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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.

Keywords: Electron transfer; Cycloadditions; Natural products; Alkaloids.

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

Although several syntheses of canthin-6-one (**7**) have been reported,[4-9] 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.[10]

The acceptor substituted 2-vinylindoles for the cycloaddition can be prepared from harmalane (**1**), which is easily available,[11] and acyl halides or anhydrides.[12] In our experiments the trifyl substituted harmalane derivative **2a**,[13] which was prepared from harmalane (**1**) and triflic anhydride in presence of triethyl amine in CH_2Cl_2 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**)[14] as the dienophile was carried out electrochemically at a potential of 400 mV in CH_3CN/CH_2Cl_2 (1/4; 0.1 M $LiClO_4$) at room temperature following our previously published general procedure.[1] A ratio of 5:1 between the

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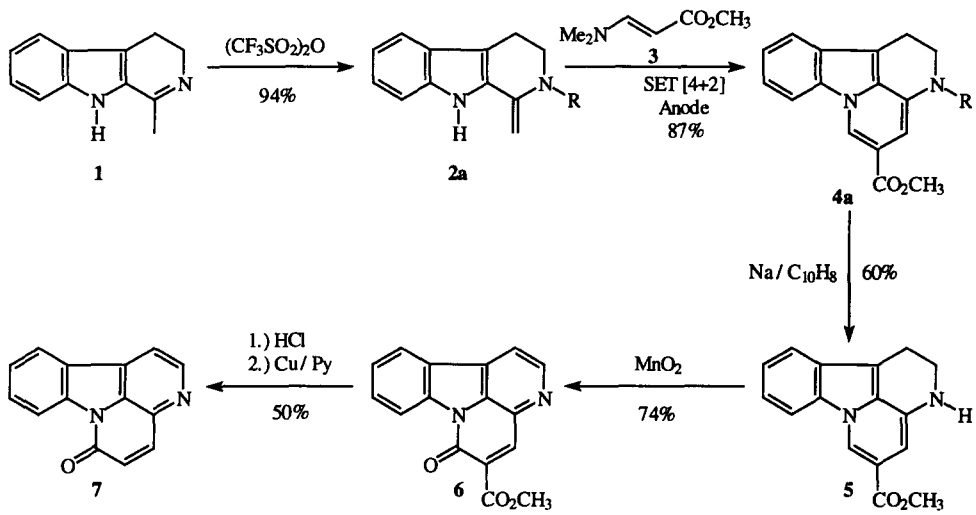

Scheme 1

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 / %
2a	SO_2CF_3	**4a**	5 : 1	87
			2 : 1	73
			1 : 5	64
			1 : 2	57
2b	$SO_2C_6H_4CH_3$	**4b**	1 : 5	58
			1 : 2	48
2c	$COCF_3$	**4c**	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**[15] (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 trifyl acceptor group with Na/naphthalene in DME at 0°C[16] gave the secondary amine **5**[17] in 60% yield. The latter was oxidized with MnO_2 in CH_2Cl_2 at room temperature[18] to give the tetracyclic compound **6**[19] in 74% yield. Compound **6** is also an intermediate of the canthin-6-one synthesis of Mitscher et al.[6] 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[2c] – by a reduction of the ester group. This is currently under investigation in our laboratory.

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13. All new compounds gave satisfying analytical data. Selected analytical data for compound **2a**: M.p. 133°C. ^{1}H NMR (200 MHz, $CDCl_3$): 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 ($C_{13}H_{11}F_3N_2O_2S$), found 316.0491 (M^+). UV (MeOH): λ_{max} / nm = 210, 242, 302, 330 (sh). C,H,N-Anal. $C_{13}H_{11}F_3N_2O_2S$ (316.29): calcd. C 49.37, H 3.51, N 8.86, found C 49.71, H 3.85, N 8.51. E_P (Ox.): 870 mV vs. $Ag/AgNO_3$ (0.1 M $LiClO_4$ in CH_3CN).

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. ^{1}H NMR (200 MHz, $CDCl_3$): 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 ($C_6H_{11}NO_2$), found 129.0788 (M^+). E_P (Ox.): 770 mV vs. $Ag/AgNO_3$ (0.1 M $LiClO_4$ in CH_3CN).

15. Selected analytical data for compound **4a**: M.p. 196°C. ^{1}H NMR (200 MHz, $CDCl_3$): 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 ($C_{17}H_{13}F_3N_2O_4S$), found 398.0544 (M^+). UV (MeOH): λ_{max} / nm = 206, 227, 266 (sh), 279, 288, 296, 322, 336, 353. C,H,N-Anal. $C_{17}H_{13}F_3N_2O_4S$ (398.35): calcd. C 51.26, H 3.29, N 7.03, found C 50.96, H 3.66, N 6.72.

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17. Compound **5** was prepared by a variation of the given procedure in ref.[16] : 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. ^{1}H NMR (200 MHz, $CDCl_3$): 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 ($C_{16}H_{14}N_2O_2$), found 266.1055 (M^+). UV (MeOH): λ_{max} / nm = 214 (sh), 222, 246, 257, 291, 300, 326, 339, 363.

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19. Selected analytical data for compound **6**: M.p. 184°C. ^{1}H NMR (200 MHz, $CDCl_3$): 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 ($C_{16}H_{10}N_2O_3$), found 278.0688 (M^+). UV (MeOH): λ_{max} / nm = 221, 236 (sh), 262, 271, 308, 382.