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Design and Synthesis of *N*-[2- (2,3-dimethoxy-strychnidin-10-ylidenamino)-ethyl]-succinamic acid 4-allyl-2-methoxy-phenyl ester

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In this study a brucine derivative was synthesized using several strategies. In the first stage the compound 4-(4-allyl-2-methoxy-phenoxy)-4-oxobutanoic acid (**3**) was obtained by the reaction of 4-allyl-2-methoxyphenol with succinic acid using N,N'-diciclohexylcarbodiimide/*p*-toluensulfonic acid as a catalyst. The second stage was achieved by the reaction of **3** with ethylenediamine to form 4-allyl-2-methoxyphenyl 4-[(2-aminoethyl)amino]-4-oxobutanoate (**5**) in presence of a carbodiimide derivative. Finally, the compound *N*-[2-(2,3-dimethoxy-strychnidin-10-ylidenamino)-ethyl]-succinamic acid 4-allyl-2-methoxy-phenyl ester (**7**) was prepared by the reaction of **3** with N^1-(2,3-dimethoxystrychnidin-10-yliden)-ethane-1,2-diamine using as a catalyst a carbodiimide derivative. The compound **7** was also synthesized by the reaction between **5** and brucine using boric acid as a catalyst.

Keywords. Brucine, ethylenediamine, succinic acid, carbodiimide.

INTRODUCTION

Since several years ago, some derivatives of brucine have been developed for use in different biological and analytical methods1[1-4]. For example, there are studies which show the synthesis of N-chloromethylbrucine chloride by the reaction of brucine with dichloromethane [5]. Other studies have shown the preparation of a brucine derivative (brucidine) by electrolytic reduction of brucine [6]. In addition, there are reports of the synthesis of N-(5-carboxypentyl)brucinium bromide via N-alkylation of brucine with 6-bromohexanoic acid [7]. Other experimental data showed the preparation of the compounds brucinium hydrogen (S)-malate pentahydrate and anhydrous brucinium hydrogen (2R,3R)-tartrate by the reaction between brucine and D-L-malic acid or L-tartaric acid in ethanol-water medium [8]. Additionally, porphyrin-brucine conjugates were synthesized by N-alkylation of brucine with alkylbromotetraphenylporphyrin derivatives [9].

Recently, a brucine derivative (N^1-(2,3-dimethoxystrychnidin-10-yliden)-ethane-1,2-diamine) was synthesized by the reaction of brucine and ethylenediamine using boric acid as a catalyst. Another brucine derivative (11-[(2-amino-ethylamino)-methyl]-2,3-dime-thoxystrychnidin-10-one) was prepared by the reaction of brucine with ethylenediamine in presence of formaldehyde [10]. Another study described the synthesis of a brucine-dihydropyrimidine derivative using the multi-component system (brucine, benzaldehyde and thiourea) [11]. All these experimental data reveal that several procedures for synthesis of brucine derivatives are available; however, expensive reagents and special conditions are required. Therefore, in this study a new brucine derivative (*N*-[2-(2,3-dimethoxy-strychnidin-10-ylidenamino)-ethyl]-succinamic acid 4-ally-2-methoxy-phenyl ester) was synthetized using several chemical methods.

EXPERIMENTAL

General methods

N^1-(2,3-dimethoxystrychnidin-10-yliden)-ethane-1,2-diamine (**6**) was prepared according to a previously reported method by Figueroa [10]. The other compounds used in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model) device. Infrared spectra (IR) were recorded in KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT

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NMR spectrometer at 300 and 75.4 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elemental analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

4-(4-allyl-2-methoxyphenoxy)-4-oxobutanoic acid (3)

A solution of 4-allyl-2-methoxyphenol (100 mg, 0.61 mmol), succinic acid (144 mg, 1.22 mmol), N,N'-dicyclohexylcarbodiimide (190 mg, 0.92 mmol) and *p*-toluenesulfonic acid anhydrous

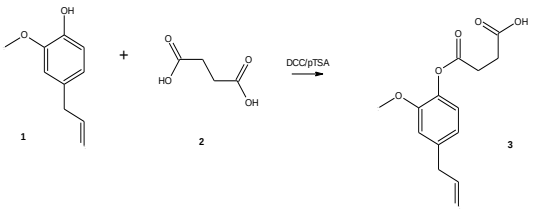

Fig. 1. Synthesis of 4-(4-allyl-2-methoxy- phenoxy)-4-oxobutanoic acid (**3**). Reaction between 4-allyl-2-methoxyphenol (**1**) and succinic acid (**2**) using N,N'-dicyclohexylcarbodiimide/*p*-toluenesulfonic acid (DCC/p-TSA) as a catalyst.

(110 mg, 0.64 mmol) in 10 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. Then the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 62 % of product, m.p. 190–194 ºC; IR (V_{max}, cm^{-1}): 1734, 1720 and 1624; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.60 (t, 2H, *J* = 6.00 Hz), 2.90 (t, 2H, *J* = 6.00 Hz), 3.32 (m, 2H), 3.76 (s, 3H), 5.03 (d, d, 1H, *J* = 1.76 Hz, 16.07), 5.10 (d, d, 1H, *J* = 1.76 Hz, 11.05), 5.97 (m, 1H), 6.74 (d, 2H, *J* = 8.13), 7.05 (d, 1H, *J* = 8.13), 8.60 (s, 1H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 29.31(**C**-16), 29.63 (**C**-15), 39.35 (**C**–12), 55.80 (**C**-8), 113.24 (**C**-6), 115.52 (**C**–14), 122.14 (**C**–3), 122.43 (**C**–4), 137.70 (**C**–13), 139.43 (**C**–5), 151.98 (**C**–2), 171.39 (**C**–10), 174.10 (**C**–17) ppm. MS (70 ev): *m/z* = 234.10 (M^+). Anal. calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10; O, 30.27. Found: C, 63.60; H, 6.12.

4-allyl-2-methoxyphenyl 4-[(2-aminoethyl)amino]-4-oxobutanoate (5)

A solution of **3** (100 mg, 0.38 mmol), ethylenediamine (144 mg, 1.22 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (90 mg, 0.58 mmol) in 10 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. Then the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 45 % of product, m.p. 198–200 ºC; IR (V_{max}, cm^{-1}): 3382, 1730, 1680 and 1622; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.44 (t, 2H, *J* = 6.20 Hz), 2.74 (t, 2H, *J* = 6.20 Hz), 2.98 (t, 2H, *J* = 6.00 Hz), 3.28 (m, 2H), 3.33 (t, 2H, *J* = 6.00 Hz), 3.80 (s, 3H), 4.86 (broad), 5.02 (d, d, 1H, *J* = 1.76 Hz, 16.07), 5.10 (d, d, 1H, *J* = 1.76 Hz, 16.07), 5.97 (m, 1H), 6.78 (d, d, 1H, *J* = 1.76 Hz, 16.07), 6.90 (d, d, 1H, *J* = 1.76 Hz, 16.07) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 29.58 (**C**–15), 30.42 (**C**–16), 39.35 (**C**-12), 41.99 (**C**-21), 42.68 (**C**-20), 55.80 (**C**–8), 112.86 (**C**–6), 115.51 (**C**–14), 121.51 (**C**–3), 129.41 (**C**–4), 137.70 (**C**–13), 139.45 (**C**–2, **C**–5), 151.60 (**C**–1), 169.56 (**C**–10), 172.71 (**C**-17) ppm. MS (70 ev): *m/z* = 306.20 (M^+). Anal. calcd. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14; O, 20.89. Found: C, 62.70; H, 7.20; N, 9.10.

N-[2-(2,3-dimethoxy-strychnidin-10-ylidenamino)-ethyl]-succinamic acid 4-allyl-2-methoxy-phenyl ester (7).
Method A.

A solution of **3** (100 mg, 0.38 mmol) and **6** (170 mg, 0.39 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (110 mg, 0.70 mmol) in 10 mL of methanol was stirred for 48 h at room temperature. The reaction mixture was evaporated to a smaller volume. Then the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (4:1) yielding 72 % of product, m.p. 164–166 ºC; IR (V_{max}, cm^{-1}): 2812, 1738, 1678, 1628; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.40–1.46 (m, 2H), 1.64–1.72 (m, 3H), 1.80-1.89 (m, 3H), 2.23–2.37 (m, 2H), 2.49 (t, 2H, *J* = 6.3 Hz), 2-52-2.66 (m, 2H), 2.69-2.71 (m, 2H), 2.72 (t, 2H, *J* = 6.3 Hz), 2.75 (m, 1H), 2.92 (m, 1H), 3.22 (m, 2H,), 3.33 (t, 2H, *J* = 6.3 Hz), 3.52-3.58 (m, 2H), 3.60–3.64 (m, 2H), 3.73 (t, 2H, *J* = 6.3 Hz), 3.80 (s, 6H), 3.94 (s, 3H), 4.70 (m, 1H), 5.03 (d, d, 1H, *J* = 1.75 Hz, 16.03), 5.10 (d, d, 1H, *J* = 1.75 Hz, 11.05), 5.83 (s, 1H), 5.97 (m, 1H), 6.71–6.79 (d, 2H, *J* = 8.50 Hz), 6.95 (d, 2H, *J* = 8.50 Hz), 7.55 (s, 1H), 8.12 (broad) ppm. ^{13} C NMR (75.4 Hz, $CDCl_3$) □$_C$□□ 28.12 (**C**-13), 29.22 (**C**-

36), 29.58 (**C**–4), 30.43 (**C**-17), 38.79 (**C**–8), 39.35 (**C**-48), 40.72 (**C**-27), 45.65 (**C**-9), 51.6 (**C**-26), 52.24 (**C**-7), 55.80 (**C**-47), 56.01 (**C**–34), 56.29 (**C**–32), 59.92 (**C**–5), 64.62 (**C**-18), 65.06 (**C**–10), 66.82 (**C**–2), 79.27 (**C**-27), 98.33 (**C**–21), 105.71 (**C**–24), 113.22 (**C**-41), 115.53 (**C**–50), 121.51 (**C**–44), 122.87 (**C**-43), 129.27 (**C**–19), 137.76 (**C**–49), 138.80 (**C**–20), 139.15 (**C**–42), 139.45 (**C**–39), 143.26 (**C**–23), 147.76 (**C**–22), 147.82 (**C**-12), 151.61 (**C**–40), 169.56 (**C**–37), 172.73 (**C**–29) ppm. MS (70 ev): *m/z* = 684.30 (M^+). Anal. calcd. for $C_{39}H_{48}N_4O_7$: C, 68.40; H, 7.06; N, 8.18; O, 16.35. Found: C, 68.38; H, 7.02; N, 8.06.

Method B.

A solution of **5** (100 mg, 0.32 mmol), brucine (127 mg, 0.32 mmol) and boric acid (60 mg, 0.80 mmol) in 10 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. Then the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (4:1) yielding 38 % of product. The ^{1}H NMR and ^{13}C NMR data of the product were similar to those of the product obtained by method A.

RESULTS AND DISCUSSION

It should be mentioned that some procedures for obtaining of brucine derivatives are available in the literature. Nevertheless, these procedures suffer from several drawbacks: some reagents are of limited stability; preparation can be dangerous[6–8]. Therefore, in this study we report a route for synthesis of a new brucine derivative (**7**) using several strategies. The first step involves the esterification of the hydroxyl group of compound **1** to form **3**. The synthesis of **3** has been reported previously [12]; nevertheless in this study a new strategy for its development was used. Although there are diverse reagents available to produce ester derivatives [13, 14], most of the conventional methods are of limited use for some compounds. Therefore, in this study the method reported by Erlanger and co-workers [15] for esterification of other compounds was used. Thus, compound **3** was synthesized by the reaction of compound **1** with succinic acid using 1,3-dicyclohexylcarbodiimide (DCC) as coupling reagent. When DCC is used alone as a condensing agent in ester synthesis, the yield of esters is often unsatisfactory due to formation of an N-acylurea by-product. Some reports showed that addition of a catalytic amount of a strong acid to the esterification reaction in the presence of DCC considerably increases the yield of esters and decreases the formation of N-acylurea [16]. Therefore, *p*-toluenesulfonic acid was used to increase the yield of **3** in the esterification of **1** with succinic acid in the presence of DCC.

On the other hand, in the ^{1}H NMR spectrum of **3** there are signals at 2.60–2.90 ppm for methylenes bound to carboxyl group, at 3.32 ppm for methylene bound to phenyl group; at 3.76 ppm for methoxy group; 5.03–5.97 ppm for protons involved in the alkene group; at 6.74–7.05 ppm for hydrogens of phenyl group. Finally, a signal at 8.60 ppm for carboxyl group was found. The ^{13}C NMR spectrum contains peaks at chemical shifts of 29.31–29.63 ppm for protons involved in the methylenes bound to carboxyl group. Other signals at 39.35 ppm for methylene bound to phenyl group; at 55.80 ppm for methoxy group; at 113.24, 122.14 and 139.43–171.39 ppm for phenyl group were found. Finally, signals at 115.52 and 137.70 ppm for alkene group; at 174.10 ppm for carboxyl group were displayed. The presence of **3** was further confirmed from the mass spectrum which showed a molecular ion at m/z 264.10.

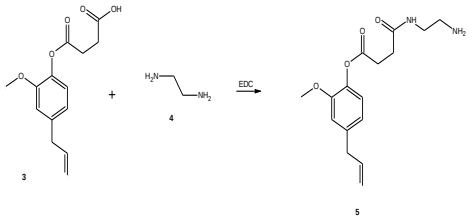

Fig.2. Synthesis of 4-allyl-2-methoxyphenyl 4-[(2-aminoethyl)amino]-4-oxobutanoate (**5**). Reaction between 4-(4-allyl-2-methoxy-phenoxy)-4-oxobutanoic acid (**3**) with ethylenediamine (**4**) in presence of N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) to form **5**.

The second step was achieved by the reaction of **3** with ethylenediamine (**4**) to form an amide group involved in compound **5** (Figure 2). Although many procedures for the formation of amides are known in the literature, the most widely used one employs carboxylic acid chlorides as electrophiles which react with the amino group in the presence of an acid scavenger [17]. Despite its wide scope, this protocol suffers from several drawbacks: limited stability of many acid chlorides and hazardous reagents needed for their preparation (e.g., thionyl chloride) [18]. Therefore, in this study N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) [19] was used to form compound **5**.

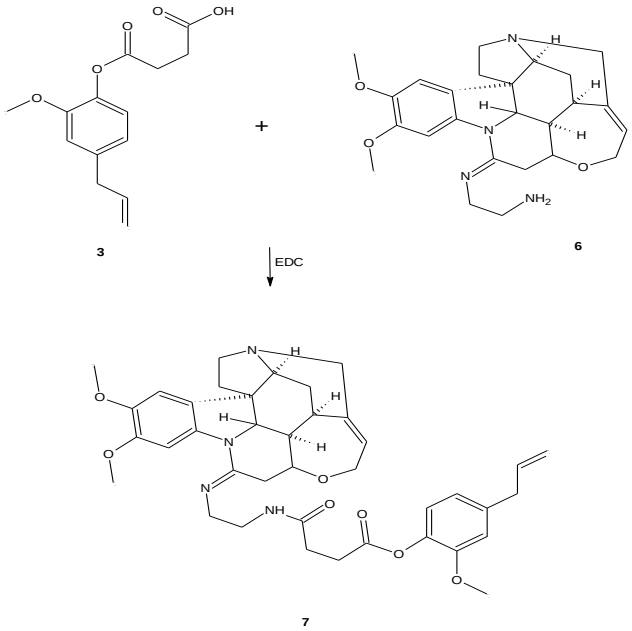

Fig. 3. Synthesis of *N*-[2-(2,3-dimethoxy-strychnidin-10-ylidenamino)-ethyl]-succinamic acid 4-ally-2-methoxy-phenyl ester (**7**). Reaction of 4-(4-allyl-2-methoxy- phenoxy)-4-oxobutanoic acid (**3**) with *N[1]-(2,3-dimethoxystrychnidin-10-yliden)-ethane-1,2-diamine* (**6**) to form **7** using N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) as catalyst.

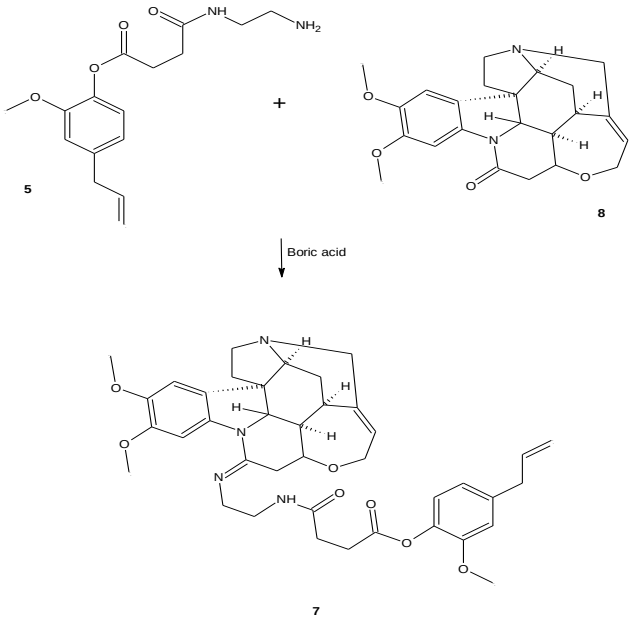

Figure 4. Synthesis of *N*-[2-(2,3-dimethoxy-strychnidin-10-ylidenamino)-ethyl]-succinamic acid 4-allyl-2-methoxy-phenyl ester (**7**). Reaction between 4-allyl-2-methoxyphenyl 4-[(2-aminoethyl)amino]-4-oxobutanoate (**5**) and brucine (**8**) to form **7** using boric acid as a catalyst.

The ^{1}H NMR spectrum of **5** shows signals at 2.44–2.74 ppm for methylenes bound to both amide and ester groups; at 2.98–3.28 ppm for methylenes bound to both amide and amine groups; at 3.33 ppm for methylene bound to phenyl group. Finally, other signals at 3.80 ppm for methoxy group; at 4.86 ppm for both amide and amine groups; at 5.02-5.97 ppm for protons involved in the alkene group; at 6.78-6.90 ppm phenyl group were found. It should be mentioned that the ^{1}H NMR spectra of the secondary amides are usually more complex than the primary amides due to the presence of a substituent bound to the amide nitrogen atom. These substituents produce a much wider range of

chemical shifts for the amide proton which may, in addition, display coupling to aliphatic groups bound to it. The chemical shifts of aliphatic groups bound to the carbonyl group are similar to those observed for the primary amides, while those groups bound to the nitrogen resonate at slightly lower field than the corresponding amines [20].

On the other hand, the ^{13}C NMR spectrum of **5** contains peaks at chemical shifts of 29.58–30.42 ppm for methylenes bound to both amide and ester groups; at 39.35 ppm for methylene bound to phenyl group; at 41.99–42.68 ppm for methylenes bound to both amide and amine groups; at 55.80 ppm for methoxy group; at 112.86, 121.51–129.41, 139.45–151.60 ppm for carbons of phenyl group. Finally, other signals at 115.51 and 137.70 ppm for alkene group; at 169.56 ppm for ester group; at 172.71 ppm for both amide and amine groups were found. The presence of **5** was further confirmed from the mass spectrum which showed a molecular ion at m/z 306.20.

On the other hand, the compounds **3** and **5** were bound to the brucine nucleus; in the first case, **3** reacted with **6** to form **7** using a carbodiimide derivative as a catalyst (method A). The ^{1}H NMR spectrum of **7** shows signals at 140–2.37, 2.52–2.71, 2.75–2.92, 3.52–3.64, 4.70, 5.83 and 7.55 ppm for the brucine nucleus; at 3.22 ppm for methylene bound to phenyl group; at 3.33 and 3.73 ppm for methylenes bound to both amide and imino groups; at 3.80–3.94 ppm for methoxy groups. Finally, other signals at 5.03–5.10 and 5.97 ppm for alkene group; at 6.71–6.95 ppm for phenyl group; at 8.12 ppm for amide group were found. The ^{13}C NMR spectrum of **7** contains peaks at chemical shifts of 28.12, 29.58–30.43, 32.08–38.79, 40.38, 45.65, 52.24, 59.92–105.71, 179.27, 138.80 and 143.26-147.82 ppm for the brucine nucleus; 29.12 and 31.70 ppm for methylenes bound to both ester and amide groups; at 39.35 ppm for methylene bound to phenyl group; at 40.72 and 51.60 ppm for methylenes bound to both amide and imino groups; at 55.80, 56.01 and 56.29 ppm for methoxy groups; at 113.22, 121.51, 122.87, 139.15, 139.45 and 151.61 ppm for phenyl group. Finally, other signals at 115.53 and 137.76 ppm for carbons involved in the alkene group; at 169.56 ppm for ester group; at 172.73 ppm for amide group were found. The presence of **7** was further confirmed from the mass spectrum which showed a molecular ion at m/z 684.30.

In the search of another way to synthesize **7,** in this study the compound **5** was bound to the brucine nucleus (**8**) to form an imino group involved in compound **7** (method B) (Figure 4). There are several procedures for the synthesis of imino groups which are described in the literature [21-23]; nevertheless, in this study boric acid was used as a catalyst, because it is not an expensive reagent and no special conditions for its use are required[10]. Similar ^{1}H NMR and ^{13}C NMR data were obtained compared to those of method A product. Following this pathway, however, a lower yield was obtained, most probably due to the insufficient time of the reaction.

In conclusion, a facile procedure for the formation of a brucine-derivative (**7**) was developed in this study.

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ДИЗАЙН И СИНТЕЗ НА 4-АЛИЛ-2-МЕТОКСИ-ФЕНИЛ ЕСТЕР НА N-[2-(2,3-ДИМЕТОКСИ-СТРИХНИН-10-ИЛИДЕ АМИНО)ЕТИЛ] АМИНОЯНТЪРНА КИСЕЛИНА

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(Резюме)

В настоящото изследване е синтезирано производно на бруцина чрез няколко стратегии. През първия етап е получено съединението 4-(4-алил-2-метокси-фенокси)-4-оксобутанова киселина (3) е получено чрез реакцията на 4-алил-2-метоксифенол с янтарна киселина, използвайки N,N'-дициклохексилкарбодиимид/р-толуенсулфонова киселина като катализатор. Вторият етап е достигнат чрез реакцията на (3) с етилендиамин, за да се получи 4-алил-2-метоксифенил 4-[(2-аминоетил) амино]-4-оксобутаноат (5) в присъствие на производно на карбодиимид. Накрая съединението 4-алил-2-метокси-фенил естер на N-[2-(2,3-диметокси-стрихнидин-10-илиденамино) етил]-аминоянтърна киселина (7) бе получено от реакцията на 3 с N^1-(2,3-диметоксистрихнидин-10-илидин) етан-1 ,2-диамин използвайки карбодиимидно производно като катализатор. Съединението 7 беше синтезирно също и чрез реакцията между 5 и бруцин, използвайки борна киселина като катализатор.