

Three Distinct Reactions of 3,4-Dihydroisoquinolines with Azlactones: Novel Synthesis of Imidazoloisoquinolin-3-ones, Benzo[*a*]quinolizin-4-ones, and Benzo[*d*]azocin-4-ones

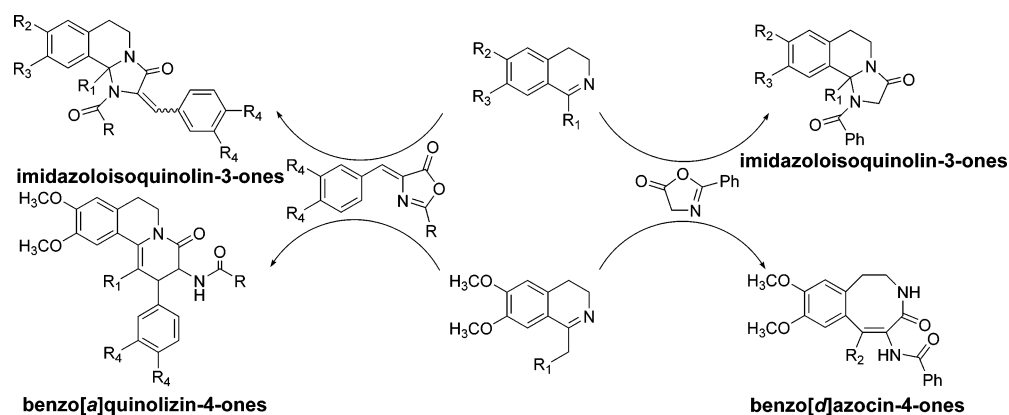
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ABSTRACT



A facile and direct synthetic entry to tricyclic imidazoloisoquinolin-3-ones and benzo[*a*]quinolizin-4-ones is reported based on the ring annulation of 1-unsubstituted and 1-substituted dihydroisoquinolines with azlactones under neutral conditions in a one-step procedure. Bicyclic 2,3-dihydrobenzo[*d*]azocin-4-ones were also prepared using simple azlactone and 1-substituted dihydroisoquinolines in a one-pot reaction.

Azlactones¹ are versatile precursors for the asymmetric syntheses of α -amino acid derivatives, lactam, and arylpyruvic acid units which have been used for the synthesis of tetrahydro- β -carbolines² and lamellarin alkaloids.³ Schulzeines A–C, new α -glucosidase inhibitors, isolated from the marine

sponge *Penares schulzei*, were the first three benzo[*a*]quinolizin-4-ones containing an amide moiety at the C-3 position.⁴

(1) (a) MacDonald, S. F. *J. Chem. Soc.* **1948**, 376. (b) Crawford, M.; Little, W. T. *J. Chem. Soc.* **1959**, 729. (c) Gelmi, M. L.; Clerici, F.; Melis, A. *Tetrahedron* **1997**, 53, 1843. (d) Wang, Y.; Shi, D.; Lu, Z.; Dai, G. *Synth. Commun.* **2000**, 30, 707. (e) Monk, K. A.; Sarapa, D.; Mohan, R. S. *Synth. Commun.* **2000**, 30, 3167. (f) Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2004**, 45, 425.

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Within the class of ring-fused isoquinolines, there have been no reports on the synthesis and biological activity of imidazoloisoquinolines. However, the related triazoloisoquinolines were reported to have some interesting pharmaceutical and agricultural properties.⁵ The berberine,⁶ emetine, and related ipecac alkaloids,⁷ all containing benzo[*a*]quinolizine moieties,⁸ are reported to possess interesting biological activities. Several methods for the preparation of the benzo[*a*]quinolizine ring system have been reported in the literature.⁹ Benzazocine was found as a structural component of pentacyclic alkaloids which exhibited highly potent cytotoxicity.¹⁰ It was also synthesized for biological study as an eight-membered B-ring of colchicine analogues.¹¹

Various 1-substituted dihydroisoquinolines have been used for the synthesis of benzazocine,¹² benzo[*a*]quinolizines,¹³ and thiazolo[2,3-*a*]isoquinolin-3-ones¹⁴ related to imidazoloisoquinolin-3-ones.

Our group has been interested in the synthesis of some pyrroloisoquinoline alkaloid derivatives.¹⁵ We now report a

convenient synthesis of tricyclic imidazoloisoquinolin-3-ones **1**, benzo[*a*]quinolizine-4-ones **2**, and benzo[*d*]azocin-4-ones **3** (Figure 1). To generate heterocyclic structures relevant to

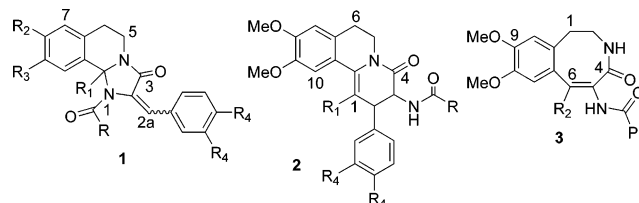


Figure 1. Structures of imidazoloisoquinolin-3-ones **1**, benzo[*a*]quinolizine-4-ones **2**, and benzo[*d*]azocin-4-ones **3**.

the alkaloid targets, we have investigated the cyclocondensation of azlactones with various dihydroisoquinolines, both unsubstituted and 1-substituted.

Azlactones **4** were prepared directly from the reaction of benzaldehydes and *N*-acetyl glycine or hippuric acid in the presence of sodium acetate and acetic anhydride.^{1a} They were obtained in moderate yields after recrystallization from ethanol. The required 3,4-dihydroisoquinolines **5** and **6** were synthesized by the well-established Bischler–Napieralski reaction starting from the arylethylamine derivatives which were converted to the corresponding amide derivatives and then cyclized to imines **5** and **6** using POCl₃.¹⁶

With both key starting materials in hand, the reaction of the simple dihydroisoquinolines with azlactones in acetonitrile was investigated. When 3,4-dihydroisoquinoline **5a** was treated with azlactone **4a** (entry 1, Table 1) in acetonitrile under reflux for 12 h, a single product was obtained in good yield (88%). The product was characterized as imidazoloisoquinolin-3-one **1a** on the basis of spectroscopic and analytical data with a singlet at δ 6.56 (C-10b) in the ¹H NMR spectrum and the amide groups at 1713 and 1668 cm^{−1} in the IR spectrum. To further demonstrate the scope of this cyclocondensation reaction, the reaction of various azlactones **4a–d** and dihydroisoquinolines **5a–c** was investigated and the corresponding imidazoloisoquinolin-3-ones **1b–h** were obtained in yields ranging from 4 to 94% as shown in Table 1.

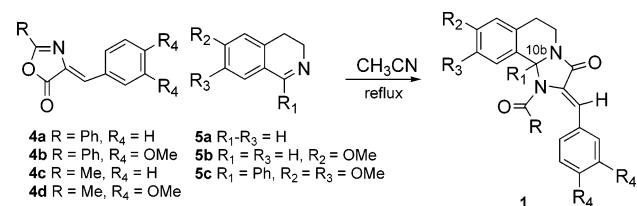
The mechanism for the formation of **1** is proposed to involve the acyl iminium salt **7** formed by the reaction of the imine group of the dihydroisoquinoline with the carbonyl group of azlactone followed by subsequent C–N bond formation to provide the imidazoloisoquinolin-3-ones **1** (Scheme 1).

- (2) Audia, J. E.; Drost, J. J.; Nissen, J. S.; Murdoch, G. L.; Evrard, D. *A. J. Org. Chem.* **1996**, *61*, 7937.
- (3) (a) Peschko, C.; Winkhofer, C.; Steglich, W. *Chem.–Eur. J.* **2000**, *6*, 1147. (b) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 155.
- (4) Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc.* **2004**, *126*, 187.
- (5) Awad, E. M.; Elwan, N. M.; Hassaneen, H. M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2002**, *85*, 320.
- (6) (a) Jeffs, P. W. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, London, 1967; p 41. (b) Singh, K. N. *Tetrahedron Lett.* **1998**, *39*, 4391. (c) Memetizidis, G.; Stambach, J. F.; Jung, L.; Schott, C.; Heitz, C.; Stocklet, J. C. *Eur. J. Med. Chem.* **1991**, *26*, 605. (d) Suan, R.; López-Romero, J. M.; Ruiz, A.; Rico, R. *Tetrahedron* **2000**, *56*, 993.
- (7) (a) Szántay, C.; Töke, L.; Kolonits, P. *J. Org. Chem.* **1966**, *31*, 1447. (b) Buzas, A.; Cavier, R.; Cossais, F.; Finet, J.-P.; Jacquet, J.-P.; Lavielle, G.; Platzer, N. *Helv. Chim. Acta* **1977**, *60*, 2122.
- (8) Reviews: (a) Saraf, S. D. *Heterocycles* **1981**, *16*, 803. (b) Popp, F. D.; Watts, R. F. *Heterocycles* **1977**, *6*, 1189.
- (9) (a) Kirschbaum, S.; Waldmann, H. *Tetrahedron Lett.* **1997**, *38*, 2829. (b) Kirschbaum, S.; Waldmann, H. *J. Org. Chem.* **1998**, *63*, 4936. (c) Van der Eycken, E.; Deroover, G.; Toppet, S. M.; Hoornaert, G. J. *Tetrahedron Lett.* **1999**, *40*, 9147. (d) Yamaguchi, R.; Otsuji, A.; Utimoto, K. *J. Am. Chem. Soc.* **1988**, *110*, 2186. (e) Itoh, N.; Sugawara, S. *J. Org. Chem.* **1959**, *24*, 2042. (f) Osbond, J. M. *J. Chem. Soc.* **1961**, 4711. (g) Bosch, J.; Domingo, A.; Linares, A. *J. Org. Chem.* **1983**, *48*, 1075. (h) Rubiralta, M.; Diez, A.; Balet, A.; Bosch, J. *Tetrahedron* **1987**, *43*, 3021. (i) Rubiralta, M.; Diez, A.; Bosch, J. *Heterocycles* **1988**, *27*, 1653.
- (10) For a review of these compounds, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (a) Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596. (b) Pettit, G. R.; Knight, J. C.; Collins, J. C.; Herald, D. L.; Pettit, R. K.; Boyd, M. R.; Young, V. G. *J. Nat. Prod.* **2000**, *63*, 793.
- (11) (a) Bergemann, S.; Brecht, R.; Büttner, F.; Guénard, D.; Gust, R.; Seitz, G.; Stubbs, M. T.; Thoret, S. *Bioorg. Med. Chem.* **2003**, *11*, 1269. (b) Brecht, R.; Gunther, S.; Guénard, D.; Thoret, S. *Bioorg. Med. Chem.* **2000**, *8*, 557. (c) Berg, U.; Bladh, H.; Svensson, C.; Wallin, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2771.
- (12) Lal, B.; Bhedi, D. N.; Gidwani, R. M.; Sankar, C. *Tetrahedron* **1994**, *50*, 9167.
- (13) (a) Abdallah, T. A.; Abdelhadi, H. A.; Ibrahim, A. A.; Hassaneen, H. M. *Synth. Commun.* **2002**, *32*, 581. (b) Roy, A.; Nandi, S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 229. (c) Nemes, P.; Balázs, B.; Tóth, G.; Scheiber, P. *Synlett* **2000**, 1327. (d) Nemes, P.; Balázs, B.; Tóth, G.; Scheiber, P. *Synlett* **1999**, 222. (e) Mikhal'chuk, A. L.; Gulyakevich, O. V.; Akhrem, A. A. *Russ. J. Org. Chem.* **1997**, *33*, 582. (f) Mikhal'chuk, A. L.; Gulyakevich, O. V.; Akhrem, A. A. *Khim. Geterotsikl. Soedin.* **1996**, *235*. (h) Naito, T.; Katsumi, K.; Tada, Y.; Ninomiya, I. *Heterocycles* **1983**, *20*, 775. (i) Shono, T.; Hamaguchi, H.; Sasaki, M.; Fujita, S.; Nagami, K. *J. Org. Chem.* **1983**, *48*, 1621. (j) Lenz, G. R. *J. Heterocycl. Chem.* **1979**, *16*, 433. (k) Ninomiya, I.; Kiguchi, T.; Tada, Y. *Heterocycles* **1977**, *6*, 1799. (l) Kametani, T.; Suzuki, Y.; Terasawa, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. I* **1979**, 1211.

(14) Rozwadowska, M. D.; Sulima, A. *Tetrahedron* **2001**, *57*, 3499.

(15) (a) Ruchirawat, S.; Mutatapat, T. *Tetrahedron Lett.* **2001**, *42*, 1205. (b) Namsaaid, A.; Ruchirawat, S. *Org. Lett.* **2002**, *4*, 2633. (c) Ploypradith, P.; Jinaglueng, W.; Pavaro, C.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 1363. (d) Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 866. (e) Ploypradith, P.; Kagan, R. K.; Ruchirawat, S. *J. Org. Chem.* **2005**, *70*, 5119.

(16) (a) Pabuccuoglu, V.; Hesse, M. *Heterocycles* **1997**, *45*, 1751. (b) Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1996**, *61*, 9596. (c) Marsden, R.; MacLean, D. B. *Can. J. Chem.* **1984**, *62*, 1392.

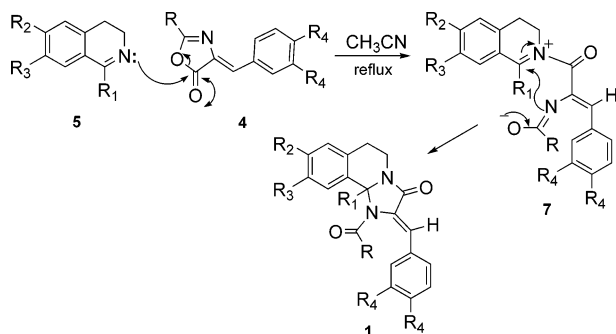
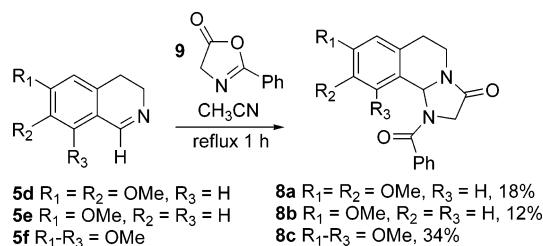
Table 1. Preparation of Imidazoloisoquinolin-3-ones **1**

entry	azlactones	isoquinolines	time (h)	yield of 1 (%)
1	4a	5a	12	1a (88)
2	4a	5b	3	1b (94)
3	4b	5a	24	1c (78)
4	4a	5c	48	1d (17) ^a
5	4c	5a	24	1e (44)
6	4c	5b	3	1f (64)
7	4d	5a	24	1g (47)
8	4c	5c	48	1h (4) ^b

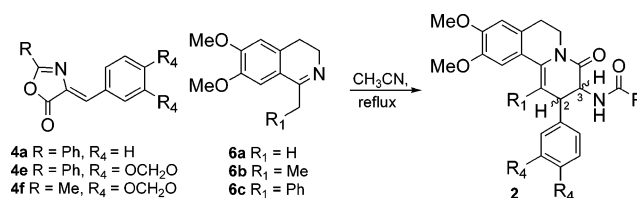
^a 78% recovery of imine **5c** and 77% recovery of azlactone **4a**. ^b 80% recovery of imine **5c** and 50% recovery of azlactone **4c**.

The following observations were made from the above reaction. The presence of an electron-donating group at position 6 of the dihydroisoquinoline **5** (R₂) increased the rate of the reaction presumably by increasing the nucleophilicity of the imine group, as shown in entries 2 and 6 where the reaction went to completion within 3 h. However, the presence of an electron-donating group on the aromatic ring of the azlactone deactivated the carbonyl reactivity resulting in a much slower rate of reaction as shown in entries 3 and 7 where a longer reaction time (24 h) was required. As expected, when the 1-position of the dihydroisoquinoline **5** is substituted with a phenyl group, only a low yield of the product was obtained as in entries 4 and 8. In general, azlactones **4** with a methyl side chain (R = Me) instead of a phenyl group gave lower yields of the product.

We next turned our attention toward the synthesis of other imidazoloisoquinolin-3-ones **8a–c** by treatment of 3,4-dihydroisoquinolines **5d–f** with a simple azlactone **9** in refluxing acetonitrile for 1 h. As indicated in Scheme 2, the low yield of products **8a–c** was observed. This could be due to the formation of other byproducts and decomposition of the simple azlactone **9**.

Scheme 1. Proposed Mechanism for the Formation of **1****Scheme 2.** Preparation of Imidazoloisoquinolin-3-ones **8**

Furthermore, a completely different pathway was observed when azlactones **4** were treated with various 1-alkyl-substituted 3,4-dihydroisoquinolines **6a–c** where an imine–enamine equilibrium is possible. For example, when 1-methyl dihydroisoquinoline **6a** (R₁ = H) was treated with azlactone **4a** in acetonitrile under reflux for 2 h, the benzo[*a*]-quinolizine-4-one **2a** was obtained in 89% yield as shown in entry 1, Table 2. The structure of the product was fully

Table 2. Preparation of Benzo[*a*]quinolizine-4-ones **2**

entry	azlactones	isoquinolines	yield of 2 (%, cis/trans) ^a
1	4a	6a	2a (89, 74:26)
2	4a	6b	2b (67, 39:61)
3	4a	6c	2c (83, 24:76)
4	4e	6a	2d (91, 78:22)
5	4e	6b	2e (77, 48:52)
6	4e	6c	2f (88, 44:56)
7	4f	6a	2g (74, 51:49)
8	4f	6b	2h (80, 36:64)

^a All reaction times are 2 h.

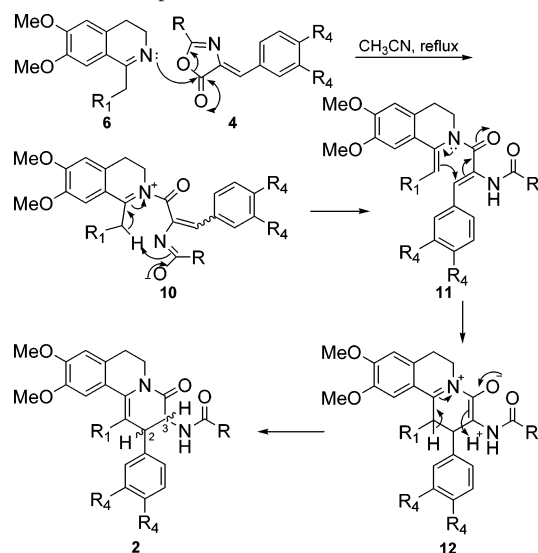
supported by spectroscopic data with absorption in the IR spectrum at 1683 and 1654 cm^{−1} for the two amide groups. The ratio of the cis/trans isomers was found to be 74:26 as judged by ¹H NMR (*J* = 7.6 Hz for the cis isomer and 14.3 Hz for the trans isomer).

The reaction was found to proceed well with other 1-ethyl and 1-benzyl dihydroisoquinoline derivatives (**6b,c**) and differently substituted azlactones **4** giving yields varying from 67 to 91% as shown in Table 2 entries 2–8. It was found that in the case where R₁ = H in **6a** the cis product predominated. When the steric bulk of the substituents increased (R₁ = Me, Ph), the trans isomer became the major product.

The formation of **2** is proposed to involve the acyliminium salt **10**, analogous to compound **7**, formed by the ring-

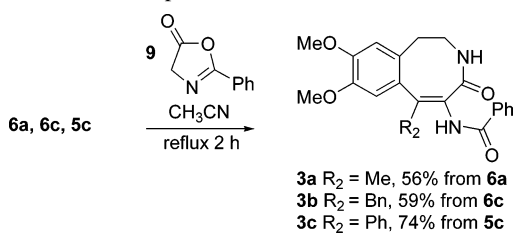
opening reaction at the carbonyl of azlactone **4** with C–N bond formation. With the alkyl substitution at the C-1 position, the acyliminium salt **10** will be readily converted to the corresponding enamide intermediate **11** which undergoes C–C bond formation to give the product **2** via the intermediate **12** as shown in Scheme 3.

Scheme 3. Proposed Mechanism for the Formation of **2**



A completely different pathway was observed when various 1-substituted 3,4-dihydroisoquinolines **5c**, **6a**, and **6c** were treated with the azlactone **9** in acetonitrile at reflux for 2 h, and benzo[*d*]azocin-4-one derivatives **3** were instead obtained in moderate yield as shown in Scheme 4. The

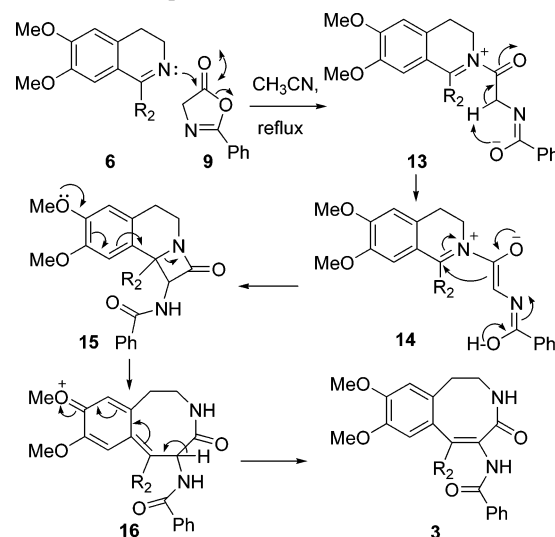
Scheme 4. Preparation of Benzo[*d*]azocin-4-ones **3**



mechanism of the reaction was proposed to involve acyliminium salt **13** which could lead to imidazoloisoquinolin-3-ones **8**, similar to the conversion of intermediate **7** to imidazoloisoquinolin-3-ones **1**, when 3,4-dihydroisoquinolines are unsubstituted. However, in the 1-substituted 3,4-dihydroisoquinolines, the formation of imidazoloisoquinolin-3-one was not favorable, and the iminium salt **13** could undergo proton transfer to generate enolate **14** followed by the β lactam ring formation to form lactam **15**. Alternatively, the lactam could be envisaged to form by the addition of the amido ketene, derived from the azlactones **9**, to imine. Cleavage of the C–N bond in the strained lactam assisted

by the lone pair of an electron on oxygen could lead to intermediate **16** which could aromatize to give the benzo[*d*]azocin-4-one derivatives **3** (Scheme 5). All compounds

Scheme 5. Proposed Mechanism for the Formation of **3**



were fully characterized, and for compound **3a**, the amide absorptions were observed at 1666 and 1631 cm^{-1} . Dihydroisoquinolines with a phenyl substituent at C-1 (**5c**) seem to work slightly better than the C-1 alkyl-substituted dihydroisoquinolines (**6a** and **6c**).

In summary, we have devised a direct, highly efficient route with very simple reaction conditions to imidazoloisoquinolin-3-ones **1**, benzo[*a*]quinolizine-4-ones **2**, and benzo[*d*]azocin-4-ones **3**. The imidazoloisoquinolin-3-ones **1** could be readily obtained by the cyclocondensation reaction of azlactones **4** with C-1 unsubstituted 3,4-dihydroisoquinolines **5**. However, under similar conditions, the C-1 substituted 3,4-dihydroisoquinolines **6** led directly to benzo[*a*]quinolizine-4-ones **2** and benzo[*d*]azocin-4-ones **3** depending on the nature of C-1 substituents and azlactone substrates. Compounds **2** lend themselves to conversion to various products, and we are applying this methodology to the synthesis of related alkaloids and other biologically important benzo[*a*]quinolizine-4-one derivatives.

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Supporting Information Available: Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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