Asian Journal of Chemistry; Vol. 26, No. 16 (2014), 4959-4962

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16268

Design and Synthesis of Two Indol-Steroid Derivatives

L. FIGUEROA-VALVERDE[1,*], F. DÍAZ-CEDILLO[2], E. GARCÍA-CERVERA[1], E. POOL GÓMEZ[1], M. ROSAS-NEXTICAPA[3] and M. LÓPEZ-RAMOS[1]

[1]Laboratory of Pharmaco-Chemistry at the Faculty of Chemical Biological Sciences of the University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P.24039 Campeche Cam., México
[2]Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, D.F. C.P. 11340, México
[3]Facultad de Nutrición, Universidad Veracruzana. Médicos y Odontólogos s/n, 91010, Xalapa, Veracruz, México

*Corresponding author: E-mail: lauro_1999@yahoo.com

Received: 2 September 2013; *Accepted*: 13 January 2014; *Published online*: 28 July 2014; AJC-15609

In this study two new indol-steroid derivatives were synthesized. The first stage involves the synthesis of 17-(2-amino-thiazol-5-yl)-10,13-dimethyl-1,2-6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta[a]phenanthren-3-one (**3**) by the reaction of progesterone with thiourea using I_2 as catalyst. The second stage was achieved by reaction of a brucine derivative with the compound **3** to form the compound N-(2,3-dimethoxystrychnidin-10-ylenamino)-N'-[10,13-dimethyl-17(2-amino-thiazol-5-yl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta-[a]phenanthren-3-ylidene]-ethane-1,2-diamine using boric acid as catalyst. The third stage was achieved by reaction of compound **3** with brucine to form 10,13-dimethyl-17-[2-(2,3-dimethoxy-strychnidin-10-ylideneamino)-thiazol-5-yl]-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta[a]phenanthren-3-onausing boric acid as catalyst. The structure of compounds obtained was confirmed by spectrometry data.

Keywords: Design, Synthesis, Indol-steroid.

INTRODUCTION

The development of indol derivatives are a very important heterocyclic compounds which induced several biological activities such as antibacterial characteristics[1,2]. There are several methods reported for synthesis of aromatic-condensed derivatives *e.g.*, the synthesis of indol derivatives *via* palladium-catalyzed heteroannulation of internal alkynes[3]. Other studies showed the synthesis of an indol derivative by reaction of N-aryl amides with ethyl diazoacetate[4]. In addition, some indol derivatives were developed using the palladium-catalyzed coupling of alkynes with iodoaniline derivatives[5]. In addition, other data showed that ruthenium catalyzed synthesis of indol from N-substituted anilines and alkanolamines[6]. Also a study shows the synthesis of 2-substituted indol derivatives from 2-ethynylanilines with tetrabutylammonium fluoride[7].

On the other hand, several years ago a series of indol-steroid derivatives have been developed *e.g.*, the synthesis of 17-indazole androstene derivatives[8] using dehydroepiandrosterone acetate as substrate. Other data showed a procedure for synthesis of 1'-methylindolo(3',2':2, 3)2(5a)-androsten-17-one which was prepared by the Fischer indole synthesis[9]. Additionally, other studies show the synthesis of 1'*H*-5 α-cholest-2-eno[3,2-*b*]indol using the Fisher reaction[10]. Recently, a facile synthesis of an indol-dihydro-testosterone succinate derivative by the reaction of dihydrotestosterone with phenylhydrazine using hydrochloric acid as catalyst was reported[11]. All these experimental results show several procedures which are available for synthesis of indol derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, in this study two indol-steroid derivatives were synthetized using some strategies.

EXPERIMENTAL

The compounds N[1]-(2,3-dimethoxystrychnidin-10-yliden)-ethane-1,2diamine (**4**) was prepared according to previously reported methods[12]. The other compounds evaluated in this study were purchased from Sigma-Aldrich Co. Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Infrared spectra (IR) were recorded using 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 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. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

17-(2-Amino-thiazol-5-yl)-10,13-dimethyl-1,2-6,7,8,9,10,11,12,13,14,15,16,17-tetrade-cahydrocyclopenta[a]-phenanthren-3-one (3) (Fig. 1): A solution of progesterone (100 mg, 0.32 mmol), thiourea (50 mg, 0.66 mmol) and I_2 (50.8 mg, 0.2 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to dryness under reduced pressure. The obtained solid was washed with aqueous sodium thiosulfate to remove excess iodine and then washed with water, yielding 43 % of product, m.p. 194-195 °C; IR (KBr, ν_{max}, cm^{-1}) = 3380, 1712, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ_H:0.82 (s, 3H), 0.95-1.04 (m, 2H), 1.18 (s, 3H), 1.19-1.50 (m, 5H), 1.64-1.79 (m, 4), 1.88-1.98 (m, 2H), 2.04-2.40 (m, 6H), 2.74 (m, 1H), 5.85 (s, 1H), 6-71 (m, 1H), 6.82 (broad, 2H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ 13.88 (C-24), 17.32 (C-26), 22.40 (C-12), 28.26 (C-15), 28.52 (C-14), 32.16 (16), 32.41 (C-17), 33.95 (C-21), 34.60 (10), 35.66 (C-22), 37.40 (C-23), 42.20 (13), 45.60 (C-8), 53.76 (C-4), 46.05 (C-7), 54.02 (11), 60.90 (C-9), 123.78 (C-19), 126.00 (C-4), !30.90 (C-5), 170.79 (C-18), 179.02 (C-2), 196.90 (C-20) ppm. EI-MS *m/z*: 370.11 (M+, 12).

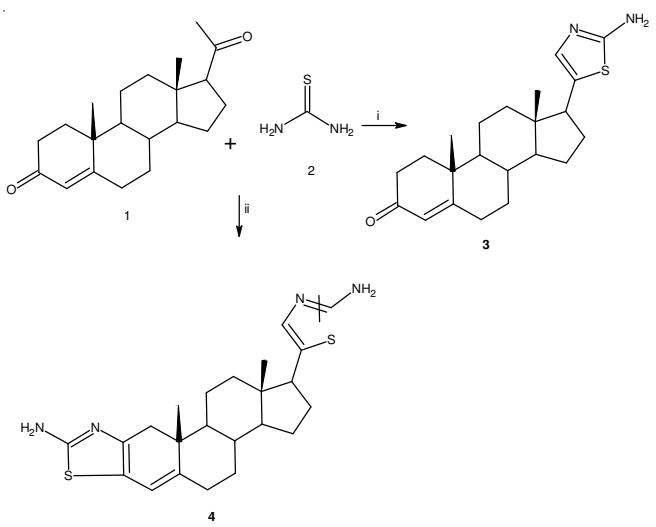

Fig. 1. Synthesis of 17-(2-Amino-thiazol-5-yl)-10,13-dimethyl-1,2-6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclo-penta[a]-phenanthren-3-one (**3**). Reaction of progesterone (**1**) with thiourea (**2**) to form 3 using I_2 as catalyst. The compound **3** was not formed. i and ii = methanol/rt

N-(2,3-Dimethoxystrychnidin-10-ylenamino)-N'-[10,13-dimethyl-17(2-amino-thiazol-5-yl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta[a] phenanthren-3-ylidene]ethane-1,2-diamine (5) (Fig. 2): A solution of compound **3** (100 mg, 0.27 mmol), brucine derivative (114 mg, 0.27 mmol) and boric acid (40 mg, 0.65 mmol) in 10 mL of methanol was stirring for 48 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with methanol/chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (4:1) yielding 73 % of product, m.p. 202-204 °C; IR (KBr, ν_{max}, cm^{-1}) = 3378, 3320, 2812, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ_H:0.85 (s, 3H), 0.96-1.02 (m, 2H), 1.20 (s, 3H), 1.22-1.39 (m, 4H), 1.43 (m, 1H), 1.50-1.76 (m, 6H), 1.84 (m, 1H), 1.85 (m, 1H), 1,86 (m, 1H), 2.00-2.24 (m, 4H), 2.27 (m, 1H), 2.30 (m, 1H), 2.34 (m, 1H), 2.39 (m, 1H) 2.70 (m, 2H), 2.72 (m, 2H), 2.84-3.24 (m, 4H), 3.40 (t, 2H, *J* = 8.67), 3.54 (m, 1H), 3.56 (t, 2H, *J* = 8.67), 3.62-3.69 (m, 4H), 3.80 (s, 3H), 3.90 (s, 3H), 4.30 (d, 1H, *J* = 1.82), 5.22 (m, 1H), 5.82 (m, 1H), 5.90 (s, 1H), 6.60 (d, 1H, *J* = 0.84), 6.82 (broad, 2H), 7.65 (d, 1H, *J* = 0.68)ppm.^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 13.80 (C-24), 17.72 (C-53), 22.48 (C-12), 26.68 (C-44), 28.12 (C-46), 28.28 (C-15), 28.50 (C-14), 29.22 (C-45), 30.40 (C-21), 31.13 (C-22), 31.31 (C-17), 31.69 (C-16), 34.60 (C-10), 35.26 (C-23), 39.90(C-41), 42.12 (C-13), 45.65 (C-42), 45.86 (C-8, C-32), 46.00 (C-7), 49.54 (C-27), 50.67 (C-38), 51.43 (C-26), 51.97 (C-11), 52.24 (C-40), 56.00 (C-57), 56.6 (C-55), 59.90 (C-43), 60.90 (C-9), 64.62 (C-35), 65.06 (C-31), 79.27 (C-33), 98.43 (C-48), 105.7 (C-51), 115.5 (C-19), 126.20 (C-4), 127.87 (C-36), 129.05 (C-52), 130.86 (C-5), 139.15 (C-47), 140.3 (C-37), 143.26 (C-50), 147.76 (C-49), 147.80(C-29),158.12 (C-18), 165.90(C-20), 179.66 (C-2) ppm. EI-MS *m/z*: 788.40 (M+, 12).

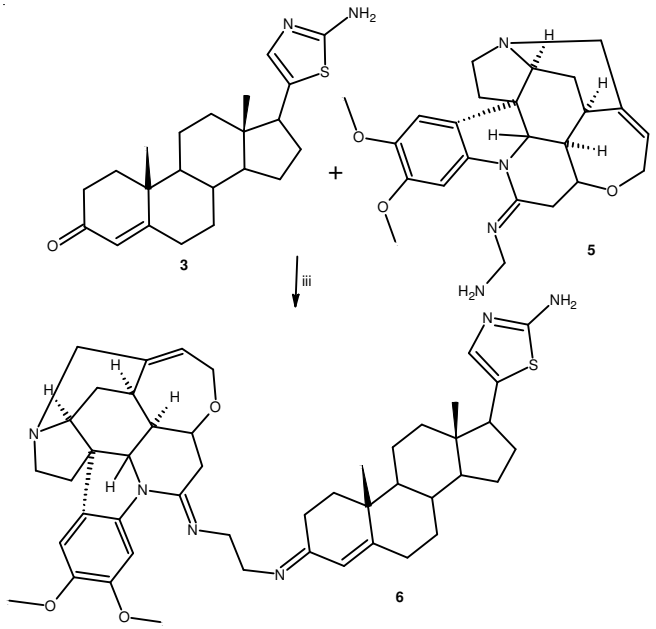

Fig. 2. Synthesis of N-(2,3-dimethoxystrychnidin-10-ylenamino)-N'-[10,13-dimethyl-17(2-amino-thiazol-5-yl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17,-tetradecahydro-cyclopenta-[a]phenanthren-3-ylidene]-ethane-1,2-diamine (**5**). Reaction of compound **3** with a brucine derivative (**5**) to form **6** using boric acid as catalyst. iii = methanol/rt

10,13-Dimethyl-17-[2-(2,3-dimethoxy-strychnidin-10-ylideneamino)-thiazol-5-yl]-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclopenta[a]phenanthren-3-one (8) (Fig. 3): A solution of compound **3** (100 mg, 0.27 mmol), brucine (110 mg, 0.28 mmol) and boric acid (40 mg, 0.65 mmol) in 10 mL of methanol was stirring for 48 h to room temperature. The reaction mixture was evaporated to a smaller volume. After 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 68 % of product, m.p. 219-220 °C; IR (KBr, ν_{max}, cm^{-1}) = 3320, 2810, 1718; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 0.84 (s, 3H), 0.96-1.03 (m, 2H),

1.19 (s, 3H), 1.21-1.39 (m, 3H), 1.43 (m, 1H), 1.50-1.76 (m, 6H), 1.82-1.85 (m, 2H), 1.90-2.09 (m, 4H), 2.27 (m, 1H), 2.30-2.34 (m, 2H), 2.35 (m, 1H), 2.39 (m, 1H) 2.70-2.84 (m, 2H), 2.90 (m, 1H), 2.94-3.74 (m, 9H), 3.80 (s, 3H), 3.90 (s, 3H), 4.34 (d, 1H, *J* = 1.82), 5.26 (m, 1H), 5.82 (m, 1H), 5.90 (m, 1H), 7.48 (d, 1H, *J* = 0.84), 7.90 (d, 1H, *J* = 0.68) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 13.80 (C-52), 17.70 (C-54), 22.46 (C-36), 26.68 (C-22), 28.28 (C-39), 28.50 (C-38), 29.22 (C-24), 30.40 (C-23), 32.13 (C-40), 32.50 (C-41), 33.60 (C-45), 34.62 (C-34), 35.26 (C-46), 37.42 (C-47), 39.90 (C-19), 42.12 (C-37), 42. 26 (C-31), 45.65 (C-20), 45.70 C-320), 45.80 (C-10), 50.67 (C-16), 52.24 (C-18), 54.10 (C-35), 56.00 (C-51), 56.60 (C-49), 59.90 (C-21), 60.90 (C-33), 64.20 (C-9), 64.62 (C-13), 79.27 (C-1), 98.43 (C-26), 106.70 (C-29), 122.50 (C-43), 126.20 (C-5), 127.76 (C-4), 127.87 (C-14), 129.05 (C-30), 139.20 (C-25), 140.32 (C-15), 143.26 (C-28), 148.76 (C-27), 158.12 (C-7), 170.50 (C-42), 171.66 (C-2), 198.80 (C-44) ppm. EI-MS *m/z*: 746.32 (M+, 12).

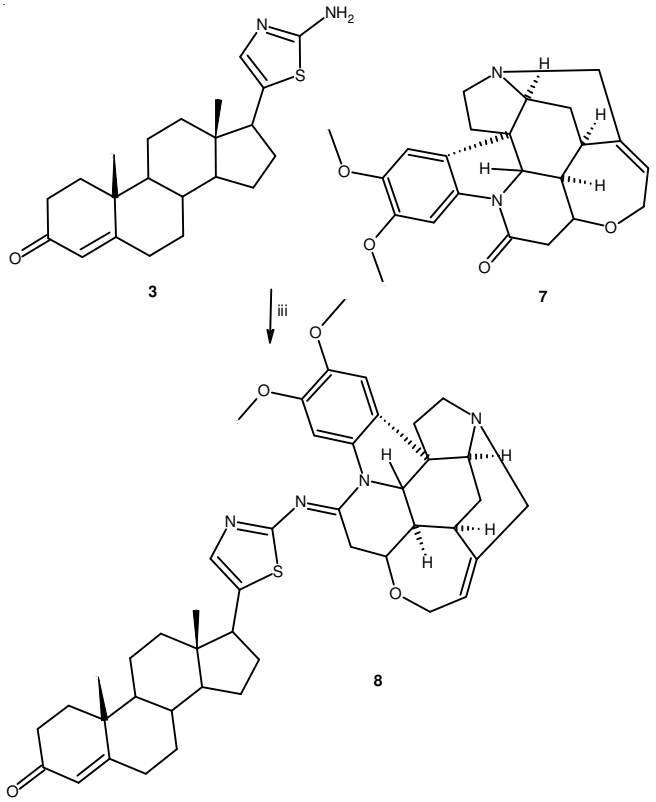

Fig. 3. 10,13-Dimethyl-17-[2-(2,3-dimethoxy-strychnidin-10-ylidene-amino)-thiazol-5-yl]-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetra-decahydro-cyclopenta[a]phenanthren-3-ona (**8**). Reaction of compound **3** with brucine (**7**) to form **8** using boric acid as catalyst. iii = methanol/rt

RESULTS AND DISCUSSION

There are many procedures for synthesis of indol derivatives. Nevertheless, despite its wide scope, the former protocols suffer from several drawbacks because some reagents have a limited stability[13-16]. Therefore, in this study several straightforward routes are reported for the synthesis of two new indol derivatives. The first step involves preparation of **3** and **4** by the reaction of progesterone with thiourea using I_2 as catalyst. It is important to mention that in this study, we expected the formation of compounds **3** and **4**. However, spectroscopy and spectrometry data confirmed that only the compound **3** was formed. This phenomenon possibly is influenced by higher reactivity of 17-acetyl group. The ^{1}H NMR spectrum of compound **3** shows signals at 0.82 and 1.18 ppm for methyl groups; at 0.95-5.85 ppm for protons involved in the steroid nucleus; at 6.71 ppm for proton of indol; at 6.82 for amino group. The ^{13}C NMR spectrum contains peaks at 13.88 and 17.32 ppm for methyl groups; at 22.40-123.78 and 170.79 ppm for steroid nucleus; at 126.00, 130.90 and 179.02 ppm for carbons involved in the indol group; at 196.90 ppm for ketone group. In addition, the presence of **3** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 370.11.

The second stage was achieved by reaction of a brucine derivative with the compound **3** resulting in imino bond formation involved in the compound **5**. It is important to mention that many procedures for the synthesis of imino groups are described in the literature[17-19]. 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[20]. The results indicate that ^{1}HNMR spectrum of **5** showed several signals at 0.85 and 1.20 ppm for methyl groups; at 0.96-1.02, 1.22-1.39, 1.50-1.76, 1.85, 2.00-2.24, 2.30, 2.39, 2.72 and 5,90 ppm for protons involved in the steroid nucleus; at 1.43, 1.84, 1.86, 2.27, 2.34, 2.70, 2.84-3.24, 3.54, 3.62, 3.69, 4.73, 5.22 and 5.82 ppm for the brucine fragment; at 3.40 and 3.56 ppm for arm bound to both steroid and brucine fragments. Finally, other signals at 3.80 and 3.90 ppm for methoxy groups; at 6.60 for proton involved in indol group; at 6.82 for amino group were found. The ^{13}C NMR spectrum contains peaks at 13.80 and 17.72 ppm for methyl groups; at 22.48, 28.28-28.50, 30.40-35.26, 42.12, 45.85, 46.51, 51.88, 60.90, 114.80, 158.12 and 165.90 ppm for steroid nucleus; at 26.68-28.12, 29.22, 39.40, 45.65, 45.86, 50.67, 52.20, 59.90, 64.62-105.20, 127.80-129.00 and 139.10-147.80 ppm for brucine fragment; 49.54 and 51.40 ppm for arm bound to both steroid and brucine fragments; at 56.00 and 56.60 ppm for methoxy groups; at 126.20, 130.86 and 176.66 ppm for carbons involved in the indol group. In addition, the presence of **5** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 788.40.

Third stage was achieved by reaction of brucine with the compound **3** resulting in imino bond formation involved in the compound **8**. The ^{1}H NMR spectrum of **8** shows signals at 0.84 and 1.19 for methyl groups; at 0.96-1.03, 1.21-1.39, .50-1.76, 1.90-2.09, 2.30-2.34, 2.39, 2.90 and 5.26 ppm for steroid nucleus; at 1.43, 1.82-1.85, 2.27, 2.35, 2.70-2.84, 2.94-3.74, 4.34 and 5.82-7.48 ppm for brucine fragment; at 380 and 3.90 ppm for methoxy groups. Finally, a signal at 7.90 for proton involved in the indol group was found. The ^{13}C NMR spectrum contains peaks at 13.80 and 17.70 ppm for methyl groups; at 22.46, 22.28-28.50, 32.13-7.42, 42.12-42.26, 45.70, 54.10, 60.90, 122.50 and 170.50 ppm for steroid nucleus; at 26.68, 29.22-30.40, 39.90, 45.65, 45.80-52.24, 59.90, 64.20-106.70, 127.87-158.12 ppm for brucine fragment; at 56.00 and 56.60 ppm for methoxy groups; 126.20, 127.76 and 171.66 ppm for carbons involved in the indol group; at 198.80 for ketone group.

Finally, the presence of 8 was further confirmed from mass spectrum which showed a molecular ion at *m/z* 746.32.

In conclusion, a facile procedure for the formation of two indol-derivatives was developed in this study.

REFERENCES

1. M.C. Rodríguez-Argüelles, E.C. López-Silva, J. Sanmartín, P. Pelagatti and F. Zani, *J. Inor. Biochem*., **99**, 2231 (2005).
2. T.C. Leboho, J.P. Michael, W.A.L. van Otterlo, S.F. van Vuuren and C.B. de Koning, *Bioorg. Med. Chem. Lett*., **19**, 4948 (2009).
3. R.C. Larock and E.K. Yum, *J. Am. Chem. Soc*., **113**, 6689 (1991).
4. S.-L. Cui, J. Wang and Y.-G. Wang, *J. Am. Chem. Soc.*, **130**, 13526 (2008).
5. M.C. Fagnola, I. Candiani, G. Visentin, W. Cabri, F. Zarini, N. Mongelli and A. Bedeschi, *Tetrahedron Lett*., **38**, 2307 (1997).
6. D. Lee, C. Cho, J. Kim, Y. Youn, S. Shim and H. Song, *Bull. Korean Chem. Soc*., **17**, 1132 (1996).
7. A. Yasuhara, Y. Kanamori, M. Kaneko, A. Numata, Y. Kondo and T. Sakamoto, *J. Chem. Soc. Perkin Trans*., 529 (1999).
8. V.M.A. Moreira, T.S. Vasaitis, V.C.O. Njar and J.A.R. Salvador, *Steroids*, **72**, 939 (2007).
9. R. Haugland, J. Yguerabide and L. Stryer, *Proc. Natl. Acad. Sci. USA*, **63**, 23 (1969).
10. J. Samu, J. Botyanszki, H. Duddeck and G. Snatzke, *Liebigs Ann. Chem*., 1225 (1993).
11. L. Figueroa-Valverde, F. Diaz-Cedillo and E. Garcia-Cerver, *Bulgarian Chem. Comm*., **44**, 83 (2012).
12. L. Figueroa-Valverde, F. Díaz-Cedillo, M. López-Ramos, E. García-Cervera and E. Pool-Gómez, *Asian J. Chem*, **24**, 2173 (2012).
13. R. Mannhold and H. Van de Waterbeemd, *J. Comput. Aided Mol. Des*., **15**, 337 (2001).
14. T. Österberg and U. Norinder, *Eur. J. Pharm. Sci*., **12**, 327 (2001).
15. D. Boger and J. McKie, *J. Org. Chem*., **60**, 1271 (1995).
16. M. Gallant, J.T. Link and S.J. Danishefsky, *J. Org. Chem*., **58**, 343 (1993).
17. A. Shirayev, I. Moiseev and S. Karpeev, *ARKIVOC*, 199 (2004).
18. D. Jean-Noël Uppiah, M.G. Bhowon and J. Laulloo, *E-J. Chem*., **6**, 195 (2009).
19. M. Hania, *E-J. Chem*., **6**, 629 (2009).
20. L. Figueroa-Valverde, F. Díaz-Cedillo, E. García-Cervera, E. Pool-Gómez and M. López-Ramos, *Bulgarian Chem. Comm.*, **45**, 71 (2013).