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## Single Electron Transfer Induced Total Synthesis of Canthin-6-one

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### Abstract

The cytotoxic alkaloid canthin-6-one was synthesized from harmalane in a short sequence (six steps) with good overall yield (18%) using a single electron transfer (SET) induced radical cationic hetero [4+2] cycloaddition as high yielding key step.

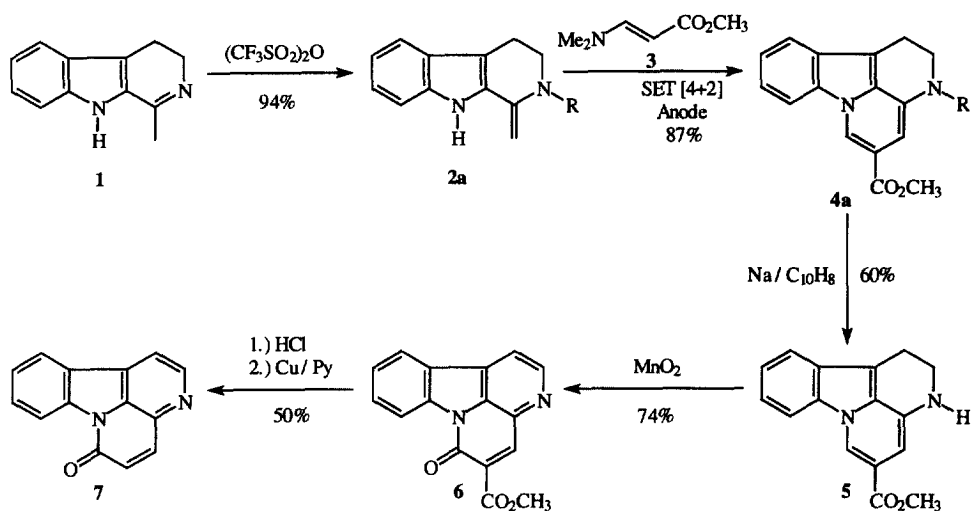
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As we previously reported, acceptor-substituted 2-vinylindoles undergo single electron transfer induced radical cationic hetero [4+2] cycloadditions with  $\beta$ -acceptor-substituted enamines to give functionalized pyrido[1,2-*a*]indoles.<sup>1</sup> In this paper we present the total synthesis of the cytotoxic alkaloid canthin-6-one (**7**)<sup>2,4</sup> (Scheme 1) using this novel reaction as a key step in the construction of the tetracyclic skeleton of the natural product.<sup>5</sup>

Although several syntheses of canthin-6-one (**7**) have been reported,<sup>4,9</sup> the presented route (Scheme 1) is exceptionally short (six synthetic steps) and has a good overall yield (18%) due to the high yielding key step. Moreover, it is one of the first electron transfer induced total syntheses of a natural product.<sup>10</sup>

The acceptor substituted 2-vinylindoles for the cycloaddition can be prepared from harmalane (**1**), which is easily available,<sup>11</sup> and acyl halides or anhydrides.<sup>12</sup> In our experiments the triflyl substituted harmalane derivative **2a**,<sup>13</sup> which was prepared from harmalane (**1**) and triflic anhydride in presence of triethyl amine in CH<sub>2</sub>Cl<sub>2</sub> at 0°C in 94% yield, turned out to be the best starting material for the following cycloaddition reaction (Table 1). This SET induced cycloaddition between **2a** and methyl *E*-3-(*N,N*-dimethylamino)-acrylate (**3**)<sup>14</sup> as the dienophile was carried out electrochemically at a potential of 400 mV in CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> (1/4; 0.1 M LiClO<sub>4</sub>) at room temperature following our previously published general procedure.<sup>1</sup> A ratio of 5:1 between the



Scheme 1

Total synthesis of canthin-6-one (7) from harmalane (1) using a SET induced hetero [4+2] cycloaddition

Table 1

Results of the SET induced cycloadditions between harmalane derivatives 2 and dienophile 3

Diene 2	Acceptor R	Product 4	Ratio 2 : 3	Yield of 4 / %
<b>2a</b>	$SO_2CF_3$	<b>4a</b>	5 : 1	87
			2 : 1	73
			1 : 5	64
			1 : 2	57
<b>2b</b>	$SO_2C_6H_4CH_3$	<b>4b</b>	1 : 5	58
			1 : 2	48
<b>2c</b>	$COCF_3$	<b>4c</b>	1 : 10	44
			1 : 5	37
			1 : 2	22

diene **2a** and the dienophile **3** gave the best yield (87%) of the cycloaddition product **4a**<sup>15</sup> (Table 1). This is one of the highest yields reported for this type of cycloaddition reaction. Furthermore, 84% of the residual diene **2a** was recovered after chromatography.

Reductive cleavage of the triflyl acceptor group with Na/naphthalene in DME at 0°C<sup>16</sup> gave the secondary amine **5**<sup>17</sup> in 60% yield. The latter was oxidized with MnO<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at room temperature<sup>18</sup> to give the tetracyclic compound **6**<sup>19</sup> in 74% yield. Compound **6** is also an intermediate of the canthin-6-one synthesis of Mitscher et al.<sup>6</sup> It could be converted to the natural product in 50% yield via acidic ester hydrolysis and decarboxylation with Cu/pyridine.

A short and effective route to the cytotoxic alkaloid canthin-6-one (**7**) was presented. Starting from the easily available harmalane (**1**) the natural product is synthesized in six synthetic steps in a good overall yield of 18% by a SET induced hetero [4+2] cycloaddition, which was carried out in 87% yield. Compound **6** could also be a good precursor for another alkaloid – 5-hydroxymethylcanthin-6-one<sup>2c</sup> – by a reduction of the ester group. This is currently under investigation in our laboratory.

### Acknowledgements

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### References and Notes

- C. F. Gürtler, S. Blechert, E. Steckhan, *Synlett* **1994**, 141;
  - C. F. Gürtler, S. Blechert, E. Steckhan, *Angew. Chem.* **1995**, *107*, 2025;
  - C. F. Gürtler, S. Blechert, E. Steckhan, *J. Org. Chem.* **1996**, *61*, 4136;
  - C. F. Gürtler, S. Blechert, E. Steckhan, *Chem. Eur. J.* **1997**, *3*, 447.
- T. Ohmoto, R. Tanaka, T. Nikaido, *Chem. Pharm. Bull.* **1976**, *24*, 1532;
  - T. Ohmoto, K. Koike, Y. Sakamoto, *Chem. Pharm. Bull.* **1981**, *29*, 390;
  - T. Ohmoto, K. Koike, *Chem. Pharm. Bull.* **1984**, *32*, 170.
- H. F. Haynes, E. R. Nelson, J. R. Price, *Austral. J. Sci. Research* **1952**, *5*, 385.
- S. C. Benson, J.-H. Li, J. K. Snyder, *J. Org. Chem.* **1992**, *57*, 5285;
  - J.-H. Li, J. K. Snyder, *J. Org. Chem.* **1993**, *58*, 516;
  - J.-H. Li, J. K. Snyder, *Tetrahedron Lett.* **1994**, *35*, 1485.
- U. Rößler, Diploma Thesis, Technische Universität Berlin, 1997.
- L. A. Mitscher, M. Shipchandler, H. D. H. Showalter, M. S. Bathala, *Heterocycles* **1975**, *3*, 7.
- H. J. Rosenkranz, G. Botyos, H. Schmid, *Liebigs Ann.* **1966**, *691*, 159.
- R. Oehl, G. Lenzer, P. Rosenmund, *Chem. Ber.* **1976**, *109*, 705.
- M. Cain, O. Campos, F. Guzman, J. M. Cook, *J. Am. Chem. Soc.* **1983**, *105*, 907.
- The first electron transfer induced synthesis of a natural product is to the best of our knowledge the photo electron transfer induced synthesis of (–)-β-selinene: B. Harirchian, N. L. Bauld, *J. Am. Chem. Soc.* **1989**, *111*, 1826.
- E. Späth, E. Lederer, *Chem. Ber.* **1930**, *63*, 120;
  - E. Späth, E. Lederer, *Chem. Ber.* **1930**, *63*, 2102;
  - M. Sainsbury, N. L. Uttley, *J. Chem. Soc., Perkin Trans. 1* **1977**, *6*, 2109.
- J. Laronge, J. Y. Laronge, M. Garnier, C. Trentesaux, J. Lévy, *Bull. Soc. Chim. Fr.* **1992**, *129*, 303.

13. All new compounds gave satisfying analytical data. Selected analytical data for compound **2a**: M.p. 133°C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 3.01 (2H, t, J = 6.0 Hz), 4.09 (2H, t, J = 6.0 Hz), 5.28 (1H, d, J = 3.0 Hz), 5.46 (1H, d, J = 3.0 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.28 (1H, t, J = 8.0 Hz), 7.35 (1H, d, J = 8.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 8.09 (1H, br s). MS (EI, 70 eV) *m/z* (%) = 316 (82), 247 (51), 183 (100), 167 (8), 156 (58), 154 (62), 128 (22), 115 (14), 69 (91). HRMS: calcd. 316.0493 (C<sub>13</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S), found 316.0491 (M<sup>+</sup>). UV (MeOH): λ<sub>max</sub> / nm = 210, 242, 302, 330 (sh). C,H,N-Anal. C<sub>13</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S (316.29): calcd. C 49.37, H 3.51, N 8.86, found C 49.71, H 3.85, N 8.51. E<sub>p</sub> (Ox.): 870 mV vs. Ag/AgNO<sub>3</sub> (0.1 M LiClO<sub>4</sub> in CH<sub>3</sub>CN).
14. Compound **3** can be easily prepared by adding an excess of dimethyl amine to a solution of propiolic acid methyl ester in ether at -20°C, stirring three hours in the cold, and evaporation of the solvent and excess amine. Selected analytical data for compound **3**: M.p. 51°C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 2.83 (6H, br s), 3.60 (3H, s), 4.45 (1H, d, J = 13.0 Hz), 7.38 (1H, d, J = 13.0 Hz). MS (EI, 70 eV) *m/z* (%) = 129 (70), 114 (20), 98 (100), 82 (9), 70 (23), 55 (20). HRMS: calcd. 129.0790 (C<sub>6</sub>H<sub>11</sub>NO<sub>2</sub>), found 129.0788 (M<sup>+</sup>). E<sub>p</sub> (Ox.): 770 mV vs. Ag/AgNO<sub>3</sub> (0.1 M LiClO<sub>4</sub> in CH<sub>3</sub>CN).
15. Selected analytical data for compound **4a**: M.p. 196°C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 3.27 (2H, t, J = 5.5 Hz), 3.97 (3H, s), 4.22 (2H, t, J = 5.5 Hz), 7.42 (1H, t, J = 8.0 Hz), 7.47 (1H, s), 7.50 (1H, t, J = 8.0 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.99 (1H, d, J = 8.0 Hz), 9.00 (1H, s). MS (EI, 70 eV) *m/z* (%) = 398 (28), 265 (100), 238 (20), 205 (15), 178 (22), 152 (4), 69 (13). HRMS: calcd. 398.0548 (C<sub>17</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>S), found 398.0544 (M<sup>+</sup>). UV (MeOH): λ<sub>max</sub> / nm = 206, 227, 266 (sh), 279, 288, 296, 322, 336, 353. C,H,N-Anal. C<sub>17</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>S (398.35): calcd. C 51.26, H 3.29, N 7.03, found C 50.96, H 3.66, N 6.72.
16. N. Ishizuka, T. Sato, Y. Makisumi, *Chem. Pharm. Bull.* **1990**, *38*, 1396.
17. Compound **5** was prepared by a variation of the given procedure in ref.<sup>16</sup>: A solution of Na and naphthalene in DME was added to a solution of **4** in DME at 0°C until no educt was detectable (TLC). Selected analytical data for compound **5**: M.p. 190°C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 3.18 (2H, t, J = 5.5 Hz), 3.59 (2H, t, J = 5.5 Hz), 3.91 (3H, s), 4.30 (1H, br s), 6.31 (1H, s), 7.31 (1H, t, J = 8.0 Hz), 7.41 (1H, t, J = 8.0 Hz), 7.71 (1H, d, J = 8.0 Hz), 7.91 (1H, d, J = 8.0 Hz), 8.61 (1H, s). MS (EI, 70 eV) *m/z* (%) = 266 (100), 265 (65), 238 (11), 205 (16), 178 (12), 152 (2). HRMS: calcd. 266.1055 (C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>), found 266.1055 (M<sup>+</sup>). UV (MeOH): λ<sub>max</sub> / nm = 214 (sh), 222, 246, 257, 291, 300, 326, 339, 363.
18. a) A. J. Fatiadi, *Synthesis* **1976**, 65;  
b) A. J. Fatiadi, *Synthesis* **1976**, 133.
19. Selected analytical data for compound **6**: M.p. 184°C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 4.03 (3H, s), 7.55 (1H, t, J = 8.0 Hz), 7.74 (1H, t, J = 8.0 Hz), 8.02 (1H, d, J = 5.0 Hz), 8.12 (1H, d, J = 8.0 Hz), 8.71 (1H, s), 8.73 (1H, d, J = 8.0 Hz), 8.90 (1H, d, J = 5.0 Hz). MS (EI, 70 eV) *m/z* (%) = 278 (100), 247 (100), 220 (92), 191 (36), 164 (26), 139 (9), 111 (9). HRMS: calcd. 278.0691 (C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>), found 278.0688 (M<sup>+</sup>). UV (MeOH): λ<sub>max</sub> / nm = 221, 236 (sh), 262, 271, 308, 382.