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Photochemical Rearrangement of *N*-Mesyloxylactams: Stereospecific Formation of *N*-Heterocycles

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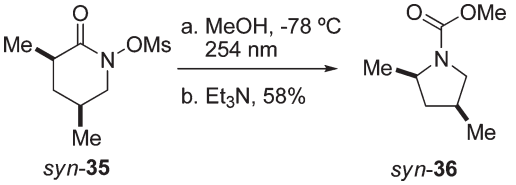

syn-**35** *syn*-**36**

N-Mesyloxylactams undergo an efficient ring-contraction to *N*-heterocycles of various ring sizes. Yields increase with the degree of substitution α to the carbonyl. The stereochemical information of a chiral migrating carbon is conserved making this reaction a synthetically useful complement to the well-known Hofmann, Curtius, Lossen, and Schmidt rearrangements.

Introduction

The key biochemical roles played by alkaloids in nature make this class of molecules the center of intense research in the fields of medicinal and synthetic chemistry.[1] Alkaloids comprising *N*-heterocycles where the nitrogen atom is flanked by one or two chiral carbons have attracted special attention because of the number of biologically active compounds that possess this structural feature and also because they are particularly challenging molecular targets for synthesis. A variety of methods exist for the synthesis of *N*-heterocycles that is inventoried in several reviews[2] and books.[3]

The well-known Schmidt, Hofmann, Curtius, and Lossen rearrangements have been used extensively to create a C−N bond from a C−C bond in a stereospecific fashion.[4] Thus far, all of these methods can only transform primary acyclic acyl azides or amide derivatives **1a**−**c** to carbamate **2** (Scheme 1), with the exception of the Hofmann rearrangement of cyclic imides, which, in any case, probably involves an acyclic intermediate.[5] We have previously reported a novel photochemical ring-contraction of *N*-chlorolactams **3b** (X = Cl) to *N*-heterocycles **4** in yields ranging from 5% to 56% (Scheme 1).[6] By contrast to

(1) For selected books and reviews, see: (a) Hesse, M. In *The Alkaloids, Nature's Curse or Blessing?*; Wiley VCH: Zürich, Switzerland, 2002; pp 1−413. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139−165. Cordell, G. A. In *The Alkaloids: Chemistry and Biology*; Elsevier: San Diego, CA, 2003; Vol. 60, pp 1−282. (c) Kobayashi, J.; Morita, H. *Alkaloids* **2003**, *60*, 165–205. (d) Yamamura, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 29, 265 pp. (e) Moldvai, I.; Temesvari-Major, E.; Incze, M.; Doernyei, G.; Szentirmay, E.; Szantay, C. *Helv. Chim. Acta* **2005**, *88*, 1344–1356. (f) Reynolds, T. *Phytochemistry* **2005**, *66*, 1399–1406. (g) Lewis, J. R. *Nat. Prod. Rep.* **2001**, *18*, 95–128.

(2) (a) Martin, S. F. *Pure Appl. Chem.* **1997**, *69*, 571–576. (b) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed.* **1989**, *28*, 1067–1068. (c) Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*, 1339–1347. (d) Fox, D. J.; House, D.; Warren, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2462–2482. (e) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325. (f) Shibata, I.; Kato, H.; Kanazawa, N.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 466–467. (g) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (h) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (i) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433–2480. (j) Jagodzinski, T. S. *Chem. Rev.* **2003**, *103*, 197–228. (k) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2310. (l) Barluenga, J.; Santamaria, J.; Tomas, M. *Chem. Rev.* **2004**, *104*, 2259–2284.

(3) (a) Fattorusso, E.; Taglialatela-Scafati, O. In *Modern alkaloids; structure, isolation, synthesis and biology*; WILEY-VCH, Weinheim, Germany, 2008; pp 1−665. (b) van der Eycken, E.; Kappe, C. O. In *Microwave-Assisted Synthesis of Heterocycles*, 1st ed.; Springer: Paris, France, 2006; pp 1−309. (c) Padwa, A.; Pearson, W. H. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, 1st ed.; WILEY-Interscience: London, UK, 2002; pp 1−952. (d) El Ashry, E. S. H.; El Nemr, A. In *Synthesis of Naturally Occurring Nitrogen Heterocycles from Carbohydrates*, 1st ed.; WILEY-Blackwell: Oxford, UK, 2005; pp 1−464. (e) Eicher, T.; Hauptmann, S.; Suschitzky, H. In *The Chemistry Of Heterocycles: Structure, Reactions, Syntheses and Applications*, 2003 ed.; John WILEY & Sons: Etobicoke, Canada, 2002; pp 1−514.

(4) (a) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, S.; Wiley: New York, 1971; pp 1−626. (b) Walis, E. S.; Lane, J. F. *Org. React.* **1946**, *3*, 267–306. (c) Wolff, H. *Org. React.* **1946**, *3*, 307–336. (d) Smith, P. A. S. *Org. React.* **1946**, 337–449. (e) Senanayake, C. H.; Fredenburg, L. E.; Reamer, R. A.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 7947–7948. (f) Gogoi, P.; Konwar, D. *Tetrahedron Lett.* **2007**, *48*, 531–533. (g) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed.* **1974**, *13*, 376. (h) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146–156.

(5) See, for example: Jianga, X.; Wanga, J.; Hua, J.; Gea, Z.; Hua, Y.; Hua, H.; Covey, D. F. *Steroids* **2001**, *66*, 655–662.

(6) (a) Drouin, A.; Lessard, J. *Tetrahedron Lett.* **2006**, *47*, 4285–4288. (b) Winter, D. K.; Drouin, A.; Lessard, J.; Spino, C. *J. Org. Chem.* **2010**, *75*, 2610–2618.

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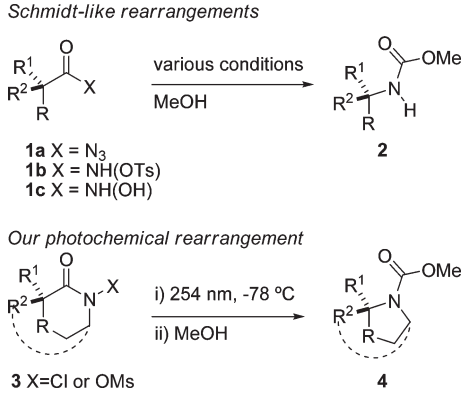
SCHEME 1. Schmidt-Like Rearrangements and the Ring-Contraction of *N*-Heterosubstituted Lactams



the Lossen rearrangement, only cyclic or polycyclic structures like **3** undergo rearrangement in this photochemical ring-contraction. Importantly, chirality at the migrating carbon in **3** is wholly retained in the ring-contraction product **4**. The complementary nature of our rearrangement to the Lossen rearrangement makes it a highly desirable transformation for organic chemists. Some advantages include the ease of construction of *N*-substituted lactams from the cyclization of carboxylic acid and amine derivatives,[7] and the ease of introduction of chirality α to carbonyls.[8] Yet, the low yields (usually $<40\%$) of the desired products **4** from **3b** (X = Cl) represented a major obstacle to the application of this methodology in synthesis. The parent amide **3a** (X = H) and chlorinated byproduct account for the remaining material, owing to the presence of chlorine radical.[6b] We therefore investigated alternative *N*-substituents in order to prevent the formation of such byproduct in the hope of augmenting the yield of the desired product **4**. We now report that the photochemical ring contraction of *O*-mesylated hydroxamic acids **3c** (X = OMs) gives high yields of the desired ring-contracted *N*-heterocycles **4** unaccompanied by the parent amide or byproduct derived from radical pathways.[9] This rearrangement is unique,[10,11] and now represents a useful complement to the arsenal of existing methods for the synthesis of chiral *N*-heterocycles.

Results and Discussion

The photochemical ring contractions of 6-membered *N*-mesyloxylactams **5c** and **6c** were carried out at 254 nm in anhydrous methanol at −78 °C. To our delight, pyrrolidines **17** and **18** were obtained in useful yields (Table 1, entries 1 and 2). The photolysis can be carried out at room temperature and/or with wet methanol (15% water) with, as a consequence, a lower yield of the desired products (10−20% decrease in yields) and the formation of some unidentified decomposition products. At −78 °C, the yields were higher by 40% and 30%, respectively, than those obtained from the corresponding *N*-chlorolactams.[6b] The very fact that we could run the reaction in methanol hints to the absence of free radicals in the solution. In addition, a constant bubbling of oxygen through the reaction mixture had no noticeable effect on the outcome of the reaction. The rearrangement of *N*-chlorolactams was best run in dichloromethane and could not be performed in solvents like methanol, presumably due to fast hydrogen abstraction from a C−H bond by a chlorine radical. Piperidines **19** and **20** were obtained from the photochemical ring-contraction of 7-membered *N*-mesyloxylactams **7c** and **8c** (entries 3 and 4). Azepane **21** was obtained in 56% yield from the corresponding 8-membered *N*-mesyloxylactam **9c** (entry 5).

As was the case for the analogous *N*-chlorolactams, a higher substitution at the migrating carbon led to a higher yield of rearrangement product (compare entries 1 and 2 as well as 3 and 4). However, the yield of **19** (entry 3) is *much higher than expected* since irradiation of the homologous *N*-chlorolactam **7b** (structure **7c** with OMs = Cl) gave only a 6% yield of rearranged product **19**.[6]

The result of entry 3 compelled us to try the photochemical rearrangement of acyclic *N*-mesyloxyamide **30c** and to our great surprise, an 18% yield of rearranged product **31** was obtained, along with 60% of the expected[10] *N*-acyl hemiaminal ether **32** (Scheme 2). The analogous *N*-chlorolactam **30b** (OMs = Cl) gave no trace of the rearranged product **31**, 36% of the parent amide **30a** (OMs = H), 23% of product **32**, and several other products (see the Supporting Information). In fact, acyclic *N*-chloroamides have never yielded rearrangement products under our irradiation conditions. To the best of our knowledge, this is the first example of a rearrangement involving an acyclic *secondary* amide derivative of any kind. We are further exploring the scope of this reaction for acyclic amide derivatives.

Rigid bicyclic compounds are good substrates for the rearrangement as the yield of product **22** from *N*-mesyloxylactam **10c** suggests (entry 6). Contrary to what was found in the photochemical ring-contraction of the corresponding *N*-chlorolactams, the parent amides **5a**−**16a** (OMs = H) were never detected after photolysis, which is, again, indicative of the absence of radical pathways.[6b] The mechanism of the reaction is still unclear but we believe that either an excited state **3*** decays directly to the rearranged product **4′** (Scheme 3) or that homolytic cleavage to **3′** occurs followed by either electron transfer with concomitant rearrangement to **4′** from a tight radical pair or electron transfer to the ion pair **3′′**, which we deem unlikely. If one of the electron transfer pathways is operative, the electron transfer must occur before the mesyloxy radical in **3′** escapes from the solvent cage, thus faster than in the case of the *N*-chlorolactams.[10] Methanol then reacts with the intermediate **4′** to give the final product **4**.

Photolysis of *O*-mesyloxylactam **11c** in dichloromethane followed by a methanolic treatment yielded a 71% yield of **23** and 12% of **34** (entry 7 and Scheme 3). When carried out in methanol, carbamate **23** was obtained in only 48% yield from irradiation of **11c**, accompanied by 51% of the linear acetal **34**. Irradiation in methanol of *N*-mesyloxylactam **12c**, bearing a less electron-donating acetate on the migrating

(7) Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Lactones and Lactams*; John WILEY & Sons Inc.: Hoboken, NJ, 1993; pp 1−1100 and references cited therein.

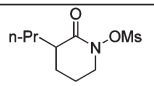
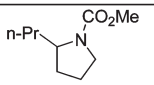
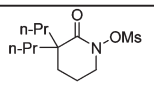
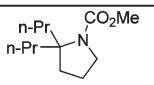
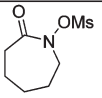
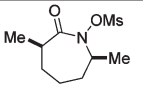
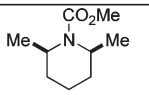
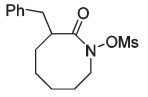
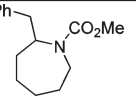
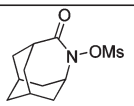
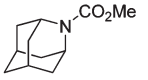
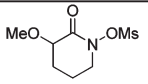
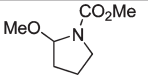
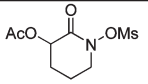
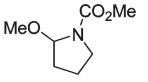
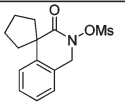
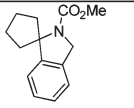
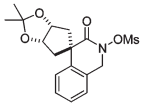
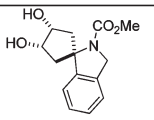
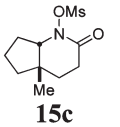
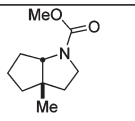
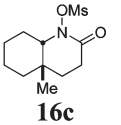
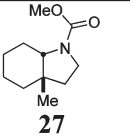
(8) For reviews, see: (a) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947. and references cited therein. (b) Spino, C. *Org. Prep. Proced. Int* **2003**, *35*, 1–140.

(9) See the Supporting Information for the synthesis of the *N*-mesyloxy lactams.

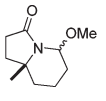
(10) Edwards et al. have reported that the photolysis of *N*-mesyloxy-4-aza-cholestane-3-one in methanol at room temperature gave the undesired ring contracted carbamate in 35% yield besides several other products. To the best of our knowledge, no further study of this reaction has been reported since. See: Edwards, O. E.; Grue-Sorensen, G.; Blackwell, B. A. *Can. J. Chem.* **1997**, *75*, 857–872.

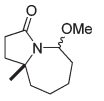
(11) Di Maio and Tardella have reported two low-yielding examples of thermal ring-contraction of hydroxamic acid in phosphoric acid at 180 °C. See: DiMaio, G.; Tardella, P. A. *Proc. Chem. Soc.* **1963**, 224.

TABLE 1. Results Obtained from the Irradiation of *N*-Mesyloxylactams 5c−16c of Varying Ring Sizes

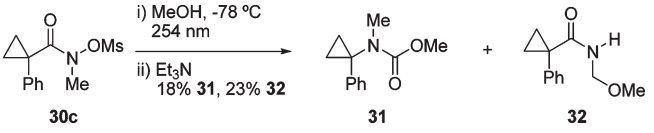
Entry	*N*-Mesyloxylactam	Products	(yield)[a]
1	 **5c**	 **17**	77
2	 **6c**	 **18**	86
3	 **7c**	 **19**	37
4[b]	 **8c**	 **20**	63
5	 **9c**	 **21**	56
6	 **10c**	 **22**	72
7[c]	 **11c**	 **23**	71 (+12% **34**[d])
8[e]	 **12c**	 **23**	65 (+30% **34**[d])
9[e]	 **13c**	 **24**	48
10	 **14c**	 **25**	44
11[f]	 **15c**	 **26**	47
12[f]	 **16c**	 **27**	54

[a]Reaction conditions: MeOH, 254 nm, −78 °C, Et_3N. [b]Isolated yields. [c]Conditions: (i) DCM, 254 nm, −78 °C; (ii) MeOH, Et_3N. [d]See Scheme 3. [e]Conditions: (i) DCM, Et_3N, 254 nm, −78 °C; (ii) MeOH. [f]The isomeric rearrangement products **28** (20%, entry 10) and **29** (19%, entry11) were also isolated.

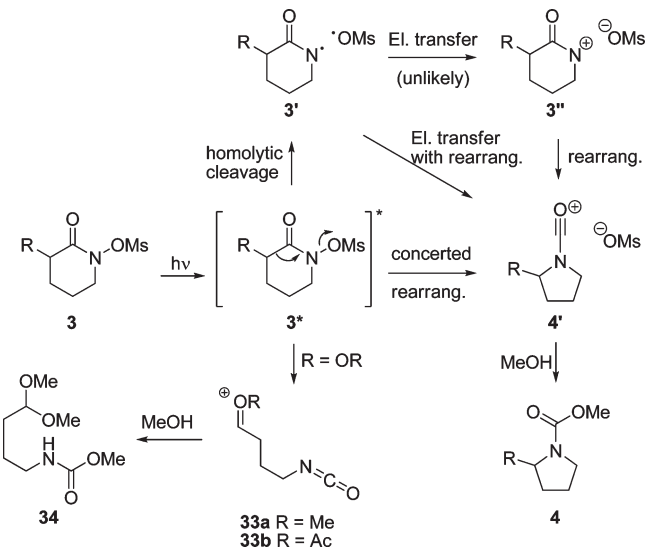

28


29

SCHEME 2. Rearrangement of Acyclic *N*-Mesyloxylactam 30c



SCHEME 3. Mechanistic Pathways for the Formation of Product 4 or Acetal 34



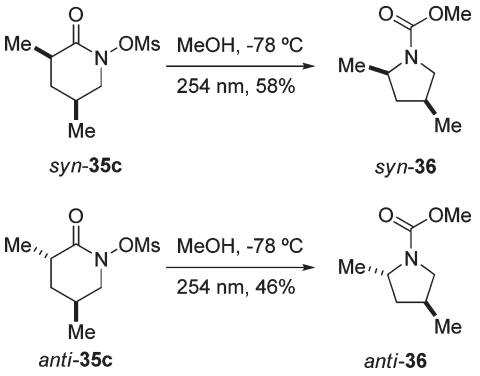
carbon, afforded 65% yield of **23**, along with 30% yield of **34** (entry 8). The substitution of acetate for a methoxy group in this experiment indicates that the reaction medium becomes acidic upon irradiation. Though the mechanistic details of this fragmentation are still unknown, it is probable that ring cleavage to intermediate **33a** or **33b** is in competition with the ring contraction pathway leading to **23**. It is also probable that the increased polarity of methanol as compared to dichloromethane favors the formation of the charged species **33a** or **33b**. This fragmentation is analogous to the abnormal Beckmann rearrangement.[12]

Two spirocyclic *N*-mesyloxylactams **13c** and the more complex **14c** rearranged efficiently to isoindolines **24** and **25**, respectively (entries 9 and 10). In this particular case, the rearrangement product **24** was sensitive to light and decomposed upon prolonged exposure to irradiation, which explains the lower than expected yield. Again, the increasing acidity of the solution upon irradiation is probably responsible for the cleavage of the acetonide group in the case of **14c**. Strangely, the addition of base (triethylamine) during irradiation had little effect on the yield of rearrangement and on the cleavage of the acetonide.

Lastly, bicyclic products **26** and **27** were formed in 47% and 54% yield, respectively (entries 11 and 12). These yields are quite impressive *considering that there is no substitution* α to the carbonyl in these two cases. In each of these two particular cases, a product from the migration of the angular quaternary carbon was also isolated (see footnote f of Table 1). The latter are rarely seen and we are currently looking at structural features of the precursors that may favor this migration.

(12) Błaszczyk, K.; Koenig, H.; Mel, K.; Paryzek, Z. *Tetrahedron* **2006**, *62*, 1069–1078. and references cited therein.

SCHEME 4. Stereospecific Rearrangement of *cis*- and *trans*-35



Importantly, the rearrangement of *N*-mesyloxylactams is stereospecific and occurs with complete retention of stereochemistry at the migrating carbon. Indeed, racemic *syn*-**35c** and *anti*-**35c** each gave a single diastereomer *syn*-**36** and *anti*-**36**, respectively (Scheme 4).

The photochemical ring-contraction of six- to eight-membered *N*-mesyloxylactams constitutes a unique and synthetically useful route to *N*-heterocycles. Generally speaking, 6-membered *N*-substituted lactams rearrange in slightly higher yields than their 7- or 8-membered counterpart, and higher substitution α to the amide carbonyl leads to increased yields. The method is complementary to the Lossen and related rearrangements, and should be a useful addition in the arsenal of the synthetic chemist. Mechanistic as well as synthetic explorations of this reaction are presently underway and will be reported in due course.

Experimental Section

Methyl 2-Benzylazepane-1-carboxylate (21). A solution of the mesylated hydroxamic acid **9c** (18 mg, 0,058 mmol) in anhydrous MeOH at −78 °C was placed in a quartz cell and irradiated at 254 nm until no more starting material was seen. After 5 h the reaction was warmed to room temperature and 1 mL of Et_3N was added to the mixture. After 1 h at room temperature the mixture was concentrated under reduced pressure. The crude mixture was purified on silica gel, eluting with 1:9 EtOAc/hexanes. Methylcarbamate **21** (8 mg, 0,03 mmol, 56% yield) was recovered as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) rotamer A: 7.29−7.10 (m, 5H), 4.30−4.17 (m, 1H), 3.70 (s, 3H), 3.66 (br d, 1H, J = 12.9 Hz), 2.87 (dd, 1H, J_1 = 12.9 Hz, J_2 = 4.7 Hz), 2.78−2.57 (m, 2H), 1.97−1.56 (m, 4H), 1.50−1.10 (m, 4H); rotamer B: 7.29−7.10 (m, 5H), 4.10 (hex, 1H, J = 6.0 Hz), 3.85 (br d, 1H, J = 14.1 Hz), 3.52 (s, 3H), 2.78−2.57 (m, 3H), 1.97−1.56 (m, 4H), 1.50−1.10 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) (rotamers noted with*) 157.0, 138.8, 129.4, 129.3*, 128.2, 126.1, 57.5, 57.3*, 52.4, 52.2*, 42.0, 41.5, 41.0, 33.6, 32.7, 29.7, 29.6*, 28.9, 25.1. LRMS (*m*/*z*, rel intensity) 248 ([MH]$^+$, 1), 216 (40), 157 (80), 102 (80), 86 (80), 84 (100). HRMS calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1577. IR ($CHCl_3$) ν (cm^{-1}) 3067, 3022, 2976, 2897, 1671.

Methyl 2-Methoxypyrrolidine-1-carboxylate (23) and Methyl 4,4-Dimethoxybutylcarbamate (34) From 11c. *N*-mesylate **11c** (97.0 mg, 0.435 mmol) was dissolved with anhydrous dichloromethane (29 mL) and added into a Rayonet reactor chamber equipped with 254 nm UV lamps. The reaction mixture was then exposed to UV light at −78 °C under N_2 atmosphere until completion (1.5 h). The solution was then transferred to a stirring solution of MeOH (5 mL) and triethylamine (61 μL, 0.435 mmol) and left stirring for 16 h. The solution was then concentrated under reduced pressure to a light yellow oil. The oil was partitioned

between dichloromethane (50 mL) and H_2O (50 mL). The aqueous was extracted twice more with dichloromethane (25 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to a clear oil. The oil was taken up in dichloromethane and purified by flash chromatography with a 1:1 to 9:1 ether/hexanes solvent system to yield **23** as clear oil (48.9 mg, 71%). The acetal **34** (9.8 mg, 12%) was also isolated as a colorless oil.

Compound **23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) rotamer A: 5.10 (d, 1H, J = 4.7 Hz), 3.61 (s, 3H), 3.40−3.20 (m, 2H), 3.27 (s, 3H), 2.05−1.57 (m, 4H), rotamer B: 4.99 (d, 1H, J = 4.7 Hz), 3.61 (s, 3H), 3.40−3.20 (m, 2H), 3.20 (s, 3H), 2.05−1.57 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) rotamer A: 156.3 (s), 89.0 (d), 55.7 (q), 52.3 (q), 45.6 (t), 31.8 (t), 22.6 (t); rotamer B: 156.3 (s), 88.4 (d), 55.0 (q), 52.3 (q), 45.8 (t), 32.3 (t), 21.6 (t). LRMS (m/z, rel intensity) 144 ($M^+ - CH_3$, 10), 128 (M− -OMe, 100). HRMS calcd for $C_6H_{10}NO_3$ ($M^+ - CH_3$) 144.0661, found 144.0663. IR (neat) ν (cm^{-1}) 2951, 2886, 2839, 1700, 1446.

Compound **34**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.78 (br s, 1H), 4.36 (t, 1H, J = 5.2 Hz), 3.65 (s, 3H), 3.32 (s, 6H), 3.19 (dd, 2H, J = 12.1, 6.1 Hz), 1.67−1.51 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 157.0 (s), 104.2 (d), 52.9 (q), 52.0 (q), 40.7 (t), 29.7 (t), 25.0 (t). LRMS (m/z, rel intensity) 158 ($M^+ - CH_5O$, 2), 144 ($M^+ - C_2H_7O$, 1), 128 ($M - C_2H_7O_2$, 100). HRMS calcd for $C_7H_{12}NO_3$ ($M^+ - C_1H_5O$) 158.0817, found 158.0824. IR (neat) ν (cm^{-1}) 3342, 2949, 2830, 1708, 1540, 1258.

Methyl 2-Methoxypyrrolidine-1-carboxylate (23) and Methyl 4,4-Dimethoxybutylcarbamate (34) From 12c. *N*-Mesylate **12c** (0.261 g, 1.04 mmol) was dissolved with anhydrous methanol (69 mL) and added into a Rayonet reactor chamber equipped with 254 nm UV lamps. The reaction mixture was then exposed to UV light at −78 °C under N_2 atmosphere until completion (3 h). The solution was then transferred to a round-bottomed flask containing triethylamine (0.15 mL, 1.04 mmol) and left stirring for 30 min. The solution was then concentrated under reduced pressure to a light yellow oil. The oil was partitioned between dichloromethane (50 mL) and H_2O (50 mL). The aqueous was extracted twice more with dichloromethane (25 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. The oil was taken up in dichloromethane and purified by flash chromatography with a 1:1 to 9:1 ether/hexanes solvent system to yield **23** as clear oil (0.108 g, 65%). The acetal **34** (50.1 mg, 30%) was also isolated as a colorless oil. See the formation of the same compounds from **11c** for the characterization data.

Methyl Spiro[cyclopentane-1,1′-isoindoline]-2′-carboxylate (24). *N*-Mesylate **13c** (0.201 g, 0.679 mmol) was dissolved with dichloromethane (45 mL) and added into a Rayonet reactor chamber equipped with 254 nm UV lamps. Triethylamine (0.19 mL, 1.36 mmol) was added to the reaction mixture and the resulting solution was then exposed to UV light at −78 °C under N_2 atmosphere until no more starting material was seen by TLC (8 h). Methanol (10 mL) was then added and the resulting solution was allowed to stir for 15 h at room temperature. The solution was then concentrated to yield a light yellow oil. The oil was then partitioned between dichloromethane (50 mL) and H_2O (25 mL). The aqueous layer was extracted twice more with dichloromethane (25 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield an orange oil. The oil was taken up in dichloromethane and purified by flash chromatography on silica gel (5:1 to 1:1 hexanes/diethyl ether) to yield **24** as a clear oil (71 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) rotamer A: 7.31−7.16 (m, 4H), 4.73 (s, 2H), 3.79 (s, 3H), 2.62−2.38 (m, 2H), 2.22−2.12 (m, 2H), 2.09−1.78 (m, 4H); rotamer B: 7.31−7.16 (m, 4H), 4.67 (s, 2H), 3.73 (s, 3H), 2.62−2.38 (m, 2H), 2.22−2.12 (m, 2H), 2.09−1.78 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) rotamer A: 154.2 (s), 149.5 (s), 133.8 (s), 128.0 (d), 127.0 (d), 121.8 (d), 121.4 (d), 75.5 (s), 53.1 (t), 52.0 (q), 41.3 (t), 27.0 (t); rotamer B: 154.2 (s), 149.5 (s), 133.8 (s), 128.0 (d), 127.0 (d), 121.8 (d), 121.4 (d), 75.5 (s), 52.3 (t), 52.0 (q), 40.0 (t), 27.0 (t). IR (neat) ν (cm^{-1}) 2958, 2869, 1704, 1452, 1377. LRMS (m/z, rel intensity) 231 (M^+, 25), 202 (100), 172 ($M^+ - C_2H_3O_2$, 15), 144 (40). HRMS calcd for $C_{14}H_{17}N_1O_2$ 231.1259, found 231.1254.

Methyl (1*S,3*R**,4*S**)-3,4-Dihydroxyspiro[cyclopentane-1,1′-isoindoline]-2′-carboxylate (25).** *N*-Mesylate **14c** (0.141 g, 0.384 mmol) was dissolved with dichloromethane (26 mL) and added into a Rayonet reactor chamber equipped with 254 nm UV lamps. Triethylamine (0.11 mL) was added to the reaction mixture and the resulting solution was then exposed to UV light at −78 °C under N_2 atmosphere until no more starting material was seen by TLC (4 h). Methanol (10 mL) was then added and the resulting solution was allowed to stir for 15 h at room temperature. The solution was then concentrated to yield an orange oil. The oil was then partitioned between dichloromethane (50 mL) and H_2O (25 mL). The aqueous layer was extracted twice more with dichloromethane (25 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give an orange oil. The oil was taken up in dichloromethane and purified by flash chromatography on silica gel (1:2 to 6:1 EtOAc/hexanes) to yield **25** a clear oil (45 mg, 44%). Note that the ^{13}C assignment contains both rotamers. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) rotamer A: 7.79 (d, 1H, J = 7.3 Hz), 7.32 (t, 1H, J = 7.3 Hz), 7.24 (t, 1H, J = 7.3 Hz), 7.14 (d, 1H, J = 7.3 Hz), 4.75 (t, 2H, J = 4.4 Hz), 4.65 (s, 2H), 3.73 (s, 3H), 2.89 (br s, 2H), 2.68 (dd, 2H, J = 14.6, 6.3 Hz), 2.18 (dd, 2H, J = 14.6, 5.0 Hz); rotamer B: 7.79 (d, 1H, J = 7.7 Hz), 7.32 (t, 1H, J = 7.7 Hz), 7.24 (t, 1H, J = 7.7 Hz), 7.14 (d, 1H, J = 7.7 Hz), 4.71 (s, 2H), 4.58−4.52 (m, 2H), 3.79 (s, 3H), 2,61 (dd, 2H, J = 14.9, 6.6 Hz), 2.20 (dd, 2H, J = 14.9, 5.0 Hz), 1.79 (br s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) rotamer A + B: 154.6 (s), 147.8 (s), 133.7 (s), 128.4 (d), 127.3 (d), 123.8 (d), 121.3 (d), 74.7 (d), 73.2 (s), 53.1 (t), 52.3 (t), 52.3 (q), 47.6 (t), 46.4 (t). IR (neat) ν (cm^{-1}) 3560−3150 (br), 2949, 2869, 1681, 1452, 1381, 1112, 1085. LRMS (m/z, rel intensity) 263 (M^+, 20), 218 (40), 160 (100). HRMS calcd for $C_{14}H_{17}N_1O_4$ 263.1157, found 263.1164.

Photolysis Products 26 and 28. *O*-Mesylhydroxamic acid **15c** (400 mg, 1.62 mmol) was dissolved in methanol (110 mL) at room temperature. The solution was transferred to a quartz cell, cooled to −78 °C, and irradiated with 254 nm light in a Rayonet for 3.5 h. The reaction mixture was transferred to a round-bottomed flask and triethylamine (0.25 mL, 1.8 mmol) was added. After being stirred at room temperature for 18 h, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (25 mL) and water (25 mL). The aqueous layer was extracted with dichloromethane (3 × 25 mL), the organic extracts were then combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, using ethyl acetate and hexanes (15:85 to 75:25) as eluent to give **26** as a colorless oil (139 mg, 47%) and **28** as a colorless oil (58 mg, 20%).

26: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.67 (s, 3H), 3.65−3.36 (m, 3H), 1.94−1.40 (m, 8H), 1.15 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) rotamer A: 155.4 (s), 69.6 (d), 52.1 (q), 50.3 (s), 46.5 (t), 39.1 (t), 38.1 (t), 33.8 (t), 26.3 (q), 24.9 (t); rotamer B: 155.4 (s), 69.0 (d), 52.1 (q), 49.4 (s), 46.1 (t), 39.1 (t), 37.5 (t), 32.9 (t), 26.3 (q), 24.9 (t). IR (neat) ν (cm^{-1}) 2946, 2867, 1723, 1712, 1690, 1447, 1350, 1243, 1189, 1122, 1086. LRMS (m/z, rel intensity) 183 (M^+, 15), 168 (60), 140 (100), 81 (30). HRMS calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1254.

28: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.28 (d, 1H, J = 3.8 Hz), 3.27 (s, 3H), 2.63−2.50 (m, 1H), 2.32 (ddd, 1H, J = 17.2, 9.8, 2.1 Hz), 2.05−1.33 (m, 8H), 1.37 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 175.0 (s), 78.6 (d), 59.1 (s), 55.3 (q), 39.0 (t), 35.9 (t), 29.9 (t), 29.3 (t), 24.4 (q), 15.7 (t). IR (neat) ν (cm^{-1}) 2942, 2874, 2849, 2842, 1701, 1690, 1672, 1393, 1079. LRMS (m/z, rel intensity) 183 (M^+, 5), 168 (100), 152 (100), 140 (30), 98 (50). HRMS calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1254.

Photolysis Products 27 and 29. *O*-Mesylhydroxamic acid **16c** (230 mg, 0.879 mmol) was dissolved in methanol (60 mL) at room temperature. The solution was transferred to a quartz cell, cooled to −78 °C, and irradiated with 254 nm light in a Rayonet for 2 h. The reaction mixture was transferred to a round-bottomed flask and triethylamine (0.14 mL, 0.97 mmol) was added. After the solution was stirred at room temperature for 18 h, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (25 mL) and water (25 mL). The aqueous layer was extracted with dichloromethane (2 × 25 mL), the organic extracts were then combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with ethyl acetate and hexanes (25:75 then 50:50) as eluent to give **27** as a colorless oil (94 mg, 54%) and **29** as a colorless oil (33 mg, 19%).

27: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.67 (s, 3H), 3.60−3.23 (m, 3H), 2.27−1.84 (m, 2H), 1.65−1.03 (m, 8H), 0.98 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) rotamer A: 155.9 (s), 62.6 (d), 52.0 (q), 43.7 (t), 40.3 (s), 34.7 (t), 33.1 (t), 28.9 (t), 27.8 (q), 23.7 (t), 21.7 (t); rotamer B: 155.5 (s), 62.6 (d), 52.0 (q), 43.5 (t), 39.5 (s), 34.5 (t), 31.6 (t), 28.1 (t), 27.6 (q), 23.3 (t), 21.7 (t). IR (neat) ν (cm^{-1}) 2958, 2936, 2861, 1704, 1452, 1386, 1107. LRMS (*m*/*z*, rel intensity) 197 (M^+, 30), 182 ([M − Me]$^+$, 100), 140 (80), 122 (30), 88 (30). HRMS calcd for $C_{11}H_{19}NO_2$ 197.1416, found 197.1418.

29: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.37 (dd, 1H, J_1 = 8.2 Hz and J_2 = 6.0 Hz), 3.21 (s, 3H), 2.40 (dd, 2H, J_1 = 8.8 Hz and J_2 = 7.2 Hz), 2.06−1.92 (m, 1H), 1.85−1.49 (m, 8H), 1.34 (s, 3H), 1.27−1.12 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 176.1 (s), 83.0 (d), 63.9 (s), 55.8 (q), 39.5 (t), 34.9 (t), 33.7 (t), 29.8 (t), 25.8 (q), 25.0 (t), 22.7 (t). IR (neat) ν (cm^{-1}) 2936, 2861, 1695, 1461, 1403, 1337, 1081. LRMS (*m*/*z*, rel intensity) 197 (M^+, 1), 182 ([M − Me]$^+$, 50), 166 (40), 98 (100). HRMS calcd for $C_{11}H_{19}NO_2$ 197.1416, found 197.1412. Mp 40−44 °C.

***N*-Methyl *O*-Methyl 1-Phenylcyclopropylcarbamate (31) and *N*-(Methoxymethyl)-1-phenylcyclopropanecarboxamide (32).** *N*-Mesylate **30c** (0.120 g, 0.447 mmol) was dissolved in methanol (30 mL) and added to a Rayonet reactor chamber equipped with 254 nm UV lamps. The reaction mixture was then exposed to UV light at −78 °C under N_2 atmosphere until no more starting material was seen by TLC (6 h). The solution was then concentrated to a light yellow oil. The oil was dissolved with dichloromethane (30 mL) and washed with H_2O (30 mL). The aqueous layer was extracted twice more with dichloromethane (30 mL). The organic layers were then combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. The oil was taken up in dichloromethane and purified by flash chromatography on silica gel (6:1 hexanes/diethyl ether to 100% diethyl ether to 1:1 MeOH: EtOAc) to yield **31** as a clear oil (16 mg, 18%) and **32** as a white solid (60 mg, 60%). Note that characterization includes both rotamers.

31: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.33−7.28 (m, 2H), 7.22−7.18 (m, 2H), 7.06−7.03 (m, 1H), 3.70 (s, 3H), 3.01 (s, 3H), 2.96 (s, 3H), 1.38−1.21 (m, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 158.2 (s), 142.1 (s), 141.3 (s), 128.4 (d), 126.4(d), 126.1 (d), 125.7 (d), 124.6 (d), 52.7 (q), 52.4 (q), 41.9 (s), 34.7 (q), 34.5 (s), 29.7 (t), 20.4 (t), 18.8 (t). IR (neat, NaCl) ν (cm^{-1}) 2958, 2922, 2852, 1708, 1456, 1368, 1200, 1160. LRMS (*m*/*z*, rel intensity) 205 (M^+, 65), 204 (60), 147 (50), 118 (100), 91 (50). HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1104.

32: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43−7.30 (m, 5H), 6.00 (br s, 1H), 4.57 (d, 2H, J = 6.9 Hz), 3.26 (s, 3H), 1.65−1.63 (AB quartet, 2H), 1.12−1.09 (AB quartet, 2H). ^{13}C NMR (100.7 MHz, $CDCl_3$) δ (ppm) 175.1 (s), 139.5 (s), 131.4 (d), 129.4 (d), 128.4 (d), 71.9 (t), 56.0 (q), 30.7 (s), 16.4 (t). IR (neat, NaCl) ν (cm^{-1}) 3355, 2931, 2830, 1655, 1496, 1068. LRMS (*m*/*z*, rel intensity) 205 (M^+, 90), 173 (35), 117 ($M^+ - C_3H_6NO_2$, 100). HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1102. Mp 68−72 °C.

Racemic Methyl *anti*-2,4-Dimethylpyrrolidine-1-carboxylate (*anti*-36). The mesylhydroxamic acid *anti*-**35c** (112 mg, 0.507 mmol) was dissolved in methanol (35 mL), then the solution was transferred to a quartz cell, cooled to −78 °C, and irradiated with 254 nm light for 1 h. The reaction mixture was transferred to a round-bottomed flask and triethylamine (80 μL, 0.55 mmol) was added. After the solution was stirred at room temperature for 15 min, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (25 mL) and water (25 mL), the phases were separated, and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The organic extracts were then combined, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography with ethyl acetate and hexanes (15:85) as eluent to give *anti*-**36** as a colorless oil (37 mg, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) mix of rotamers: 4.07−3.80 (m, 2H), 3.65 (s, 6H), 3.60−3.42 (m, 2H), 2.97−2.75 (m, 2H), 2.43−2.24 (m, 2H), 1.71−1.51 (m, 4H), 1.17 (d, 3H, J = 6.3 Hz), 1.12 (d, 3H, J = 6.3 Hz), 1.00 (d, 6H, J = 6.4 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) rotamer 1: 155.8 (s), 76.6 (q), 53.6 (t), 53.0 (d), 40.5 (t), 31.2 (d), 20.3 (q), 17.6 (q); rotamer 2: 155.2 (s), 76.6 (q), 53.3 (t), 51.9 (d), 41.2 (t), 30.3 (d), 20.9 (q), 17.6 (q). IR (neat) ν (cm^{-1}) 2964, 2937, 2817, 1701, 1450, 1379, 1188. LRMS (*m*/*z*, rel intensity) 157 (M^+, 5), 142 ([M − Me]$^+$, 100). HRMS calcd for $C_8H_{15}NO_2$:157.1103, found 157.1107.

Racemic Methyl *syn*-2,4-Dimethylpyrrolidine-1-carboxylate (*syn*-36). The mesylhydroxamic acid *syn*-**35c** (142 mg, 0.64 mmol) was dissolved in methanol (42 mL). The solution was transferred to a quartz cell, cooled to −78 °C, and irradiated with 254 nm light for 1 h. The reaction mixture was transferred to a round-bottomed flask and triethylamine (0.10 mL, 0.70 mmol) was added. After the solution was stirred at room temperature for 15 min, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (25 mL) and water (25 mL), the phases were separated ,and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography with ethyl acetate and hexanes (15:85) as eluent to give *syn*-**36** as a colorless oil (58 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) mix of rotamers: 3.90−3.76 (m, 2H), 3.65 (s, 3H), 2.85−2.68 (dd, 1H, J = 10.2, 10.2 Hz), 2.28−2.14 (m, 1H), 2.13−1.94 (m, 1H), 1.33−1.15 (m, 3H), 1.14−1.03 (m, 1H), 0.99 (d, 3H, J = 6.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) rotamer 1: 155.8 (s), 54.2 (q), 53.6 (t), 51.9 (d), 42.6 (t), 32.5 (d), 20.6 (q), 17.1 (q); rotamer 2: 155.3 (s), 54.2 (q), 53.8 (t), 51.9 (d), 43.3 (t), 32.3 (d), 21.6 (q), 17.1 (q). IR (neat) ν (cm^{-1}) 2960, 2930, 2874, 1705, 1450, 1383, 1203, 1106, 769. LRMS (*m*/*z*, rel intensity) 157 (M^+, 10), 142 ([M − Me]$^+$, 100). HRMS calcd for $C_8H_{15}NO_2$ 157.1103, found 157.1099.

Supporting Information Available: Procedures and characterization data for all new compounds and X-ray crystallographic data for **76a**. This material is available free of charge via the Internet at http://pubs.acs.org.