Tetrahedron Letters 52 (2011) 4938–4940

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient, economical synthesis of hydroxytyrosol and its protected forms via Baeyer–Villiger oxidation

Giovanni Piersanti [a], Michele Retini [a], José L. Espartero [b], Andres Madrona [b], Giovanni Zappia [a,*]

[a] Department of Biomolecular Sciences, University of Urbino, "Carlo Bo" P.zza Rinascimento 6, 61029 Urbino (PU), Italy
[b] Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, C/Prof. García González 2, 41012 Sevilla, Spain

ARTICLE INFO

Article history:
Received 17 June 2011
Accepted 13 July 2011
Available online 23 July 2011

Keywords:
Hydroxytyrosol
Baeyer–Villiger oxidation
Orthogonally-protected
Selectivity
Natural products

ABSTRACT

An efficient and practical preparation of hydroxytyrosol and its orthogonally-protected forms was developed from inexpensive tyrosol. The utilization of Baeyer–Villiger oxidation enables the chemoselective introduction of a phenolic hydroxyl group in good yield.

Hydroxytyrosol (HyT) (**1**, Fig. 1) is a well-known natural antioxidant derived from the enzymatic or chemical hydrolysis of oleuropein, one of the major phenolic compounds, found in olive fruits[1] and wastewaters from olive oil industry[2], which has been reported to exhibit, mainly, a protective action for the cells against oxidative stress.[3a,b] Several in vitro and in vivo studies carried out with pure HyT reported its capacity to reduce the risk of coronary heart disease and atherosclerosis.[3c,d] Other biological properties of the HyT and its derivatives including antimicrobial,[3e,f] antiinflammatory,[3g] hypotensive and hypoglycaemic activities,[3h] inhibition of platelet aggregation[3i] and several lipoxygenases,[3l] or induction of apoptosis in HL-60 cells.[3m] In addition, recently a direct association between hydroxytyrosol urinary concentrations and alcohol consumption in a population at high risk of coronary artery disease has been proved.[3n]

Therefore, it is not surprising that many efforts have been made to obtain pure hydroxytyrosol, directly from natural sources or by synthesis, for its potential use as a dietary supplement or as a stabilizer in foods and cosmetic preparations.[4] The reported HyT synthetic approaches are based on reduction with the problematic $LiAlH_4$ of commercial and expensive 3,4-dihydroxyphenyl-acetic acid in 79% yield[5e] or the corresponding methyl ester[5f], while an IBX-mediated oxidation of tyrosol acetate has been proposed by Bernini et al. very recently.[5a,b] Enzymatic preparation[6] of HyT has been also investigated using *Serratia marcescens* strain or whole cells of *Pseudomonas aeruginosa*. Recovery from natural sources is based on both chemical and enzymatic methodologies.[7]

In the recent years, a growing interest has been dedicated to the study of Hyt-derivatives. In particular, Hyt-esters derived from fatty acids[8] have been considered with the aim of increasing the lipophilicity and extending the utilization of hydroxytyrosol as additive in foods or for cosmetic applications. These compounds have shown to retain the antioxidative activity in lipid matrices as well as in biological systems[8d], while the peracetylated HyT was active against oxidative stress in human cells.[8f] Regarding the preparation of Hyt-derivatives differentially functionalized at the catechol moiety, a reduced number of compounds have been reported[9,8i], mainly using the homovanillic alcohol as starting material, as a consequence of the objective difficulties to the chemoselective functionalization of the two hydroxyl groups.

As part of an ongoing project direct to explore the therapeutic potentialities of selectively functionalized new Hyt-derivatives,

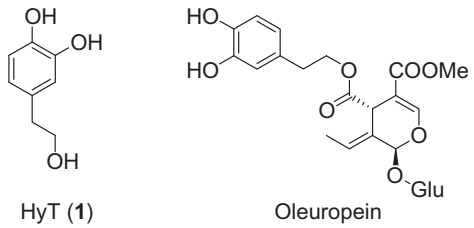


Figure 1. Chemical structures of hydroxytyrosol and oleuropein.

* Corresponding author. Tel.: +39 0722303320; fax: +39 0722303313.
E-mail address: giovanni.zappia@uniurb.it (G. Zappia).

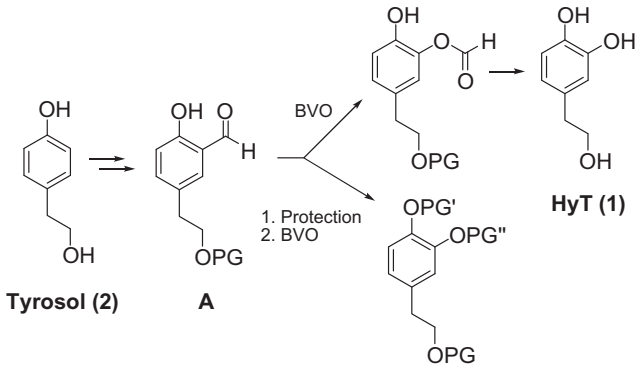
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.07.063

herein we report a convenient and practical synthesis of HyT **1** in multigram scale from tyrosol **2**, as well as, the preparation of orthogonally protected forms of HyT, through a judicious management of the protecting groups. It is worth mentioning that tyrosol was chosen because of its commercially availability and low cost. We postulated that we could gain access to HyT and its protected forms via a Baeyer–Villiger oxidation (BVO)[10] of a easily achievable salicylaldehyde derivatives. Thus, with suitable protecting groups, synthesis of HyT and their orthogonally protected forms could be accomplished from the common intermediate **A**. (Scheme 1).

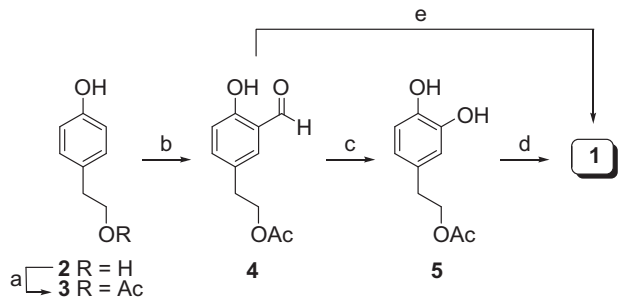
Our synthesis (Scheme 2) begins with simple protection of tyrosol **2** to give in almost quantitative yield the acetate **3** (which is also commercially available).[8h] In general, formylation of phenol[11] is quite often low-yielding and the lack of regioselectivity is problematic. However, treatment of the phenol **3** with $MgCl_2/(CH_2O)n$ in presence of triethylamine, gave the desired *ortho*-formyl **4**[12] in 72% as isolated product. A screening of different reaction conditions or Lewis acids did not increase significantly the yield of **4**.

The 4-substituted salicylaldehyde **4** was then subjected[13] to a BVO reaction[10] to introduce the second hydroxyl to generate the catechol moiety. Of the different oxidizing reagents and reaction conditions tested, the use of *m*-chloroperoxybenzoic acid in CH_2Cl_2 under optimized conditions gave the best conversion rate. Addition to the reaction mixture of an excess of NH_3/MeOH (2 M) and stirring at rt for 1 h allowed the hydrolysis of the resulting formate intermediate which provided cathecol **5** in 97% of isolated yield. The subsequent acid hydrolysis afforded HyT **1** in 79% of yield. On the other hand, when to the oxidation mixture was added an excess of a solution of NH_3/MeOH (4 M) and the mixture left stirring for 48 h, the HyT was obtained directly in 87% yield and 60% overall yield from tyrosol **2**. A 50 mmol scale-up of the above synthetic procedure afforded reproducible overall yields. In Scheme 3 is reported the synthetic approach to the differently protected forms of HyT. Benzylation of the salicylaldehyde **4** to give **6** was easily accomplished in 90% of yield using standard reaction conditions ($BnBr/NaI/K_2CO_3$) and later was subjected to the BVO reaction.

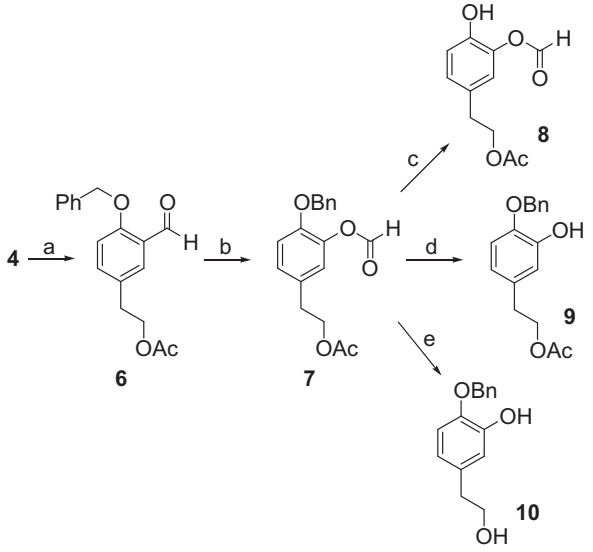
The best result was obtained according to the procedure developed by Syper,[14] by using of a catalytic amount (5 mol %) of diphenylselenide as activator of H_2O_2, to give the fully protected Hyt derivative **7** in a gratifying 84% yield. Notably the use of *m*-chloroperoxybenzoic acid under different reaction conditions did not give any results and the starting material was recovered almost quantitatively, whereas the use of 30% H_2O_2 alone gave a complex reaction mixture. The inherent orthogonality between esters/formates and benzyl ethers allows selective manipulation of the two OH-groups of the cathecol in **7**. To exemplify this orthogonality we deprotected the 4-hydroxyl group by cleaving the benzyl protective group using hydrogen. The chemoselective high yield



Scheme 1. Proposed synthesis of HyT and protected forms.



Scheme 2. Reagents and conditions for the synthesis of HyT: (a) AcOEt, TsOH, $T = 70$ °C, 94%; (b) $MgCl_2$, Et_3N, $(CH_2O)_n$, $T = 80$ °C, 72%; (c) (1) MCPBA, CH_2Cl_2, 24 h $T = 40$ °C; (2) NH_3 2 M in MeOH, 1 h rt 97%; (d) HCl 2 M, CH_2Cl_2,79%; (e) (1) MCPBA, CH_2Cl_2, 24 h $T = 40$ °C; (2) NH_3 4 M in MeOH, 48 h rt 87%.



Scheme 3. Reagents and conditions: (a) BnBr, NaI, K_2CO_3 DMF 60 °C, 90%; (b) H_2O_2 (30%), Ph_2Se_2, 84%; (c) H_2, 10% Pd/C (cat.), dry AcOEt, 98%; (d) NH_3 (2 M in MeOH) 5 equiv, 0.1 M CH_2Cl_2, 1 h 0 °C, 89%; (e) NH_3 2 M in MeOH, 96 h, 95%.

debenzylation reaction proved to be difficult and several reaction conditions were tested. Finally, hydrogenolysis reaction took place using hydrogen at atmospheric pressure in presence of 10% Pd/C in dry[15] and freshly distilled AcOEt to provide **8** in 98% of isolated yield. On the other hand, taking advantage from the above experiences, treatment of **7** with 5 equiv NH_3 (2 M, MeOH) in CH_2Cl_2 (0.2 M) at 0 °C gave after 1 h the diprotected HyT 3-hydroxyl group free derivative **9** in high yield (89%), whereas the 4-hydroxyl monoprotected HyT derivative **10** was obtained in 95% by direct treatment with NH_3 (2 M) in MeOH at room temperature for 96 h. The above reaction sequence performed on 30 mmol scale gave reproducible yields. Thus, in either four or five operations, one can covert tyrosol (**2**) into the selectively protected cathecol suitable for regioselective derivatization of hydroxytyrosol, an important natural biophenol.

In conclusion, in the present communication we have described a new and scalable approach to the preparation of HyT starting from the cheap and commercially available tyrosol, as well as the development of a practicable and simple way to obtain the different protected forms of HyT. The route features a highly effective and controlled oxidation of aromatic derivatives bearing alkyl substituents and expeditious protecting-groups manipulations. This new approach provides facile access to novel HyT derivatives, and should be useful in medicinal and food chemistry to better

explore the therapeutic role and potentialities of this intriguing class of compounds.

Acknowledgment

A.M. thanks the University of Seville (Spain) for a mobility grant.

References and notes

1. (a) Angerosa, F.; D'Alessandro, N.; Konstantinou, P.; Giacinto, I. *J. Agric. Food Chem.* **1995**, *43*, 1802–1807; (b) Montedoro, G.; Servili, N.; Baldioli, M.; Miniati, E. *J. Agric. Food Chem.* **1992**, *40*, 1571–1576.
2. (a) Dellagreca, M.; Previtera, L.; Temussi, F.; Zarrelli, A. *Phytochem. Anal.* **2004**, *15*, 184–188; (b) Allouche, N.; Fki, I.; Sayadi, S. *J. Agric. Food Chem.* **2004**, *52*, 267–273; (c) DellaGreca, M.; Fiorentino, A.; Monaco, P.; Previtera, L.; Temussi, F. *Nat. Prod. Lett.* **2000**, *14*, 429–434; (d) Capasso, R.; Evidente, A.; Avolio, S.; Solla, F. *J. Agric. Food Chem.* **1999**, *47*, 1745–1749; (e) Capasso, R.; Cristinzio, G.; Evidente, A.; Scognamiglio, F. *Phytochemistry* **1992**, *12*, 4125–4128.
3. (a) Nousis, L.; Doulias, P.; Aligiannis, N.; Bazios, D.; Agalias, A.; Galaris, D.; Mitakou, S. *Free Radical Res.* **2005**, *39*, 787–795; (b) Hashimoto, T.; Ibi, M.; Matsuno, K.; Nakashima, S.; Tanigawa, T.; Yoshikawa, T.; Yabe-Nishimura, C. *Free Radical Bio. Med.* **2004**, *36*, 555–564; (c) Carluccio, M. A.; Massaro, M.; Ancora, M. A.; Scoditti, E.; Storelli, C.; Distante, A. *Eur. Heart J.* **2006**, *27*, 455; (d) Salami, M.; Galli, C.; De Angelis, L.; Visioli, F. *Pharmacol. Res.* **1995**, *31*, 275–279; (e) Bisignano, G.; Tomaino, A.; Lo Cascio, R.; Crisafi, G.; Uccella, N.; Saija, A. *J. Pharm. Pharmacol.* **1999**, *51*, 971–974; (f) Furneri, P. M.; Piperno, A.; Sajia, A.; Bisignano, G. *Antimicrob. Agents Chemother.* **2004**, *48*, 4892–4894; (g) Bitler, C. M.; Viale, T. M.; Damaj, B.; Crea, R. *J. Nutr.* **2005**, *135*, 1475–1479; (h) Visioli, F.; Bellomo, G.; Montedoro, C.; Galli, C. *Atherosclerosis* **1995**, *117*, 25–32; (i) Visioli, F.; Bellomo, G.; Galli, C. *Atherosclerosis* **1995**, *117*, 25–32; (j) De la Puerta, R.; Ruiz-Gutiérrez, V.; Hoult, J. R. *Biochem. Pharmacol.* **1999**, *57*, 445–449; (k) Manna, C.; Galletti, P.; Cucciolla, V.; Moltedo, O.; Leone, A.; Zappia, V. *J. Nutr.* **1997**, *127*, 286–292; (l) Schröder, H.; de la Torre, R.; Estruch, R.; Corella, D.; Martínez-González, M. A.; Salas-Salvadó, J.; Ros, E.; Arós, F.; Flores, G.; Civit, E.; Farré, M.; Fiol, M.; Vila, J.; Fernandez-Crehuet, J.; Ruiz-Gutiérrez, V.; Lapetra, J.; Sáez, G.; Covas, M. I. *Am. J. Clin. Nutr.* **2009**, *90*, 1329–1335.
4. (a) See, for example: Tabera, G.J.J.; Ruiz, R.A. WO2005075614.; (b) Beverungen, C.; Rull, P.S. EP 1582512.; (c) Fernandez- Bolanõs, G.J.; Moreno, A.H. U.S. 2004102657.; (d) Crea, R. WO 2004005228.; (e) Crea, R. U.S. 2003108651.
5. (a) Bernini, R.; Mincione, E.; Crisante, F.; Barontini, M.; Fabrizi, G. *Tetrahedron Lett.* **2009**, *50*, 1307–1310; (b) Bernini, R.; Mincione, E.; Crisante, F.; Barontini, M.; Fabrizi, G.; Gentili, P. *Tetrahedron Lett.* **2007**, *48*, 7000–7003; (c) Bovicelli, P.; Antonioletti, R.; Mancini, S.; Causio, S.; Borioni, G.; Ammendola, S.; Barontini, M. *Synth. Comm.* **2007**, *37*, 4245–4252; (d) Ammendola, S.; Bovicelli, P. IT 2006RM0003 A1 20060404.; (e) Capasso, R.; Evidente, A.; Avolio, S.; Solla, F. *J. Agric. Food Chem.* **1999**, *47*, 1745–1748; (f) Bai, C.; Yan, X.; Takenaka, M.; Sekyya, S.; Nagata, T. *J. Agric. Food Chem.* **1998**, *46*, 3998–4001.
6. (a) Achkar, J.; Fernandez, A. WO 20088064835 A1 20080605.; (b) Achkar, J.; Fernandez, A.; Sonke, T.; Wubbolts, M.G. WO 20088064837 A2 20080605.; (c) Liebgott, P.-P.; Labat, M.; Casalot, L.; Amouric, A.; Lorquin, J. *FEMS Microbiol. Lett.* **2007**, *276*, 26–33; (d) Allouche, N.; Sayadi, S. *J. Agric. Food Chem.* **2005**, *53*, 6525–6530; (e) Allouche, N.; Damak, M.; Ellouz, R.; Sayadi, S. *Appl. Environ. Microbiol.* **2004**, *70*, 2105–2109.
7. (a) Fernandez-Bolanos, J.; Rodríguez, G.; Gómez, E.; Guillén, R.; Jimenez, A.; Heredia, A.; Rodriguez, R. *J. Agric. Food Chem.* **2004**, *52*, 5849–5855; (b) Briante, R.; Patumi, M.; Febbraio, F.; Nucci, R. *J. Biotechnol.* **2004**, *111*, 67–77.
8. (a) Gordon, M. H.; Paiva-Martins, F.; Almeida, M. *J. Agric. Food Chem.* **2001**, *49*, 2480–2485; (b) Appendino, G.; Minassi, A.; Daddario, N.; Bianchi, F.; Tron, G. C. *Org. Lett.* **2002**, *4*, 3839–3841; (c) Alcudia, F.; Cert, A.; Espartero, J.L.; Mateos, B.R.; Trujillo, M. **2004**, PCT 2004005237.; (d) Torregiani, E.; Seu, G.; Minassi, A.; Appendino, G. *Tetrahedron Lett.* **2005**, *46*, 2193–2196; (e) Trujillo, M.; Mateos, R.; Collantes deTeran, L.; Espartero, J. L.; Cert, R.; Jover, M.; Alcudia, F.; Bautista, J.; Cert, A.; Parrado, J. *J. Agric. Food Chem.* **2006**, *54*, 3779–3785; (f) Grasso, S.; Siracusa, L.; Spatafora, C.; Renis, M.; Tringali, C. *Bioorg. Chem.* **2007**, *35*, 137–152; (g) Torres de Pinedo, A.; Peñalver, P.; Pérez-Victoria, I.; Rondón, D.; Morales, J. C. *Food Chem.* **2007**, *105*, 657–665; (h) Mateos, R.; Trujillo, M.; Pereira-Caro, G.; Madrona, A.; Cert, A.; Espartero, J. L. *J. Agric. Food Chem.* **2008**, *56*, 10960–10966; (i) Tofani, D.; Balducci, V.; Gasperi, T.; Incerpi, S.; Gambacorta, A. *J. Agric. Food Chem.* **2010**, *58*, 5292–5299; (j) Bernini, R.; Mincione, E.; Barontini, M.; Crisante, F. J. *J. Agric. Food Chem.* **2008**, *56*, 8897–8904; (k) Capasso, R.; Sannino, F.; de Martino, A.; Manna, C. *J. Agric. Food Chem.* **2006**, *54*, 9063–9070.
9. (a) Procopio, A.; Costanzo, P.; Curini, M.; Nardi, M.; Oliverio, M.; Paonessa, R. *Synthesis* **2011**, 73–78; (b) Riggs-Saulthier, J., Deng, B-L.; Ren, Z.; Zhang, W.; Gu, X.; Duarte, F.J. WO 2008112286.; (c) Weitkamp, P.; Weber, N.; Vosmann, K. *J. Agric. Food Chem.* **2008**, *56*, 5083–5090; Shah, S.; Guiry, P. J. *Org. Biomol. Chem.* **2008**, *6*, 2168–2172; (d) Denis, A.; Gerusz, V.; Bonvin, Y. EP 1845087 A1 20071017.; Khymenets, O.; Joglar, J.; Clapes, P.; Parella, T.; Covas, M.-I.; de la Torre, R. *Adv. Synth. Catal.* **2006**, *348*, 2155–2162.
10. For a review of Baeyer–Villiger reaction, see: Krow, G. R. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1993; 43, pp 251–798.
11. (a) Olah, G.; Ohannasian, L.; Arvanaghi, M. *Chnn, K. Em. Rev.* **1987**, *87*, 671; (b) Skattebøl, L.; Hansen, T. V. *Org. Synth.* **2005**, *82*, 64; (c) Akselsen, Ø. W.; Skattebøl, L.; Hansen, T. V. *Tetrahedron Lett.* **2009**, *50*, 6339–6341.
12. Maruyama, K.; Kobayashi, F.; Osuka, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2672–2681.
13. **1**: To a solution of **4** (2.98 g, 15.5 mmol) in 100 ml of CH_2Cl_2 was added in small portions MCPBA (4.93 g, 28.6 mmol) and the mixture was stirred for 24 h at 40 °C. The solution was concentrated under reduced pressure, the residue dissolved in 60 ml of methanolic NH_3 (4 M) and stirred for 72 h at rt. The mixture was concentrated and quickly filtered through a short pad of SiO_2 using AcOEt/petroleum ether to give **1** (2.08 g, 87%) ^1H and ^{13}C NMR according to Lit.[5e]; **7**: To a 0.5 M solution of **6** (3 g, 10.6 mmol) in CH_2Cl_2 was added a catalytic amount of diphenylselenide (180 mg) followed by the addition of 2.7 ml of 30% H_2O_2. The reaction mixture was stirred at rt for 48 h followed by work-up according to Syper et al.[14] Flash chromatography (SiO_2, CH_2Cl_2) gave **7** (2.66 g, 84%) as an oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.28 (s,1H), 7.38 (m, 5H), 6.98–7.1 (m, 3H), 5.10 (s, 2H), 4.26 (t, 2H, J = 6.94 Hz), 2.89 (t, 2H, J = 6.94 Hz), 2.05 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.9, 159.1, 184.6, 139.0, 136.4, 131.1, 128.6, 128.1, 127.5, 127.3, 123.1, 114.2, 70.8, 64.6, 34.0, 20.9; **8**: To a solution of **7** (2.64 g, 8.86 mmol) in dry AcOEt (80 ml) was added 10% Pd/C (100 mg) and hydrogenated using 1 atm of H_2 (balloon) at room temperature. After 30 min the mixture was filtered through a pad of celite and washed with EtOH abs (3 × 5 ml). The filtrate was concentrated under reduced pressure to give **8** (1.83 g, 98%) as an oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.31 (s, 1H), 6.75–7.07 (m, 3H), 4.21–4.30 (m, 2H), 2.84–2.92 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.42, 159.9, 146.9, 145.5, 130.7, 127.8, 122.4, 121.2, 64.8, 34.3, 21.0; **9**: To a cooled (T = 0 °C) 0.1 M solution of **7** (1.65 g, 5.25 mmol) in CH_2Cl_2 were added 12.5 ml of NH_3 (2 M MeOH) and the reaction was stirred at the same temperature for 1 h. The reaction mixture was concentrated, dissolved in CH_2Cl_2 (50 ml) and washed with sat. $NaHCO_3$, H_2O and dried over Na_2SO_4. Flash chromatography (SiO_2, CH_2Cl_2/aceton 98:2) gave **9** (g, 89%) as an oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.42 (m,5H), 6.66–6.89 (m, 3H), 5.10 (s, 2H), 4.25 (t, 2H, J = 7.06 Hz), 2.85 (t, 2H, J = 7.06 Hz), 2.05 (s, 3H), 1.27 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.4, 146.1, 144.8, 136.7, 131.8, 129.1, 128.7, 128.1, 120.6, 115.6, 112.5, 71.5, 65.4, 34.8, 21.3; **10**: A solution of **7** (2.8 g, 9.4 mmol) in 20 ml NH_3 (2 M, MeOH) was stirred for 96 h and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 ml), washed with 0.1 M of citric acid (10 ml), 0.1 M $NaHCO_3$ (10 ml) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give pure **10** (2.18 g, 95%) as judged by NMR. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.44–7.39 (m, 5H), 6.90–6.85 (m, 2H), 6.72–6.67 (m, 1H), 5.10 (s, 2H), 3.83 (t, 2H, J = 6.0 Hz), 2.79 (t, 2H, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.0, 144.5, 136.4, 132.1, 128.7, 128.3, 127.7, 120.4, 115.3, 112.4, 71.3, 63.6, 38.5.
14. Syper, L. *Synthesis* **1989**, 167.
15. Dry AcOEt was obtained according to: Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1997.