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Convenient syntheses of biogenic aldehydes, 3,4-dihydroxyphenylacetaldehyde and 3,4-dihydroxyphenylglycolaldehyde

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Abstract

The title compounds were prepared from a common precursor, a bis-THP-protected dihydroxyphenylacetic acid methyl ester. Key steps are the introduction of the α-hydroxyl group by Davis oxaziridine reagent and formation of the aldehydes by DIBALH ester reduction. Published by Elsevier Science (USA).

Keywords: Dopal; Dopegal; Davis reagent; Amine metabolites; Neurotoxicity

1. Introduction

As the primary mechanism of deactivation, monoamine neurotransmitters are metabolized to the corresponding aldehydes by monoamine oxidase (MAO)-catalyzed deamination within the nerve terminal. 3,4-Dihydroxyphenylacetaldehyde (dopal) is produced by the action of MAO on dopamine and 2-(3,4-dihydroxyphenyl)-2-hydroxyacetaldehyde (dopegal) is formed by MAO deamination of norepinephrine. The oxidative deactivation of the amines is key to maintenance of proper concentrations of these neurotransmitters. The further degradation of the aldehydes, either through

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further oxidation to acid metabolites or reduction to the corresponding alcohols is an important subsequent process. There is substantial evidence that high concentration of reactive aldehydic metabolites may be detrimental, since these can undergo non-enzymatic reactions with a number of compounds normally present in the CNS. Examples include Pictet–Spengler reactions with biogenic amines to form tetrahydroisoquinolines or Schiff base formation with endogenous amines such as lysine residues [1]. Recent reports provide evidence for the selective toxicity of both dopal [2] and dopegal [3]. As part of our research to study these reactions and to examine the appearance of the biogenic aldehydes under pathological conditions, we had need for authentic samples of dopal and dopegal, synthetic routes to which have been published [4,5]. We report herein alternative convenient procedures for the preparation of these compounds. The convenience of the syntheses together with the importance of these compounds prompt us to publish our alternative procedures.

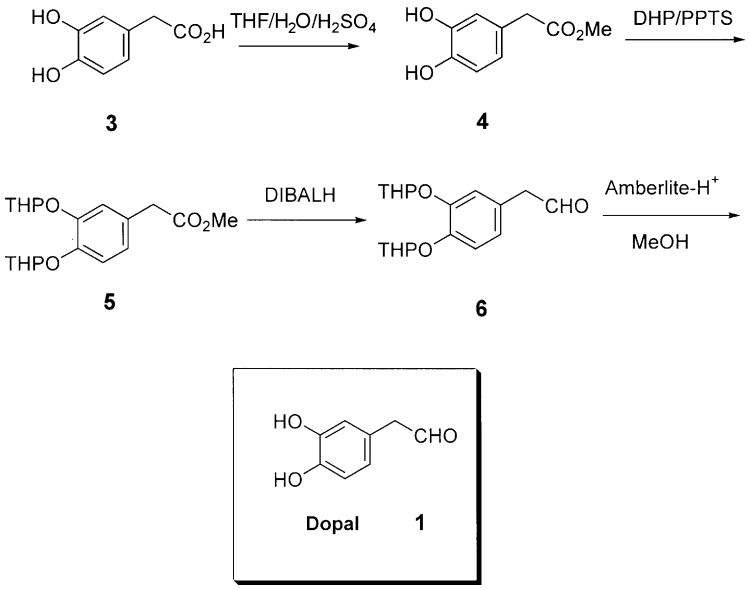
2. Results and discussion

A recent report describes the preparation of dopal from piperanal using a Darzens glycidic ester synthesis, as well as its complete characterization [4]. We have chosen a different approach that involves reduction of carboxylic ester to carbanal in a substrate possessing the requisite carbon framework, thus obviating the carbon–carbon bond-forming step. DIBALH reduction of readily available bis-THP-protected 3,4-dihydroxyphenylacetic acid methyl ester (**5**) proceeded in high yield to give bis-THP-protected dopal. The THP groups were removed under mild condition (stirring with Amberlite–H^+) to give dopal (Scheme 1). The physical and spectral data agreed with the literature values [4].

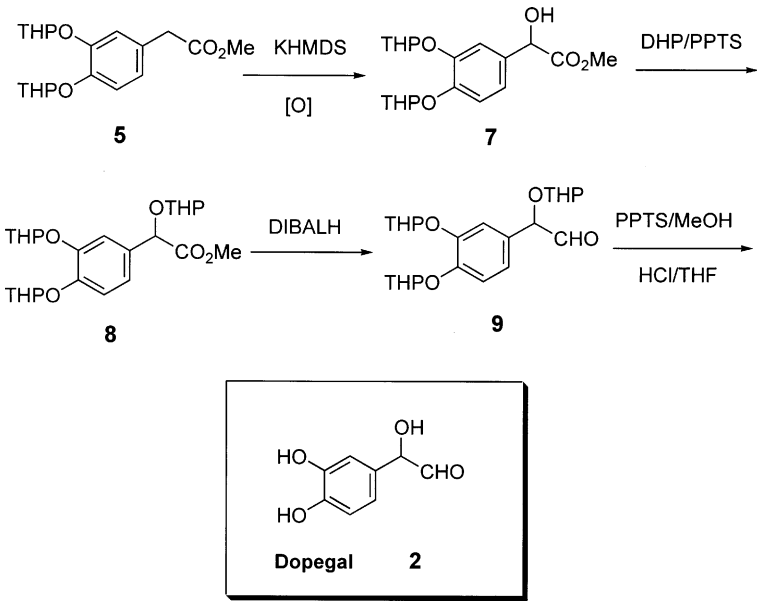
The simplicity of this approach prompted us to examine the intermediate ester **5** as a source of dopegal. In the previously reported synthesis [5], the lithium salt of dithiane was added to bis-3,4-tetrahydropyranoxybenzaldehyde in order to introduce an aldehyde equivalent. Subsequent hydrolysis of the dithiane using mercuric salts elaborated the aldehyde. Our approach again adjusts functionality of the pre-existing carbon framework. The benzylic OH group was introduced by oxygenation of the ester enolate using Davis oxaziridine reagent. Additional OH protection by THP and DIBALH reduction gave the tris-THP protected intermediate. Mild acid treatment of the tris-THP-protected product afforded dopegal. Physical and spectral data agreed with literature values [5] (Scheme 2).

3. Conclusion

We describe an efficient and convenient synthesis of the biologically important aldehydes, dopal, and dopegal. The chemical procedures are simple, and the yields are satisfactory. In addition to the simplicity of this procedure, we avoid the use of environmentally unfriendly mercuric salts that were required in a previous synthesis of dopegal.



Scheme 1.



Scheme 2.

4. Experimental

All the reagents were from Aldrich and used without further purification. NMR spectra were run in $CDCl_3$ or DMSO-d_6 on a Varian Gemini 300 MHz spectrometer. Mass spectra were determined in Jeol SX-102 instrument. Infra red spectra were recorded in BioRad Win FTIR instrument.

*4.1. 3,4-Dihydroxyphenylacetic acid methyl ester (**4**)*

A solution of 2.85 g (16.9 mmol) of 3,4-dihydroxyphenylacetic acid **3** in 100 mL of MeOH containing 3 mL of con. H_2SO_4 was refluxed overnight. The MeOH was evaporated and the residue was dissolved in 100 mL of EtOAc. The organic layer was washed with dilute $NaHCO_3$, water, brine, and then dried (Na_2SO_4). The solvent was evaporated to give 2.99 g of the ester **4** (97%) that was used in the next step without further purification.

IR (Film, cm^{-1}) : 3369, 1715, 1608, 1521, 1463, 1113, 1013, 964, 797, 720.

^1H NMR (300 MHz, $CDCl_3$) δ: 6.77–6.49 (m, 3H, ArH), 3.71 (s, 3H, OCH_3), 3.52 (s, 2H, $ArCH_2$).

^{13}C NMR δ: 174.23, 143.97, 143.25, 126.05, 121.81, 116.56, 115.68, 52.59, 40.51.

MS (FAB): $C_9H_{10}O_4$, 182.11 (M^+).

*4.2. 3,4-Bis-(tetrahydropyranyloxy)phenylacetic acid methyl ester (**5**)*

A solution of 3.40 g (18.7 mmol) of **4** and 120 mg (0.48 mmol) of pyridinium *p*-tosylate in 70 mL of CH_2Cl_2 was treated dropwise with 16 mL (175.0 mmol) of dihydropyran in 20 mL of CH_2Cl_2. The mixture became homogeneous after about 1 h and the reaction was essentially complete. When the TLC indicated the absence of starting material the reaction mixture was washed twice with water, dried (Na_2SO_4), and evaporated to give 6.5 g of **5** (98%) as a mixture of diastereoisomers, used in the next step without further purification.

IR (Film, cm^{-1}): 3063, 1738, 1588, 1508, 1463, 1434, 1388, 1356, 1260, 1202, 1108, 730, 720.

^1H NMR (300 MHz, $CDCl_3$) δ: 7.08–7.05 (m, 2H, ArH), 6.86–6.84 (m, 1H, ArH), 5.43–5.39 (m, 2H, THP), 4.01–3.97 (m, 2H, THP), 3.66 (s, 3H, OMe), 3.61–3.57 (m, 2H, THP), 3.53 (s, 2H, CH_2), 2.01–1.85 (m, 6H, THP), 1.70–1.62 (m, 6H, THP).

^{13}C NMR δ: 172.17, 143.34, 140.57, 128.35, 128.21, 123.48, 123.33, 119.49, 118.70, 118.45, 97.73, 97.37, 97.32, 61.94, 61.78, 52.00, 40.68, 30.44, 30.39, 25.37, 18.72, 18.69, 18.61, 18.57.

MS (FAB): $C_{19}H_{26}O_6$, 351.2 (MH^+).

*4.3. 3,4-Bis-tetrahydropyranyloxyphenylacetaldehyde (**6**)*

A solution of 700 mg (2.0 mmol) of **5** in 10 mL of toluene was stirred and cooled to −78 °C (dry nitrogen atmosphere). To this was added dropwise (syringe) 3.5 mL of a

1.5 M solution of DIBALH in toluene. After 30 min the reaction was quenched with aqueous ammonium chloride. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and then evaporated. The residue was chromatographed (20% EtOAc/PE) to give 330 mg of aldehyde **6** (52%) as a mixture of diasteroisomers.

IR (Film, cm^{-1}): 3060, 1726, 1588, 1508, 1464, 1356, 1260, 1109, 963, 816.

^1H NMR (300 MHz, $CDCl_3$) δ: 9.70 (s, 1H, CHO), 7.14–6.99 (m, 2H, ArH), 6.85–6.78 (m, 1H, ArH), 5.43–5.41 (m, 2H, THP), 4.03–3.96 (m, 2H, THP), 3.67–3.54 (m, 4H, $ArCH_2$ & THP), 2.05–1.87 (m, 6H, THP), 1.81–1.63 (m, 6H, THP).

^{13}C NMR δ: 199.83, 148.03, 146.81, 126.04, 126.02, 123.70, 120.15, 119.71, 100.41, 98.76, 98.37,97.78, 97.38, 96.52, 76.77, 76.72, 61.84, 52.06, 50.10, 30.42, 25.37, 24.93, 18.57.

*4.4. 3,4-Dihydroxyphenylacetaldehyde Dopal, (**1**)*

A 100 mg (0.31 mmol) of bis-THP aldehyde **6** was treated with 0.5 mL of water, 0.5 mL of THF, and 60 mg strongly acidic amberlite resin. After stirring for 25 min an additional 0.5 mL of THF was added (homogeneous). The reaction was nearly complete after 4 h (TLC). It was filtered and the solution was concentrated to dryness. The product was purified by silica gel column chromatography (5% MeOH/$CHCl_3$) to give 23 mg (50%) of 3,4-dihydroxyphenylacetaldehyde (**1**). NMR and MS were in good agreement with the literature data [4].

4.5. 3,4-Bis-(tetrahydro-pyran-2-yloxy)-phenyl-2-hydroxy-acetic acid methyl ester (7)

A 250 mL flask containing 100 mL of anhydrous of THF and 30 mL of KHMDS (0.5 M in toluene) was kept in a −78 °C bath and a solution of 3.5 g (10.0 mmol) of compound **5** in 20 mL of anhydrous THF was slowly added. The solution was stirred for an additional 30 min at the same temperature and a solution of 3.9 g (15.0 mmol) of 2-sulfonyloxaziridine [6] in 10 mL of anhydrous THF was added. After stirring the mixture at −78 °C for 20 min, the reaction was quenched by addition of 15 mL of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic fractions were combined and washed with water (2 × 20 mL) and brine (2 × 20 mL). The solution was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by chromatography on silica gel (50% EtOAc/PE) to afford 3.12 g of compound **7** (85%) as a mixture of diastereoisomers.

IR (Film, cm^{-1}): 3271, 3070, 1739, 1507, 1463, 1331, 1260, 1203, 1164, 1106, 1072, 1024, 963, 756, 721.

^1H NMR (300 MHz, $CDCl_3$) δ: 7.60–7.49 (m, 1H, ArH), 7.21–6.97 (m, 2H, ArH), 5.45–5.41 (m, 2H, THP), 5.14–5.09 (m, 1H, ArC**H**OH), 4.02–3.98 (m, 2H, THP), 3.74 (s, 3H, OCH_3), 3.62–3.57 (m, 2H, THP), 3.46 (s, 1H, OH), 2.07–1.81 (m, 6H, THP), 1.75–1.64 (m, 6H, THP).

^{13}C NMR δ: 172.89, 146.76, 143.39, 131.25, 128.22, 127.65, 126.85, 125.43, 120.40, 117.70, 96.88, 96.67, 72.10, 61.24, 59.64, 51.54, 29.72, 24.65, 18.06.

MS (FAB): $C_{19}H_{26}O_7$, 367.20 (MH^+).

4.6. 3,4-Bis-(tetrahydro-pyran-2-yloxy)-phenyl-(tetrahydro-pyran-2-yloxy)-acetic acid methyl ester (**8**)

To a solution of 1.87 g (5.0 mmol) of compound **7** in 20 mL of anhydrous dichloromethane was added 630 mg (7.5 mmol) of 3,4-dihydropyran and 125 mg (0.5 mmol) of pyridinium *p*-toluene sulfonate. The mixture was stirred at room temperature overnight after which time TLC indicated that the reaction was essentially completed. The reaction was quenched by addition of 10 mL of 30% aqueous $NaHCO_3$ and the organic layer was washed with brine and dried (Na_2SO_4). After removal of the solvent and purification of the residue with chromatography on silica gel (33% EtOAc/PE) there was obtained 2.05 g of compound **8** (91%) as a mixture of diastereoisomers.

IR (Film, cm^{-1}): 3063, 1754, 1599, 1507, 1463, 1434, 1387, 1258, 1182, 1075, 967, 872, 755, 720.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27–7.04 (m, 3H, ArH), 5.46–5.42 (m, 2H, ArOT**H**P), 5.24 (s, 1H, ArC**H),** 4.86–4.84 (m, 1H, ArCHOT**H**P), 4.05–3.91 (m, 3H, THP), 3.70 (s, 3H, OCH_3), 3.62–3.46 (m, 3H, THP), 2.04–1.49 (m, 18H, THP).

^{13}C NMR δ: 172.04, 118.29, 118.00, 100.44, 97.66, 96.52, 65.02, 62.55, 61.90, 60.07, 52.28, 38.37, 30.47, 30.28, 25.44, 18.65.

MS (FAB): $C_{24}H_{34}O_8$, 451.28 (MH^+).

4.7. 3,4-Bis-(tetrahydro-pyran-2-yloxy)-phenyl-(tetrahydro-pyran-2-yloxy)-acetaldehyde (**9**)

To a solution of 900 mg (2.0 mmol) of compound **8** in 15 mL of anhydrous toluene at −78 °C was slowly added 2.2 mL of 1 M DIBALH in CH_2Cl_2. The mixture was stirred for 2 h at the same temperature. Then 3.0 mL of cooled CH_3OH was added at −78 °C to quench the reaction. The mixture was stirred for an additional 30 min and 100 mL of CH_2Cl_2 was added. The mixture was washed with 30 mL of water and the organic layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic fractions were washed with brine and dried (Na_2SO_4). Removal of the solvent and purification of the residue with chromatography on silica gel (20% EtOAc/PE) gave 780 mg of compound **9** (93%) as a mixture of diastereomers.

IR (Film, cm^{-1}): 3070, 1726, 1698, 1588, 1464, 1434, 1356, 1266, 1118, 1071, 908, 810, 725.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.56–9.54 (m, 1H, CHO), 7.26–6.85 (m, 3H, ArH), 5.42–5.41 (m, 2H, ArOT**H**P), 4.95 (s, 1H, ArCH), 4.86 (m, 1H, ArCHOT**H**P), 4.06–3.80 (m, 3H, THP), 3.70–3.30 (m, 6H, THP), 2.04–1.51 (m, 15H, THP).

^{13}C NMR δ: 199.04, 148.01, 122.25, 121.95, 118.23, 116.52, 115.00, 100.01, 98.05, 97.81, 97.70, 97.26, 83.18, 81.49, 64.10, 63.80, 63.07, 62.40, 62.28, 62.14,

61.94, 32.11, 30.91, 30.81, 30.49, 30.29, 25.62, 25.44, 20.42, 19.98, 19.69, 18.96, 18.90.

MS (FAB): $C_{23}H_{32}O_7$, 421.40 (MH^+).

4.8. 3,4-Dihydroxyphenylglycolaldehyde (Dopegal, **2**)

To a solution of 210 mg (0.5 mmol) of compound **9** in 10 mL of methyl alcohol was added 10 mg (0.05 mmol) of pyrdinium *p*-tosylate. The mixture was stirred at room temperature for 4 h at which time TLC indicated that the starting material had almost disappeared completely. Ethyl acetate (40 mL) was added and the mixture was washed with water (2×10 mL) and brine (2×10 mL). Removal of the solvent gave brown oil. This was dissolved in 10 mL of THF and 5 mL of H_2O. To this was added 0.1 mL of 3 M HCl and the solution was stirred at room temperature for 3 h. Ethyl acetate (20 mL) was added and the resulting mixture was washed with water (2×5 mL) and brine (2×10 mL). The solution was dried (Na_2SO_4), the solvent was removed, and the residue was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) to afford 42 mg of dopegal (**2**) (50%) as a white solid. The ^1H NMR and MS were in complete agreement with the data reported in literature [5].

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References

[1] For a recent review of these issues, see G. Eisenhofer, I. Lamensdorf, K.L. Kirk, M. Kawamura, S. Sato, in: C.R. Creveling (Ed.), Role of Catechol Quinone Species in Cellular Toxicity, F.P. Graham Publishing, Johnson City, TN, 1999, pp. 103–145.
[2] B.S. Kristal, A.D. Conway, A.M. Brown, J.C. Jain, P.A. Ulluci, S.W. Li, W.J. Burke, Free Rad. Biol. Med. 30 (2001) 924–931.
[3] W.J. Burke, S.W. Li, D.S. Zahm, H. Macarthur, Lacy, L.L. Kolo, T.C. Westfall, M. Anwar, S.B. Glickstein, D.A. Rggiero, Brain Res. 891 (2001) 218–227.
[4] W.L. Shu, T.S. Vincent, J.B. William, Bioorg. Chem. 26 (1998) 45–50.
[5] W.L. Shu, H.E. William, J.B. William, Bioorg. Chem. 22 (1994) 337–342.
[6] L.C. Vishwakarma, O.D. Stringer, F.A. Davis, in: C.H. Heathcock (Ed.), Organic Syntheses, vol. 66, Wiley, NY, 1988, pp. 203–205.