Indole as a Dienophile in Inverse Electron Demand Diels–Alder Reactions. 3. Intramolecular Reactions with 1,2,4-Triazines To Access the Canthine Skeleton

Scott C. Benson, Jia-He Li, and John K. Snyder*

Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

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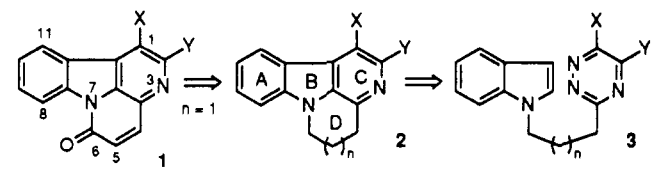
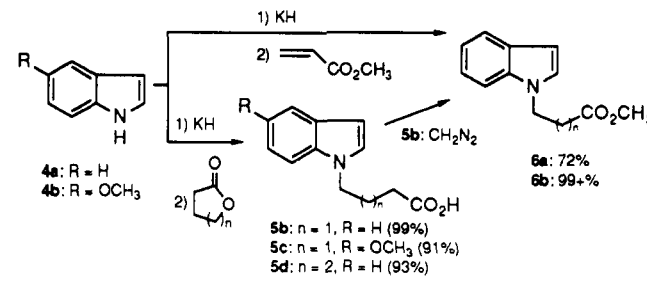
Summary: The intramolecular inverse electron demand cycloaddition of indole with 1,2,4-triazines connected by a tri- or tetramethylene tether linking the indole N-1 position with the triazinyl 3-position successfully produces the canthine skeleton and the homologous system with a seven-membered D-ring.

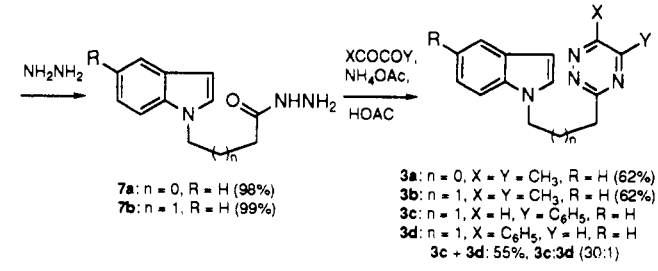
The canthin-6-one alkaloids[1] are a subclass of β-carbolines with demonstrated cytotoxicity and antimicrobial activity against a variety of cell lines and microorganisms,[1,2] and have also been shown to inhibit adenosine 3′,5′-cyclic monophosphate phosphodiesterase.[3] Past syntheses of canthinones have followed the traditional Pictet–Spengler or Bischler–Napieralski pathways employing appropriately substituted tryptamine or tryptophan derivatives to provide the desired β-carboline skeleton, with subsequent synthetic manipulation to close the canthinone D-ring.[4] In general, these strategies provide the tetrahydro-β-carbolines in excellent yields, but the aromatization of the C-ring can be capricious,[5] often due to overoxidation.[6] An additional problem is the relative difficulty in preparing analogues with diverse substituents at the C1 and C2 positions.[7]

Scheme I

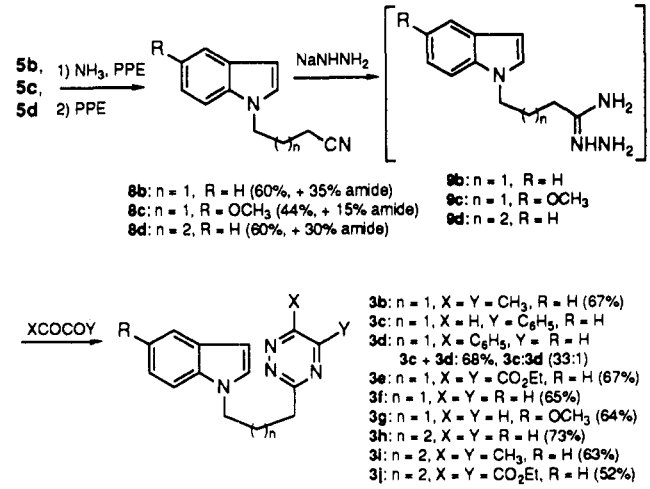


Scheme II





Scheme III



We recently reported successful intermolecular cycloadditions between indole and various 1,2,4-triazines.[8]

(1) For a review of the canthin-6-one alkaloids: Ohmoto, T.; Koike, K. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1989; Vol. 36, pp 135–170.

(2) (a) Mitscher, L. A.; Showalter, H. D. H.; Shipchandler, M. T.; Leu, R. P.; Beal, J. L. *Lloydia* **1972**, *35*, 177. (b) Handa, S. S.; Kinghorn, A. D.; Cordell, G. A.; Farnsworth, N. R. *J. Nat. Prod.* **1983**, *46*, 359. (c) Anderson, L. A.; Harris, A.; Phillipson, J. D. *J. Nat. Prod.* **1983**, *46*, 374. (d) Fukamiya, N.; Okano, M.; Aratani, T.; Negoro, K.; McPhail, A. T.; Ju-ichi, M.; Lee, K.-H. *J. Nat. Prod.* **1986**, *49*, 428. (e) Fukamiya, N.; Okano, M.; Aratani, T.; Negoro, K.; Lin, Y.-M.; Lee, K.-H. *Planta Med.* **1987**, *53*, 140. (f) Kardono, L. B. S.; Angerhofer, C. K.; Tsauri, S.; Padmawinata, K.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **1991**, *54*, 1360.

(3) Ohmoto, T.; Nikaido, T.; Koike, K.; Kohda, K.; Sankawa, U. *Chem. Pharm. Bull.* **1988**, *36*, 4588.

(4) (a) Haynes, H. F.; Nelson, E. R.; Price, J. R. *Aust. J. Sci. Res.* **1952**, *5*, 387. (b) Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, *82*, 5941. (c) Rosenkranz, H. J.; Botyos, G.; Schmid, H. *Liebigs Ann. Chem.* **1966**, *691*, 159. (d) Mitscher, L. A.; Shipchandler, M.; Showalter, H. D. H.; Bathala, M. S. *Heterocycles* **1975**, *3*, 7. (e) Oehl, R.; Lenzer, G.; Rosenmund, P. *Chem. Ber.* **1976**, *109*, 705. (f) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907. (g) Guzman, F.; Cain, M.; Larscheid, P.; Hagen, T.; Cook, J. M.; Schweri, M.; Skolnick, P.; Paul, S. M. *J. Med. Chem.* **1984**, *27*, 564. (h) Matus, I.; Fischer, J. *Tetrahedron Lett.* **1985**, *26*, 385. (i) Hagen, T. J.; Cook, J. M. *Tetrahedron Lett.* **1988**, *29*, 2421. (j) Hagen, T. J.; Narayanan, K.; Names, J.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 2170. (k) Del Giudice, M. R.; Gatta, F.; Settimj, G. *J. Heterocycl. Chem.* **1990**, *27*, 967. (l) Narayanan, K.; Schindler, L.; Cook, J. M. *J. Org. Chem.* **1991**, *56*, 359. (m) Narayanan, K.; Cook, J. M. *J. Org. Chem.* **1991**, *56*, 5733. (n) Narayanan, K.; Cook, J. M. *Heterocycles* **1991**, *32*, 2005.

(5) For a few examples, see ref 4a; see also: (a) Murakami, Y.; Takahashi, H.; Nakazawa, Y.; Koshimizu, M.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1988**, *30*, 2099. (b) Van Wagenen, B. C.; Cardellina, J. H. *Tetrahedron Lett.* **1989**, *30*, 3605. (c) Kobayashi, J.; Cheng, J.-F.; Ohta, T.; Nozoe, S.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3666. (d) Rinehart, K. L.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafarque, F. J. *Am. Chem. Soc.* **1987**, *109*, 3378. The aromatization step is also often not compatible with C-ring substituents for example: (e) Hamaguchi, F.; Ohki, S. *Heterocycles* **1977**, *8*, 383. (f) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G.-S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.

(6) For example, in the synthesis of 1-methoxycanthin-6-one, it was necessary to utilize a tetrahydro-β-carboline with C1 quaternized to prevent oxidation at this site using DDQ: refs 4i and j.

(7) Cook has overcome this to a certain extent by combining the aromatization step with C-ring functionalization. Oxidation of 4-oxo-1,2,3,4-tetrahydro-β-carbolines with hydrazine provided the 4-amino-β-carbolines: (a) Trudell, M. L.; Fukada, N.; Cook, J. M. *J. Org. Chem.* **1987**, *52*, 4293. Oxidation of 1,2,3,4-tetrahydro-β-carbolines with DDQ provided the 4-oxygenated 1,2,3,4-tetrahydro-β-carboline skeleton, which could be subsequently aromatized to the 4-oxygenated β-carboline, refs 4i,j, and n; see also: (b) Cain, M.; Montei, R.; Cook, J. M. *J. Org. Chem.* **1982**, *47*, 4933.

0022-3263/92/1957-5285$03.00/0

While certain β- and γ-carbolines could be prepared in good to excellent yields, the regioselectivity of the reaction was too sensitive to the nature of the triazine substituents to be of broad applicability. Alternatively, an intramolecular cycloaddition between indole and 1,2,4-triazines[9-11] would enable regiochemical control and provide the well-recognized entropic advantage in promoting stubborn reactions.[12] Furthermore, by incorporating a trimethylene tether from the indole nitrogen to the triazine C-3, the parent canthine skeleton would be produced with the aromatized C-ring rapidly formed subsequent to the cycloaddition by nitrogen loss and dehydrogenation (Scheme I). Such a route could allow easy access to a variety of C-1 and C-2 substituted systems restricted only by the ease of preparing the appropriately substituted tethered triazines. Herein we describe preliminary studies which demonstrate that the tethered triazines **3** are readily prepared and that the subsequent cycloadditions proceed in excellent yields, with the trimethylene-tethered 1,2,4-triazines (**3**, $n = 1$) providing the basic canthine skeleton (**2**, $n = 1$). Cycloadditions with the tetramethylene-tethered triazines (**3**, $n = 2$) proceeded in good yields to produce the seven-membered D-ring homologue (**2**, $n = 2$). The cycloaddition using a dimethylene tether (**3**, $n = 0$) to produce a five-membered D-ring proceeded in only trace amounts.

The strategy was to link the indole to the triazine via a multiple methylene tether terminating in an ester function which could be subsequently transformed into the necessary triazine. The alkyl tether would enhance the electron density of the indole 2,3-double bond and promote the desired cycloaddition with the triazine. Depending upon the length of the tether to be employed, this was accomplished in two ways (Scheme II). For a dimethylene tether, a Michael addition of the indole potassium salt to methyl acrylate produced the desired methyl 3-(1-indolyl)propionate (**6a**) in 72% yield, while for the tri- and tetramethylene tethers, S_N2-type opening of γ-butyrolactone or δ-valerolactone by the indole potassium salt gave tethered carboxylic acids **5b** and **5d** in >90% yields.[13] The 5-methoxyindole derivative **5c** was similarly produced (91% yield). Diazomethane esterification of **5b** proceeded in near-quantitative yield to produce the corresponding tethered methyl ester **6b**.

Conversion of either the indolyl-tethered carboxylic acids **5** or methyl esters **6** to the tethered triazines **3** was accomplished in one of two ways: the esters through an acylhydrazide intermediate **7** (Scheme II) and the acids through an amidrazone **9** via the corresponding nitrile **8** (Scheme III). The first route through the methyl esters had been originally employed by Laakso[14] in 1,2,4-triazine preparations and was adapted by Taylor to tether triazines to acetylenic dienophiles through the triazinyl 3-position.[10r,v] By this route, treatment of the acylhydrazides, formed from the methyl esters in quantitative yields, with NH_4OAc in acetic acid in the presence of the 2,3-butanedione gave the tethered 5,6-dimethyltriazines **3a** and **3b**, in 44% and 61% overall yield, respectively (starting from indole). The reaction of **7b** with phenylglyoxal produced a mixture of regioisomers **3c**:**3d** with **3c** as the major isomer as expected (30:1).[15] (The regiochemistry of these tethered triazines was assigned only after the cycloadditions by the observation of NOE's between the H-11 proton and substituent at C-1).

The attempted preparation of diethyl 1,2,4-triazine-5,6-dicarboxylate (**3e**) and 5,6-unsubstituted triazine **3f** in an analogous manner using diethyl dioxosuccinate[16] and glyoxal, respectively, as the 1,2-dione reactants failed. An alternative route to these tethered triazines via the corresponding amidrazones[14d,17] was successful (Scheme III). Indolylalkanoic acids **5** were converted to nitriles **8** using ethyl polyphosphate (PPE)[18] by the Imamoto procedure[19] in modest yields (44–60%), though the main byproduct from this reaction was the corresponding amide (35–15% yield) which could also be converted to the desired nitrile by a second treatment with PPE. The key intermediate amidrazones, formed from the nitriles by reaction with sodium hydrazide salt,[20] proved to be unstable and were

(8) Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257.

(9) For reviews of inverse electron demand Diels–Alder reactions using heteroaromatic azadienes including 1,2,4-triazines: (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Organic Chemistry Monograph Series, Vol. 47; Academic: New York, 1987. (d) Kametani, T.; Hibino, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1987; Vol. 42, pp 245–335. For a discussion of the cycloaddition chemistry of 1,2,4-triazines: (e) Macor, J. E. Ph.D. Thesis, Princeton University, 1986.

(10) For other reports of intramolecular inverse electron demand cycloadditions employing 1,2,4-triazines with tethered dienophiles: (a) Seitz, G.; Dietrich, S. *Archiv. Pharm. (Weinheim, Ger.)* **1984**, *317*, 379. (b) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1985**, *26*, 2419. (c) Seitz, G.; Dietrich, S. *Archiv. Pharm. (Weinheim, Ger.)* **1985**, *318*, 1048. (d) Seitz, G.; Dietirch, S. *Archiv. Pharm. (Weinheim, Ger.)* **1985**, *318*, 1051. (e) Seitz, G.; Gorge, L.; Dietrich, S. *Tetrahedron Lett.* **1985**, *26*, 4355. (f) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 431. (g) Taylor, E. C.; French, L. G. *Tetrahedron Lett.* **1986**, *27*, 1967. (h) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 2107. (i) Seitz, G.; Dietrich, S.; Gorge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747. (j) Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379. (k) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145. (l) Taylor, E. C.; Pont, J. L.; Warner, J. C. *Tetrahedron* **1987**, *43*, 5159. (m) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1987**, *52*, 4280. (n) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287. (o) Taylor, E. C.; Warner, J. C.; Pont, J. L. *J. Org. Chem.* **1988**, *53*, 800. (p) Taylor, E. C.; Pont, J. L.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 3568. (q) Taylor, E. C.; Pont, J. L.; van Engen, D.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 5093. (r) Taylor, E. C.; French, L. G. *J. Org. Chem.* **1989**, *54*, 1245. (s) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1989**, *54*, 4984. (t) John, R.; Seitz, G. *Archiv. Pharm. (Weinheim, Ger.)* **1989**, *322*, 561. (u) Sagi, M.; Wada, K.; Konno, S.; Yamanaka, H. *Heterocycles* **1990**, *30*, 1009. (v) Taylor, E. C.; Macor, J. E.; French, L. G. *J. Org. Chem.* **1991**, *56*, 1807.

(11) Kraus has reported utilizing the indole 2,3-double bond as a dienophile in an intramolecular cycloaddition with a butadiene component tethered to the indole nitrogen by a urea linkage: (a) Kraus, G. A.; Raggon, J.; Thomas, P. J.; Bougie, D. *Tetrahedron Lett.* **1988**, *29*, 5605. (b) Kraus, G. A.; Bougie, D.; Jacobsen, R. A.; Su, Y. *J. Org. Chem.* **1989**, *54*, 2425.

(12) For a review on the intramolecular Diels–Alder reaction: (a) Ciganek, E. *Org. React.* **1984**, *321*. For a discussion of the intramolecular Diels–Alder reactions of 1,2,4-triazines: (b) Taylor, E. C. *Bull. Soc. Chim. Belg.* **1988**, *97*, 599.

(13) The procedure used in these reactions was adapted from: (a) Reppe, W. *Liebigs Ann. Chem.* **1955**, *596*, 1 (actual procedure given on page 215). For related reactions of indole with lactones to form either the 3- or N1-indolylalkanoic acids: (b) Fritz, H. E. *J. Org. Chem.* **1963**, *28*, 1384.

(14) (a) Laakso, P. V.; Robinson, R.; Vandrewala, H. P. *Tetrahedron* **1957**, *1*, 103. Also, see: (b) Atkinson, C. M.; Cossey, H. D. *J. Chem. Soc.* **1962**, 1805. This one-pot procedure was in turn adapted from a two-step method reported by Metze: (c) Metze, R. *Chem. Ber.* **1955**, *88*, 772. For a review of 1,2,4-triazine preparations and chemistry: (d) Neunhoeffer, H. *Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines*; Wiley-Interscience: New York, 1978; pp 194–200. (e) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., *Rees*, C. W., Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 385–456.

(15) (a) Paudler, W. W.; Chen, T.-K. *J. Heterocycl. Chem.* **1970**, *7*, 767. (b) Taylor, E. C.; Martin, S. F. *J. Org. Chem.* **1972**, *37*, 3958. For a review of amidrazone chemistry: (c) Neilson, D. G.; Roger, R.; Heatlie, J. W. M.; Newlands, L. R. *Chem. Rev.* **1970**, *70*, 151.

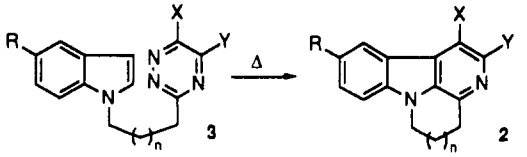
(16) Boger, D. L.; Panek, J. S.; Yasuda, M. *Org. Synth.* **1987**, *66*, 142.

(17) Neunhoeffer, H.; Hennig, H.; Fruhauf, H.-W.; Mutterer, M. *Tetrahedron Lett.* **1969**, 3147.

(18) (a) Pollmann, W.; Schramm, G. *Biochim. Biophys. Acta* **1964**, *80*, 1. (b) Kanaoka, Y.; Kuga, T.; Tanizawa, K. *Chem. Pharm. Bull.* **1970**, *18*, 397.

(19) Imamoto, T.; Takaoka, T.; Yokoyama, M. *Synthesis* **1983**, 142.

Table I. Intramolecular Cycloadditions of Indolyl-Tethered 1,2,4-Triazines (3 → 2)



item	3	2	n	X	Y	R	temp[a] (°C)/time (h)	yield[b] (%)
1	**3a**	**2a**	0	CH_3	CH_3	H	232/20	4
2	**3b**	**2b**	1	CH_3	CH_3	H	232/12	73
3	**3c**	**2c**	1	H	C_6H_5	H	232/1.5	87
4	**3d**	**2d**	1	C_6H_4	H	H	232/1.5	93
5	**3e**	**2e**	1	CO_2Et	CO_2Et	H	232/2	65
6	**3e**	**2e**	1	CO_2Et	CO_2Et	H	162/2	87
7	**3e**	**2e**	1	CO_2Et	CO_2Et	H	100/40	72
8	**3f**	**2f**	1	H	H	H	232/2.5	91
9	**3g**	**2g**	1	H	H	OCH_3	232/5	86
10	**3g**	**2g**	1	H	H	OCH_3	162/18	84
11	**3h**	**2h**	2	H	H	H	232/12	49
12	**3i**	**2i**	2	CH_2	CH_2	H	232/14	51
13	**3j**	**2j**	2	CO_2Et	CO_2Et	H	232/12	38[c]

[a] The tethered triazines **3** (0.5 mmol) were refluxed in anhydrous triisopropylbenzene (bp 232 °C), diglyme (bp 162 °C), or dioxane (bp 100 °C). [b] Isolated yields after flash chromatography (see supplementary materials). [c] Instability of **2j** made purification difficult and resulted in reduced yields.

immediately reacted in the crude state with the 1,2-dicarbonyl compounds to produce the desired triazines in good yields. 3-(1-Indolyl)propionitrile prepared from ester **6a** underwent a retro-Michael reaction upon addition of sodium hydrazide, so triazines linked to indole N-1 by two methylene units could not be prepared by this route.[21] While triazines **3b** and (**3c** + **3d**) were prepared by both routes, the acylhydrazide route (Scheme II) was preferred since a one-pot procedure from the carboxylic acid to the tethered triazine could be utilized without isolation of the intermediate esters or acyl hydrazides. The regioselectivity of the condensation of phenylglyoxal with amidrazone **9b** to produce **3c** and **3d** was virtually identical (33:1) to that observed via the acyl hydrazide route.

With the tethered triazines in hand, the intramolecular cycloadditions were easily accomplished (Table I), typically by refluxing in triisopropylbenzene (TIPB). The intramolecular cycloadditions employing trimethylene tethers **3b–3g** gave good to excellent yields of β-carbolines (73–93% under best conditions), though only moderate yields of cycloadducts were obtained with the tetramethylene tethers (**3h–3j**: 38–51%) as expected.[10i] In the sole reaction with the dimethylene tether (**3a** → **2a**) only a trace amount of cycloadduct (4%) could be obtained and tentatively identified. This cycloaddition would have required significant straining of the tether to achieve the necessary transition-state geometry.

The successful cycloaddition of **3b** and **3i** are notable in that 2,5,6-trialkylated triazines have undergone cycloadditions with the indole. In our earlier studies on the intermolecular reaction between indole and triazines, no reaction occurred with methyl 5,6-dimethyl-1,2,4-triazine-3-carboxylate.[8] Thus, potentially one of the least reactive triazines in the intermolecular reactions, a 3,4,6-trialkyl-1,2,4-triazine, underwent the desired cycloaddition in good yield in intramolecular fashion.[22]

In summary, the intramolecular inverse electron demand Diels–Alder reaction of indole with 1,2,4-triazines tethered between the indole N-1 position and the triazine C-3 has lead to the facile production of β-carbolines with the canthine carbon skeleton. (In our initial attempt to oxidize a canthine cycloadduct to the canthin-6-one, treatment of **2e** with triethylbenzylammonium permanganate[23] regioselectively produced the desired **1e** (1: X = Y = CO_2Et) in 50% yield with the remaining material being unreacted **2e**. Work is continuing on this oxidation.) Using a tether with an extra methylene unit enabled the preparation of the seven-membered D-ring homologue. While the conditions necessary to achieve the reactions were certainly robust, more importantly, the reactions were very clean and gave the cycloadducts in good to excellent yields.

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Supplementary Material Available: Full experimental procedures and characterization for all compounds and ^1H and ^{13}C NMR spectra for compounds **2** (**2b–2i**), **3** (**3a–3j**), **5** (**5b–5d**), **6a**, **6b**, **7a**, **7b**, and **8** (**8b–8d**) and ^1H NMR spectra (no ^{13}C NMR spectra) for compounds **2a** and **2j** (27 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) (a) Kauffmann, T.; Spaude, S.; Wolf, D. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 217. (b) Kauffman, T.; Spaude, S.; Wolf, D. *Chem. Ber.* **1964**, *97*, 3436. For related: (c) Case, F. H. *J. Org. Chem.* **1965**, *30*, 931.

(21) A similar loss of an acrylonitrile equivalent, possibly by a retro-Michael reaction, had been reported by Taylor in the reaction of nitriles tethered to 1,2,4-triazines, reference 10l.

(22) The ability of 1,2,4-triazines substituted with electron-donating groups to participate in intramolecular inverse electron demand cycloadditions, in contrast to the lack of reactivity in intermolecular reactions, has been previously noted: references 10j, l, and u.

(23) (a) Schmidt, H.-J.; Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 68. (b) Schmidt, H.-J.; Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 109.