F = 15.1 Hz, J = 8.4 Hz, J = 1.3 Hz, 1 H), 2.86 (ddd, J_F = 15.2 Hz, J_F = 15.1 Hz, J = 8.4 Hz, 1 H), 1.49 (s, 9 H). ^{19}F NMR (235 MHz, DMSO-d_6): δ (ppm) −170.8 (m), −177.5 (m). ^{13}C{^{1}H} NMR (91 MHz, $CDCl_3$): δ (ppm) 171.5 (d, J_F = 25.6 Hz), 154.9, 89.5, 83.9 (d, J_F = 240.7 Hz), 81.2, 65.7, 58.0 (d, J_F = 4.4 Hz), 57.7 (d, J_F = 25.6 Hz), 46.1, 41.1 (t, J_F = 27.0 Hz), 28.3. MS (EI, 70 eV): m/z (%) 234 (100) [(M − C_4H_7)$^+$]. HRMS (ESI, 70 eV): calculated for $C_{13}H_{17}F_2NO_4$ [(M)$^+$] 289.1125, found 289.1123.

***tert*-Butyl 2-Phenylallyl[(3-phenyl-2-oxo-5*H*-furan-4-yl)-methyl]carbamate (19).** To a solution of 4-(bromomethyl)-3-phenylfuran-2(5*H*)-one (7; 507 mg, 2.0 mmol, 1.0 equiv) in THF (12 mL) were added triethylamine (838 μL, 6.0 mmol, 3.0 equiv) and the 2-phenylallylamine (680 mg, 4.01 mmol, 1.0 equiv). The resulting solution was stirred at room temperature for 14 h. Water was added, the aqueous layer was extracted with EtOAc, and the extract was dried over Na_2SO_4, filtered, and evaporated to dryness. This product was dissolved in dichloromethane and the solution passed through a short pad of silica gel (heptane/EtOAc 1/3), concentrated under reduced pressure, and used in the next step without further purification (501 mg, 82%). To a solution of the crude amine (364 mg, 1.19 mmol, 1.0 equiv) in dry THF (3.0 mL) was added Boc_2O (260 mg, 1.19 mmol, 1.0 equiv). The resulting solution was heated to 40 °C for 2 h. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (heptane/EtOAc 1/1) to afford the Boc-protected product **19** as a colorless oil (426 mg, 88%). R_f = 0.62 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2971 (m, C−H), 1764 (vs, C═O), 1679 (s), 1496 (w), 1396 (m), 1367 (m), 1214 (m), 1154 (s), 1116 (vs), 1043 (s), 957 (m), 786 (m). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.46−7.36 (m, 5 H), 7.31−7.26 (m, 5 H), 5.25 (virt q, $J \approx$ 1.1 Hz, 1 H), 4.93 (virt q, $J \approx$ 1.1 Hz, 1 H), 4.67 (s, 2 H), 4.29 (s, 2 H), 4.17 (virt t, $J \approx$ 1.1 Hz, 2 H), 1.37 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 172.3, 160.1, 164.2, 130.0, 129.4, 128.9, 128.8, 128.5, 127.6, 126.9, 126.7, 125.9, 125.8, 114.8, 85.6, 70.2, 50.9, 42.8, 27.8. MS (EI, 70 EV): m/z (%) 404 (90) [(M − H)$^+$], 350 (100) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{21}H_{19}NO_4$ [(M − C_4H_8)$^+$] 349.1314, found 349.1309.

***N-tert*-Butoxycarbonyl-5,7-diphenyl-3-aza-9-oxatricyclo-[5.3.0.0^{1,5}]decan-8-one (21).** The compound was prepared from photoprecursor **19** (281 mg, 0.70 mmol) in 140 mL of acetonitrile by irradiation for 6 h at λ 300 nm (5 mM). Purification of the crude by column chromatography (heptane/EtOAc 1/1) afforded the photoproduct **21** as a white solid (169 mg, 60%). Mp: (107−108) °C. R_f = 0.53 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2868 (w), 1773 (s, C═O), 1690 (vs, C═O), 1458 (m), 1250 (m), 1233 (w), 1065 (s), 940 (w), 749 (m). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.47−7.45 (m, 3H), 7.43−7.41 (m, 2 H), 7.35−7.32 (m, 3 H), 7.20−7.18 (m, 2 H), 4.21 (d, J = 9.3 Hz, 1 H), 4.13−4.08 (m, 2 H), 3.76 (d, J = 12.6 Hz, 1 H), 3.45 (d, J = 12.1 Hz, 1 H), 3.41 (d, J = 13.5 Hz, 1 H), 3.11 (d, J = 12.6 Hz, 1 H), 2.95 (d, J = 13.5 Hz, 1 H), 1.35 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 180.1, 153.8, 137.0, 135.2, 129.2, 129.1, 128.0, 127.6, 127.3, 127.2, 80.0, 67.9, 61.5, 60.5, 50.3, 49.0, 48.2, 34.2, 28.2. MS (EI, 70 EV): m/z (%) 350 (100) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{20}H_{19}NO_2$ [(M − $C_5H_8O_2$)$^+$] 305.1416, found 305.1419.

***tert*-Butyl 1-Oxo-6a-phenyl-1,4,6,6a,7,11b-hexahydrobenzo-furo[3,4]isoindole-5(3*H*)-carboxylate (22).** The compound was obtained as a byproduct (white solid; 56.0 mg, 20%) upon irradiation of photoprecursor **19** (281 mg, 0.70 mmol) (see previous procedure). Mp: 104 °C. R_f = 0.49 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2875 (w), 1768 (s, C═O), 1650 (vs, C═O), 1400 (m), 1215 (m), 1200 (w), 1000 (s), 938 (w). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.52−7.51 (m, 1 H), 7.34−7.30 (m, 7 H), 7.27−7.25 (m, 1 H), 4.15 (d, J = 9.8 Hz, 1 H), 4.11 (s, 1 H), 4.03 (d, J = 9.8 Hz, 1 H), 3.90 (d, J = 11.6 Hz, 1 H), 3.72 (d, J = 11.8 Hz, 1 H), 3.57 (d, J = 11.8 Hz, 1 H), 3.35 (d, J = 11.6 Hz, 1 H), 3.31 (d, J = 16.4 Hz, 1 H), 3.04 (d, J = 16.4 Hz, 1 H), 1.44 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 175.2, 154.8, 141.2 and 140.7, 134.3 and 134.2, 129.7 and 129.6, 129.0 and 128.9, 128.8, 128.3 and 128.2, 127.8, 127.7, 127.4 and 127.3, 126.3 and 126.2, 80.4 and 80.3, 71.8 and 71.4, 55.6 and 55.4, 55.1 and 54.7, 51.14 and 51.11, 48.6 and 48.2, 47.8 and 46.9, 36.1 and 36.0, 28.4. *Rotamers*. MS (EI, 70 EV): m/z (%) 350 (100) [(M − C_4H_7)$^+$]. HRMS (ESI): calculated for $C_{20}H_{19}NO_2$ [(M − $C_5H_8O_2$)$^+$] 305.1416, found 305.1416.

9-Benzyl-3-*tert*-butoxycarbonyl-6,6-dimethyl-3,9-diazatri-cyclo[5.3.0.0^{1,5}]decane (24). With the photocycloaddition product **15** (103 mg, 0.37 mmol) as the starting material, the conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **24** (56.2 mg, 43%) was finally obtained as a colorless oil. R_f = 0.68 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2799 (s, C−H), 2780 (s, C−H), 1663 (vs, C═O), 1299 (m), 1154 (s), 1110 (m), 811 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.39−7.36 (m, 2 H), 7.34−7.30 (m, 2 H), 7.26−7.23 (m, 1 H), 3.74−3.71 (m, 1 H), 3.67−3.63 (m, 2 H), 3.62−3.55

dx.doi.org/10.1021/jo501302f | J. Org. Chem. 2014, 79, 7152−7161

(m, 1 H), 3.05 (d, J = 12.3 Hz, 1 H), 2.99 (d, J = 13.1 Hz, 1 H), 2.97 (d, J = 10.6 Hz, 1 H), 2.88 (d, J = 9.5 Hz, 1 H), 2.19 (d, J = 7.6 Hz, 1 H), 2.14 (dd, J = 10.6 Hz, J = 7.6 Hz, 1 H), 2.00−1.95 (m, 1 H), 1.94−1.90 (m, 1 H), 1.47 (s, 9 H), 1.10 (s, 3 H), 0.96 (s, 3 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 154.7, 139.5, 128.6, 128.2, 126.9, 79.2, 60.1, 60.0, 55.6, 51.2, 50.4, 49.5, 46.9, 32.1, 28.6, 23.9, 23.8 (*one carbon atom not observed*). MS (EI, 70 EV): m/z (%) 357 (100) [$(M + H)^+$]. HRMS (ESI): calculated for $C_{22}H_{32}N_2O_2^+$ [(M)]$^+$ 356.2464, found 356.2465.

9-Benzyl-3-*tert*-butoxycarbonyl-5,7-difluoro-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (25). With the photocycloaddition product **18** (841 mg, 2.91 mmol) as the starting material, the conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **25** (837 mg, 79%) was finally obtained as a colorless oil, which crystallized upon standing. Mp: 98 °C. R_f = 0.39 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2941 (w, C−H), 1678 (s, C═O), 1400 (s), 1199 (s), 1089 (s, C−F), 870 (w). ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.37−7.30 (m, 3 H), 7.26−7.24 (m, 2 H), 4.12−4.05 (m, 1 H), 3.95−3.85 (m, 1 H), 3.73 (d, J = 13.3 Hz, 1 H), 3.60 (d, J = 13.3 Hz, 1 H), 3.55−3.40 (m, 1 H), 3.25−3.20 (m, 1 H), 3.14 (d, J = 9.0 Hz, 1 H), 3.15−3.08 (m, 1 H), 2.87 (dd, J_F = 29.0 Hz, J = 12.2 Hz, 1 H), 2.70−2.60 (m, 1 H), 2.47 (dd, J_F = 16.4 Hz, J = 9.0 Hz, 1 H), 2.30−2.20 (m, 1 H), 1.46 (s, 9 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 154.1, 137.9, 128.5, 128.4, 127.2, 95.5 (d, ^1J_F = 226.4 Hz), 94.8 (d, J_F = 228.1 Hz), 80.1, 61.6 (d, J_F = 26.2 Hz), 59.1, 58.2 (d, J_F = 17.6 Hz), 57.6, 57.2, 52.4, 47.1, 43.3 (dd, J_F = 27.8 Hz, J_F = 23.7 Hz), 28.5. *Rotamers*. MS (EI, 70 EV): m/z (%) 365 (100) [$(M + H)^+$]. HRMS (ESI): calculated for $C_{20}H_{26}F_2N_2O_2^+$ [(M)]$^+$ 364.1962, found 364.1968.

9-Benzyl-3-*tert*-butoxycarbonyl-5,7-diphenyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (26). With the photocycloaddition product **21** (166 mg, 0.41 mmol) as the starting material, the conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **26** (110 mg, 56%) was finally obtained as a colorless oil. R_f = 0.57 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2931 (w, C−H), 1690 (vs, C═O), 1490 (w), 1419 (m), 1099 (m), 1085 (m), 1028 (m), 870 (m). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.41−7.39 (m, 5 H), 7.36−7.34 (m, 5 H), 7.30−7.28 (m, 3 H), 7.25−7.24 (m, 2 H), 4.32 (d, J = 11.9 Hz, 1 H), 4.0 (d, J = 13.1 Hz, 1 H), 3.86 (d, J = 11.1 Hz, 1 H), 3.61 (d, J = 13.1 Hz, 1 H), 3.53 (d, J = 11.1 Hz, 1 H), 3.42 (d, J = 10.9 Hz, 1 H), 3.29 (d, J = 11.9 Hz, 1 H), 3.26 (d, J = 12.6 Hz, 1 H), 3.14 (br. s, 1 H), 2.99 (br. s, 1 H), 2.91 (d, J = 13.1 Hz, 1 H), 2.40 (d, J = 13.1 Hz, 1 H), 1.48 (s, 9 H). $^{13}C\{^1H\}$ NMR (91 MHz, $CDCl_3$): δ (ppm) 153.9, 142.1, 139.3, 128.8, 128.5, 128.3, 127.5, 127.0, 126.5, 79.2, 69.9, 66.3, 60.7, 59.0, 55.1, 49.8, 48.3, 34.0, 28.4, 28.1. MS (EI, 70 eV): m/z (%) 481 (10) [$(M + H)^+$]. HRMS (ESI): calculated for $C_{32}H_{36}N_2O_2^+$ [M]$^+$ 480.2776, found 480.2770.

9-Benzyl-3-*tert*-butoxycarbonyl-5,7-dimethyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (27). With the previously reported[10] photocycloaddition product **23** (419 mg, 1.49 mmol) as the starting material, the conversion to the pyrrolidine was performed as previously described for **3** → **6**. The intermediate products, however, were not further characterized but directly taken into the next step. Pure product **27** (255 mg, 48%) was finally obtained as a colorless oil. R_f = 0.64 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2858 (m, C−H), 1690 (vs, C═O), 1310 (s), 1290 (m), 1115 (m), 1082 (s), 810 (m). ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.38−7.35 (m, 2 H), 7.33−7.29 (m, 2 H), 7.26−7.22 (m, 1 H), 3.70−3.64 (m, 1 H), 3.60 (d, J = 13.1 Hz, 1 H), 3.59−3.57 (m, 1 H), 3.56 (d, J = 13.1 Hz, 1 H), 2.97 (d, J = 11.5 Hz, 1 H), 2.87 (d, J = 10.0 Hz, 1 H), 2.85 (d, J = 11.4 Hz, 1 H), 2.79 (d, J = 9.2 Hz, 1 H), 1.97 (d, J = 10.0 Hz, 1 H), 1.93−1.91 (m, 1 H), 1.78 (d, J = 9.2 Hz, 1 H), 1.67 (d, J = 11.7 Hz, 1 H), 1.46 (s, 9 H), 1.19 (s, 3 H), 1.02 (s, 3 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 154.3, 139.8, 128.5, 128.2, 126.8, 79.2, 67.5, 61.3, 60.2, 56.6, 48.9, 45.2, 42.7, 40.4, 30.4, 28.6, 19.9, 18.9. MS (EI, 70 EV): m/z (%) 357 (100) [$(M + H)^+$]. HRMS (ESI): calculated for $C_{22}H_{32}N_2O_2^+$ [(M)]$^+$ 356.2464, found 356.2461.

9-Benzyl-3-methyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (28). Substrate **6** (250 mg, 761 μmol, 1.0 equiv) was dissolved in THF (5.00 mL), and the solution was cooled to 0 °C. $LiAlH_4$ (31.8 mg, 837 μmol, 1.1 equiv) was added carefully, and the reaction mixture stirred at room temperature for 12 h. After that time, wet Na_2SO_4 was added and the solution was filtered. Evaporation of the solvent and purification of the crude by column chromatography (heptane/EtOAc 1/1) afforded product **28** (172 mg, 93%) as a colorless oil. R_f = 0.13 (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2936 (w), 1453 (w), 1240 (w), 1138 (w), 738 (m). ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.39 (d, J = 7.4 Hz, 2 H), 7.32 (t, J = 7.4 Hz, 2 H), 7.24 (d, J = 7.4 Hz, 1 H), 3.72 (d, J = 13.4 Hz, 1 H), 3.60 (d, J = 13.4 Hz, 1 H), 2.85−2.80 (m, 3 H), 2.78 (d, J = 9.5 Hz, 1 H), 2.45 (virt dt, J = 8.6 Hz, $J \approx$ 6.0 Hz, 1 H), 2.41 (virt dt, J = 8.6 Hz, $J \approx$ 5.7 Hz, 1 H), 2.38 (s, 3 H), 2.20 (dd, J = 9.3 Hz, J = 6.0 Hz, 1 H), 2.09 (dd, J = 9.5 Hz, J = 6.0 Hz, 1 H), 1.99 (d, J = 9.4 Hz, 1 H), 1.93 (d, J = 9.5 Hz, 1 H), 1.90−1.81 (m, 2 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 139.7, 128.6, 128.1, 126.7, 63.1, 62.8, 60.7, 60.0, 59.9, 55.3, 42.7, 40.8, 39.9, 29.2. MS (EI, 70 EV): m/z (%) 243 (100) [$(M + H)^+$]. HRMS (ESI): calculated for $C_{16}H_{22}N_2^+$ [(M)]$^+$ 242.1783, found 242.1787.

***N*-*tert*-Butoxycarbonyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (29).** A solution of substrate **6** (500 mg, 1.52 mmol, 1.0 equiv) in methanol (11.4 mL) was hydrogenated (hydrogen balloon) at 23 °C for 16 h in the presence of palladium hydroxide on carbon (20% Pd; moisture ca. 60%; Pearlman's catalyst; 114 mg, 162 μmol, 0.11 equiv). The catalyst was filtered off, and washed with methanol, and all volatiles were removed under vacuum to give *N*-tert-butoxycarbonyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (**29**; 362 mg, 99%) as a colorless oil. IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2929 (w, C−H), 2850 (w, C−H), 1688 (vs, C═O), 1389 (vs), 1364 (s), 1242 (m), 1164 (s), 1125 (s), 877 (m). ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.75−3.63 (m, 1 H), 3.62−3.47 (m, 1 H), 3.36−3.33 (m, 1 H), 3.07 (d, J = 11.6 Hz, 1 H), 2.98 (d, J = 11.2 Hz, 1 H), 2.89−2.85 (m, 2 H), 2.64 (d, J = 9.1 Hz, 1 H), 2.47 (dd, J = 13.1 Hz, J = 5.9 Hz, 1 H), 2.21 (dd, J = 12.7 Hz, J = 7.3 Hz, 1 H), 1.82 (br. s, 1 H), 1.79−1.75 (m, 1 H), 1.48 (s, 9 H). *Rotamers*. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 155.2, 79.3, 56.2 and 55.3, 53.8, 53.7, 53.4, 52.4, 41.0 and 40.9, 39.6 and 38.7, 28.8, 28.6. *Rotamers*. MS (EI, 70 EV): m/z (%) 239 (100) [$(M + H)^+$]. HRMS (ESI): calculated for $C_{13}H_{22}N_2O_2^+$ [(M)]$^+$ 238.1680, found 238.1680.

***N*-Benzyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (30).** Substrate **6** (300 mg, 913 μmol, 1.0 equiv) was dissolved in HCl (4 M in dioxane) (2.28 mL, 9.13 mmol, 10 equiv), and the reaction mixture was stirred at room temperature for 3 h. After that time, the solvent was removed and saturated aqueous $NaHCO_3$ was added. The aqueous solution was extracted twice with dichloromethane. The organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness to give *N*-benzyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (**30**; 209 mg, quantitative) as a colorless oil. IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3025 (w), 2936 (w, C−H), 2778 (w, C−H), 1466 (w), 1453 (w), 1240 (w), 1138 (w), 1115 (w), 879 (m), 738 (m). ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.38 (d, J = 7.6 Hz, 2 H), 7.30 (t, J = 7.6 Hz, 2 H), 7.24 (t, J = 7.6 Hz, 1 H), 3.72 (d, J = 13.3 Hz, 1 H), 3.62 (d, J = 13.3 Hz, 1 H), 2.89−2.86 (m, 3 H), 2.86−2.82 (m, 3 H), 2.48 (dd, J = 8.9 Hz, J = 4.5 Hz, 1 H), 2.27−2.23 (m, 1 H), 2.22 (dd, J = 9.4 Hz, J = 6.5 Hz, 1 H), 2.03 (d, J = 9.4 Hz, 1 H), 1.92 (ddd, J = 12.5 Hz, J = 8.5 Hz, J = 4.5 Hz, 1 H), 1.65 (ddd, J = 12.5 Hz, J = 8.4 Hz, J = 4.5 Hz, 1 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 139.5, 128.6, 128.1, 126.7, 60.6, 60.0, 59.5, 56.1, 53.8, 53.4, 40.8, 39.4, 28.6. MS (EI, 70 EV): m/z (%) 229 (100) [$(M + H)^+$]. HRMS (ESI): calculated for $C_{15}H_{20}N_2^+$ [(M)]$^+$ 228.1620, found 228.1620.

3,9-Diazatricyclo[5.3.0.0^{1,5}]decane (31) Dihydrochloride. *N*-Boc-protected amine **29** (300 mg, 913 μmol, 1.0 equiv) was dissolved in HCl (4 M in dioxane) (2.28 mL, 9.13 mmol, 10 equiv), and the reaction mixture was stirred at room temperature for 3 h. After that time, the solvent was removed and the residue was dried to give 3,9-diazatricyclo[5.3.0.0^{1,5}]decane (**31**) dihydrochloride as a white solid (255 mg, 96%). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2900 (s), 2861 (s), 2745 (vs), 2651 (s), 2522 (m), 2436 (w), 2255 (w), 1594 (s), 1426 (m), 1399 (m), 1377 (m), 993 (m). ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.11 (br. s, 2 NH), 9.86 (br. s, 2 NH), 3.45 (dd, J = 11.9 Hz, J = 4.6 Hz, 2 H), 3.26 (dd, J = 11.7 Hz, J = 4.4 Hz, 2 H), 3.20−3.11 (m, 2 H),

dx.doi.org/10.1021/jo501302f | J. Org. Chem. 2014, 79, 7152−7161

3.09−3.02 (m, 2 H), 2.91 (virt q, $J \approx 7.3$ Hz, 2 H), 1.99 (t, $J = 7.3$ Hz, 2 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 54.2, 51.5, 49.6, 37.8, 26.0. MS (EI, 70 EV): m/z (%) 139 (100) [(M + H)$^+$]. HRMS (ESI): calculated for $C_8H_{14}N_2^+$ [(M)]$^+$ 138.1160, found 138.1154.

***N-tert*-Butoxycarbonyl-9-(2-chloro-5-fluoropyrimidin-4-yl)-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (32).** *N-tert*-Butoxycarbonyl-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (**29**; 363 mg, 1.52 mmol, 1.0 equiv) was dissolved in MeCN (5.00 mL). 2,4-Dichloro-5-fluoropyrimidine (254 mg, 1.52 mmol, 1.0 equiv) and triethlyamine (276 μL, 1.98 mmol, 1.3 equiv) were added, and the mixture was stirred at room temperature for 12 h. The solvent was removed and the residue purified by column chromatography (heptane/EtOAc 1/1) to give the desired product as a white solid (**32**; 494 mg, 88%). Mp: 138−139 °C. $R_f = 0.39$ (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2975 (w, C−H), 2941 (w), 2857 (w, C−H), 1687(vs, C═O), 1596 (vs), 1556 (m), 1376 (s), 1363 (s), 1242 (s), 1119 (s), 1021 (m), 880 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.93 (d, $^3J_F = 5.1$ Hz, 1 H), 4.25 (dd, $J = 12.3$ Hz, $^5J_F = 1.9$ Hz, 1 H), 4.04 (d, $J = 12.3$ Hz, 1 H), 3.94−3.73 (m, 1 H), 3.66 (dd, $J = 11.9$ Hz, $J = 7.7$ Hz, 1 H), 3.54−3.41 (m, 1 H), 3.36 (dd, $J = 11.9$ Hz, $J = 6.5$ Hz, 1 H), 3.35−3.34 (m, 1 H), 3.16 (d, $J = 11.0$ Hz, 1 H), 2.75 (dd, $J = 11.4$ Hz, $J = 6.5$ Hz, 1 H), 2.62 (ddd, $J = 13.6$ Hz, $J = 7.2$ Hz, $J = 6.3$ Hz, 1 H), 2.03−1.98 (m, 1 H), 1.94 (ddd, $J = 13.6$ Hz, $J = 8.6$ Hz, $J = 4.9$ Hz, 1 H), 1.50 (s, 9 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 155.2, 154.3 (d, $^4J_F = 2.2$ Hz), 152.4 (d, $^2J_F = 8.8$ Hz), 145.6 (d, $^1J_F = 256.7$ Hz), 142.7 (d, $^3J_F = 25.1$ Hz), 79.8, 55.5 (d, $^4J_F = 6.1$ Hz), 54.6 (d, $^4J_F = 5.0$ Hz), 53.1, 51.7, 40.6, 39.3, 29.4, 28.5. MS (EI, 70 EV): m/z (%) 369 (100) [(M + H)$^+$]. HRMS (ESI): calculated for $C_{17}H_{22}ClFN_4O_2^+$ [(M)]$^+$ 368.1415, found 368.1416.

9-(2-Chloro-5-fluoropyrimidin-4-yl)-3-pyrrolidin-1-ylmethanone-3,9-diazatricyclo[5.3.0.0^{1,5}]decane (33). Substrate **32** (26.3 mg, 71.3 μmol, 1.0 equiv) was dissolved in HCl (4 M in dioxane) (178 μL, 713 μmol, 10 equiv), and the reaction mixture was stirred at room temperature for 12 h. Subsequently, the solvent was removed, saturated aqueous $NaHCO_3$ was added, and the product was extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and filtered and the solvent removed to give 3,9-diazatricyclo[5.3.0.0^{1,5}]-decane as a colorless oil that was used without further purification in the next step (25.8 mg, 99.3%). The crude amine (21.8 mg, 71.4 μmol, 1.0 equiv) was dissolved in dichloromethane (2 mL). Triethylamine (29.9 μL, 214 μmol, 3.0 equiv) and pyrrolidine-1-carbonyl chloride (9.54 mg, 71.4 μmol, 1.0 equiv) were added, and the reaction mixture was stirred at room temperature for 2 h. The solvent was then removed and the crude product purified by column chromatography (heptane/EtOAc 1/1) to give the desired product **33** as a white solid (23.0 mg, 88%). Mp: 100−101 °C. $R_f = 0.21$ (heptane/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2930 (w, C−H), 1865 (w, C−H), 1744 (w), 1692 (s, C═O), 1591 (vs), 1559 (m), 1465 (m), 1364 (s), 1323 (m), 1239 (m), 1118 (m), 1010 (m), 752 (m). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.93 (d, $^3J_F = 5.1$ Hz, 1 H), 4.23 (dd, $J = 12.3$ Hz, $J = 2.0$ Hz, 1 H), 4.04 (d, $J = 12.0$ Hz, 1 H), 3.85 (d, $J = 11.5$ Hz, 1 H), 3.67 (dd, $J = 12.0$ Hz, $J = 7.9$ Hz, 1 H), 3.63 (d, $J = 11.1$ Hz, 1 H), 3.46−3.42 (m, 4 H), 3.37 (d, $J = 12.3$ Hz, 1 H), 3.28 (dd, $J = 11.1$ Hz, $J = 2.0$ Hz, 1 H), 3.13 (d, $J = 11.5$ Hz, 1 H), 2.74 (dd, $J = 12.7$ Hz, $J = 7.9$ Hz, 1 H), 2.63−2.53 (m, 1 H), 2.00 (ddd, $J = 13.5$ Hz, $J = 8.8$ Hz, $J = 5.1$ Hz, 1 H), 1.91 (ddd, $J = 13.5$ Hz, $J = 7.9$ Hz, $J = 4.9$ Hz, 1 H), 1.87 (dt, $J = 6.6$ Hz, $J = 3.3$ Hz, 4 H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 161.8, 154.3 (d, $J_F = 2.2$ Hz), 152.4 (d, $J_F = 8.8$ Hz), 145.6 (d, $J_F = 259.7$ Hz), 142.6 (d, $J_F = 25.1$ Hz), 55.6 (d, $J_F = 6.1$ Hz), 54.4 (d, $^4J_F = 5.2$ Hz), 54.3, 53.6, 53.2, 48.3, 40.2, 38.9, 29.2, 26.0. MS (EI, 70 EV): m/z (%) 357 (100) [(M + H)$^+$]. HRMS (ESI): calculated for $C_{17}H_{21}ClFN_5O^+$ [(M)]$^+$ 365.1419, found 365.1426.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and CIF files giving schemes and explanations for the synthesis of the alcohol precursor to compound **7** and for the formation of side products upon [2 + 2] photocycloaddition of substrates **8** and **19**, ^{1}H and ^{13}C NMR spectra of all compounds reported in the Experimental Section, and X-ray data for the crystal structures of **5a**, **25**, and **37a** (tosyl derivative). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

D.A.F. wishes to acknowledge funding by the Roche Postdoc Fellowship (RPF) Program. We thank Professor Klaus Müller for helpful discussions.

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