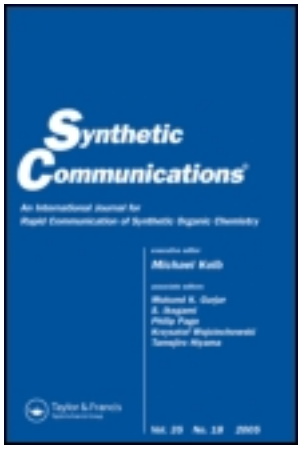

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 24 Aug 2011. Version of record first published: 11 Nov 2011

To cite this article: Zhao-Li Zhang, Jinglei Chen, Qiongming Xu, Cui Rao & Chunhua Qiao (2012): Efficient Synthesis of Hydroxytyrosol from 3,4-Dihydroxybenzaldehyde, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:6, 794-798

To link to this article: http://dx.doi.org/10.1080/00397911.2010.531369

Synthetic Communications®, 42: 794–798, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.531369

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EFFICIENT SYNTHESIS OF HYDROXYTYROSOL FROM 3,4-DIHYDROXYBENZALDEHYDE

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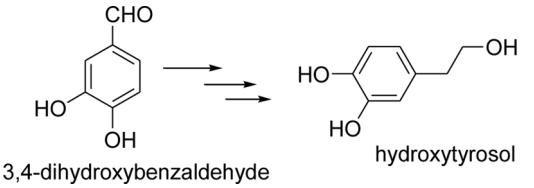
GRAPHICAL ABSTRACT



Abstract *Hydroxytyrosol is a naturally occurred orthodiphenolic component of olive oil. A variety of biological functions for this molecule have been reported. We report herein an efficient and practical method for the chemical synthesis of hydroxytyrosol from 2,3-dihydroxybenzaldehyde.*

Keywords Antioxidant; hydroxytyrosol; synthesis

INTRODUCTION

Hydroxytyrosol has been reported to exhibit a variety of biological activities, including protection against oxidative DNA damage and low-density lipoprotein (LDL) oxidation,[1] scavenging of free radicals,[2] antibacterial activity,[3] and prevention of platelet aggregation.[4] Most of these functions are related to its antioxidant capability. Hydroxytyrosol displayed 10 times more radical absorbance capacity than green tea and two times more than CoQ10.[5]

Like other catechols, the mechanism of antioxidant activity of hydroxytyrosol was attributed to the formation of the initial *o*-hydroxyquinone intermediate,[6] which could be further oxidized to quinone or attacked by another molecular of hydroxytyrosol to form a dimer.

Despite the reported biological importance of hydroxytyrosol, it is commercially available only for research purposes, and the approximate cost is $1000 per gram,[7] which is very expensive for a simple small molecule with a molecular weight

Received September 5, 2010.

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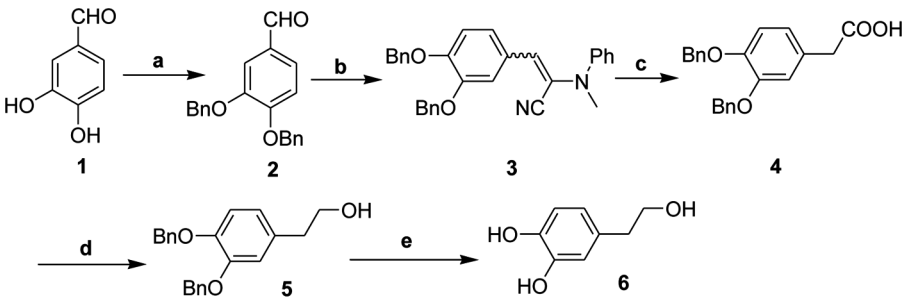
of only 154.16. Therefore, chemical synthesis of hydroxytyrosol at a competitive price should be investigated extensively.

In 1949, Schopf *et al.* reported the first chemical synthesis of hydroxytyrosol. This synthesis employed 3,4-dihydroxyphenyl acetic acid as the starting material, which was reduced with $LiBH_4$ to afford hydroxytyrosol in a one-step reaction.[8] Later on, $LiAlH_4$ in tetrahydrofuran (THF) was employed as reductant, and the total reaction yield was improved from 40% to 82.8%.[9] However, the high cost of the starting material (i.e., 3,4-dihydroxyphenyl acetic acid,) limited the practical application of this method. Recently, Bovicelli *et al.* achieved the chemical synthesis of hydroxytyrosol from tyrosol in seven steps,[10] involving monobromination, substitution, diacetylation, and deprotection, to give an overall yield of 37%. However, the practicality of this synthetic route is compromised by the required selective monobromination, demethylation using expensive nasty, BBr_3, low reaction temperature, and final deprotection using enzymes.

We report herein a new, efficient, and practical method for the synthesis of hydroxytyrosol from commercially available 2,3-dihydroxybenzaldehyde (**1**), which as an important and widely used intermediate in food and pharmaceutical industries that is inexpensive and readily commercially available. As shown in Scheme 1, the two free hydroxyl groups of **1** were first protected by the benzyl group. Subsequently, one carbon homologation of the protected aldehyde **2** was achieved by an established method employing α-(*N*-methylanilino)acetonitrile as a one-carbon building block,[11] which was the key step for this synthesis. Specific ally, the reaction between **2** and α-(*N*-methylanilino)acetonitrile afforded α-cyano enamines **3,** which was readily converted to the carboxylic acid under acidic conditions. The resulting carboxylic acid **4** was then readily transformed to the corresponding alcohol **5** upon sodium boron hydride treatment under acidic conditions. Hydroxytyrosol **6** was finally obtained by hydrogenolysis under Pd-C/H_2 conditions.

In summary, a new synthetic method for hydroxytyrosol is described, which has the advantages of mild reaction conditions, high efficiency, and low cost. The key step of this synthesis is one-carbon homologation of **2** to afford carboxylic acid **4** employing α-(*N*-methylanilino) acetonitrile as the one-carbon building block.



a: BnCl, K_2CO_3; **b**: KH, CH_3PhNCH_2CN; **c**: 10% HCl reflux; **d**: $NaBH_4$, CH_3SO_2OH; **e**: H_2/Pd

Scheme 1. Synthesis of hydroxytyrosol **6** from 3,4-dihydroxybenzaldehyde.

EXPERIMENTAL

3,4-(*O*-Dibenzylhydroxy)benzaldehyde (2)

Benzyl bromide (0.24 mL, 2.0 mmol) was added to a solution of 3,4-dihydroxybenzaldehyde (138.0 mg, 1.0 mmol) and K_2CO_3 (288.0 mg, 2.1 mmol) in 10.0 mL acetone. The reaction mixture was refluxed for 20 h. Acetone was removed, and the remaining residue was diluted by 25 mL of ethyl ether. The ether was washed with water (10 mL × 2), dried (Na_2SO_4), and concentrated under reduced pressure to afford the product as a white solid (292.0 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.49–7.37 (m, 12H), 7.02 (d, 1H, $J = 8.0$ Hz), 5.26 (s, 2H), 5.22 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 154.1, 148.9, 136.4, 136.1, 130.1, 128.6, 128.5, 128.0, 127.9, 127.2, 126.9, 126.7, 112.8, 111.9, 70.8, 70.6.

α-(*N*-Methylanilino)acetonitrile (7)

This intermediate was prepared according to reported method[11] with slightly modification. Briefly, K_2CO_3 (1380 mg, 10.0 mmol, 2.0 equiv.) was added to a solution of N-methylaniline (0.5 mL, 5.0 mmol, 1.0 equiv.) and 2-chloroacetonitrile (0.35 mL, 5.0 mmol, 1.0 equiv.) in 25 mL toluene. The reaction mixture was refluxed overnight, washed with H_2O (10 mL × 2), dried (Na_2SO_4), and concentrated under reduced pressure with flash chromatography (petroleum ether–ethyl ether = 10:1) afford the product as a brown oil (510.0 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 6.92 (t, $J = 8.0$ Hz, 1H), 6.87 (d, $J = 8.0$ Hz, 2H), 4.15 (s, 2H), 2.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 128.9, 119.4, 115.4, 114.1, 41.4, 38.5.

α-(*N*-Methylanilino)-3,4-dibenzylhydroxycinnamonitrile (3)

KH (80.0 mg, 1.2 equiv.) was added under N_2 atmosphere to a solution of α-(*N*-methylanilino)acetonitrile (104.0 mg, 0.71 mmol, 1.2 equiv.) and 3,4-(*O*-dibenzylhydroxy)benzaldehyde (188.7 mg, 0.59 mmol, 1.0 equiv.) in 10.0 mL tetrahydrofuran (THF). The reaction mixture was stirred for 2 h at room temperature, and diluted with 2.0 mL water. The reaction mixture was partitioned with ethyl acetate and water (20:10); organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (petroleum ether–ethyl acetate 20:1) afforded the product (*E*- and *Z*-mixture) as a light yellow oil (240 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, $J = 8.0$ Hz, 3H), 7.37 (t, $J = 4.0$ Hz, 3H), 7.32 (d, $J = 8.0$ Hz, 3H), 7.23 (s, 2H), 7.04–6.93 (m, 3H), 6.84 (t, $J = 8.0$ Hz, 3H), 6.76 (s, 1H), 5.19 (s, 2H), 4.95 (s, 2H), 3.24 (s, C=CH of *Z*, 1H), 3.02 (s, C=CH of *E*, 1H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.0, 150.0, 149.1, 148.7, 146.8, 145.5, 138.8, 137.2, 137.2, 137.0, 136.8, 131.4, 129.7, 129.6, 128.9, 128.8, 128.8, 128.8, 128.3, 128.2, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 126.5, 126.1, 125.3, 122.9, 122.7, 120.7, 119.9, 117.7, 117.2, 116.7, 115.9, 115.1, 115.1, 114.7, 113.9, 113.8, 71.4, 71.2, 71.0, 70.9, 40.4, 37.7.

3,4-(Dibenzylhydroxy)phenyl Acetic Acid (4)

To a solution of **3** (617.0 mg, 1.47 mmol) in 12.0 mL THF was added 10% HCl (12.0 mL). The reaction mixture was refluxed overnight and concentrated. The

remaining residue was partitioned with ethyl ether and water (30:15 mL), and organic phase was washed with 10% Na_2CO_3 (2 × 10 mL), dried (Na_2SO_4), and concentrated to afford the product (408.0 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, $J = 6.0$ Hz, 4H), 7.35 (t, $J = 6.0$ Hz, 4H), 7.30 (d, $J = 6.0$ Hz, 2H), 6.90 (d, $J = 8.0$ Hz, 1H), 6.88 (s, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 5.14 (d, $J = 4.0$ Hz, 4H), 3.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 149.2, 148.5, 137.5, 137.3, 128.7, 128.7, 128.1, 128.0, 127.6, 127.5, 126.6, 122.6, 116.4, 115.2, 71.5, 71.5, 40.8.

3,4-Dibenzylhydroxyphenethyl Alcohol (5)

$NaBH_4$ (131.0 mg, 3.5 mmol) and methanesulfonic acid (0.17 mL, 2.6 mmol) were added to a solution of **4** (241.0 mg, 0.75 mmol) in 6.0 mL DMSO. The reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of 10% NaOH (6.0 mL), extracted with diethyl ether (3 × 15 mL). The organic extraction was combined, dried (Na_2SO_4), and concentrated to afford the product as a white solid (212.0 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 4H), 7.33 (t, $J = 8.0$ Hz, 4H), 7.29–7.20 (m, 2H), 6.85 (d, $J = 8.0$ Hz, 1H), 6.79 (s, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 5.11 (d, $J = 4.0$ Hz, 4H), 3.71 (t, $J = 6.4$ Hz, 2H), 2.70 (t, $J = 6.8$ Hz, 2H), 1.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 147.9, 137.6, 137.5, 132.2, 128.7(2C), 128.1, 128.0, 127.7, 127.6, 122.2, 116.4, 115.6, 71.7, 71.6, 63.8, 38.9.

Hydroxytyrosol (6)

Pd-C (3.0 mg) was added to a solution of **5** (85.0 mg, 0.28 mmol) in 2.0 mL THF, and the reaction was placed under a H_2 atmosphere. After 3 h, the reaction mixture was filtered through a plug of celite, which was further washed with THF (5.0 mL), and the combined filtrates were concentrated under reduced pressure to afford the product 3,4-dihydroxytyrosol as a colorless oil (42.0 mg, 98%). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.79 (s, 1H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.70 (s, 1H), 6.54 (d, $J = 8.0$ Hz, 1H), 3.86 (s, 1H), 3.68 (t, $J = 8.0$ Hz, 2H), 3.39 (s, 1H), 2.66 (t, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 145.4, 143.9, 131.5, 120.8, 116.6, 115.7, 64.1, 39.4. HRMS calcd. for [M − H]: 153.0557, found [ESI$^-$]: 153.0554, error 1.96 ppm.

ACKNOWLEDGMENTS

The financial support from Soochow University and the National Science and Technology Major Project on Key Drug Creation and Manufacturing Program (2009ZX09103-129) is gratefully acknowledged. We thank Professor Zhongwu Guo at Wayne State University and Professor Zhengqiang Wang at University of Minnisota for critical revisions.

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