Enantioselective synthesis and absolute configuration of the natural *threo*-3-chloro-1-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol

Qian Wang, Kan Kan He, Yun Zhong Li, Da Wei Li, Ying Li and Zi Jie Hou*

Department of Chemistry, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R. China

An efficient method has been developed for the first asymmetric total synthesis of the natural phenylpropanoids, threo-3-chloro-1-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol in eight steps with 36% overall yield. The absolute configuration of the natural product was established using the Sharpless asymmetric dihydroxylation.

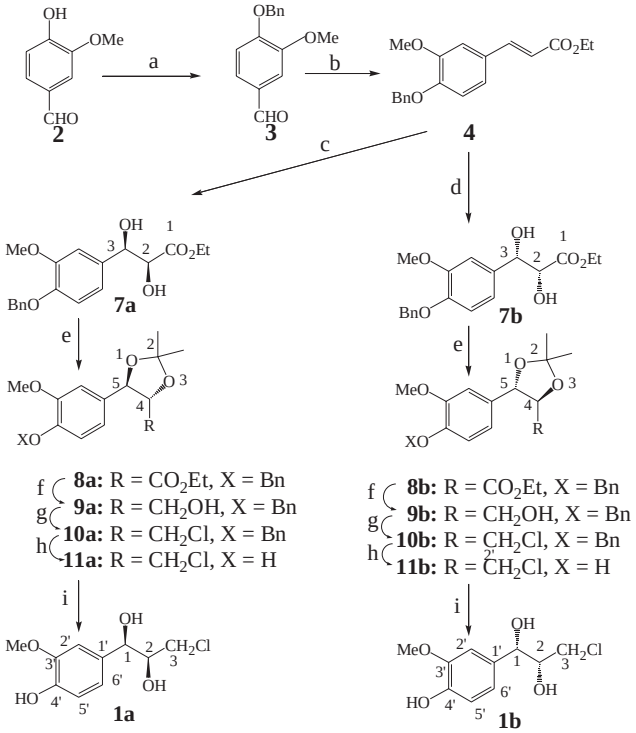
Keywords: phenylpropanoid, synthesis, absolute configuration

The synthesis of phenylpropanoids has recently attracted attention because of biological activity and their potential as important drugs.[1,2] *Threo*-3-chloro-1-(4-hydroxyl-3-methoxyphenyl)propane-1,2-diol **1** is a new phenylpropanoid which was isolated from the berries of *Pimenta dioica* in 1999. Biological tests of compound **1** showed antioxidant activity.[3] Although the relative configuration of this natural product was established using spectroscopic methods,[3] the absolute configuration has not been determined. In addition, no synthetic studies have been reported. Here, we report the first asymmetric total synthesis of the natural product **1** and the determination of its absolute configuration.

The synthesis is shown in Scheme 1. Compound **3**, which was easily obtained from the protection of vanillin **2**, was subjected to a Wittig reaction employing Ph_3P=CHCOOEt in ethylene glycol dimethyl ether to yield **4**.[4] Asymmetric dihydroxylation of **4** with AD-mix-β (or AD-mix-α) afforded the corresponding enantiomeric diol **7a** (or **7b**)[5] with 92 %e.e. which were identified by comparison with the literature.[6,7] Compound **7a** (or **7b**) was protected with 2,2-dime-thoxy-propane in CH_2Cl_2 to give **8a** (or **8b**).[8] Reduction of the ester **8a** (or **8b**) using $LiAlH_4$ and subsequent chlorination using Ph_3P in CCl_4/CH_2Cl_2 (4:1) furnished **10a** (or **10b**).[9] Removal of the benzyl group followed by treatment of the resulting phenol **11a** (or **11b**) with 1N HCl readily afforded the expected compound **1a** (or **1b**).[10]

The physical properties of **1b** ($[\alpha]_D^{20}$ = –3 (*c* 2.8, EtOH)) completely agree with those described for the natural product **1**[3] ($[\alpha]_D^{25}$ = –2 (*c* 0.5, EtOH)), establishing the absolute configuration of the natural *threo*-3-chloro-l- (4-hydroxy-3-methoxyphenyl)propane-1,2-diol (**1**) as *1S, 2R*.

In summary, we have developed a very efficient method for the asymmetric synthesis of the phenylpropanoid **1** in eight steps with a satisfactory 36% overall yield, and the absolute configuration of the natural product **1** has been shown to be *1S, 2R*.



Scheme 1 *Reagents and conditions*: (a) K_2CO_3, $C_6H_5CH_2Br$, 80°C, 2h, 99%; (b) $Ph_3PCHCOOEt$, $CH_3OCH_2CH_2OCH_3$, reflux, 10h, 52%; (c) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), r.t. 24h, 85%, 92% e.e.; (d) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), r.t. 24h, 85%, 92% e.e.; (e) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, r.t. 15min, 100%; (f) $LiAlH_4$, THF, –15°C, 1h, 100%; (g) Ph_3P, CCl_4/CH_2Cl_2 (4:1), reflux, 4h, 97%; (h) Pd/C(10%), MeOH, r.t. 3h, 100%; (i) 1N HCl, MeOH, r.t. 8h, 85%.

Experimental

Melting points were measured on a Kofler apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with Avance DRX 200 or Mercury Plus 300 MHz spectrometer. The chemical shifts are referenced in ppm relative to TMS. Mass spectra were recorded on a HP 5988 spectrometer. HRMS data were measured on an Autoster 3090 spectrometer. IR spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrometer. Flash column chromatography was generally performed on silica gel (200–300 mesh) and TLC on silica gel GF_{254} plates.

(2S, 3R)-2,3-Dihydroxy-3-[3-methoxy-4-(phenylmethoxy)phenyl] propanoic acid ethyl ester (**7a**) *and (2R, 3S)-2,3-dihydroxy-3-[3-methoxy-4-(phenylmethoxy)phenyl]propanoic acid ethyl ester* (**7b**). **7a**: a white solid, m.p. 71–72 °C, $[\alpha]_D^{25}$ –6.9 (*c* 8.0, CH_3COCH_3,). **7b**: a white solid, m.p. 71–72 °C, $[\alpha]_D^{26}$ +4.0 (*c* 0.3, CH_3COCH_3). IR (KBr/cm^{-1}): 3465, 3032, 1733, 1587. ^{1}H NMR (300MHz,$CDCl_3$): δ 1.19 (t, 3H, *J* = 7.2 Hz, $OCH_2C\mathbf{H}_3$), 3.28 (brs, 1H, OH), 3.52 (brs, 1H, OH), 3.84 (s, 3H, OCH_3), 4.16 (q, 2H, *J* = 7.2 Hz, $OC\mathbf{H}_2CH_3$), 4.26 (brs, 1H, CHCO), 4.86 (brs, 1H, ArCH), 5.11 (s, 2H, OCH_2Ph), 6.81 (s, 2H, ArH), 6.96 (s, 1H, ArH), 7.25–7.42 (m, 5H, PhH). ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.9 ($OCH_2\mathbf{C}H_3$), 55.8 (OCH_3), 61.8 (OCH_2Me), 70.8 ($PhCH_2$), 74.3 (CHAr), 74.8 (**C**HC=O), 110.0 (Ar), 113.5 (Ar), 118.5 (Ar), 127.1 (Ph), 127.7 (Ph), 128.4 (Ph), 133.0 (Ar), 136.9 (Ph), 147.6 (Ar), 149.4 (Ar), 172.6 (C=O). MS (EI): *m/z* 346 (M^+, 0.06), 255 (0.14), 243 (9), 91 (100).

(4S, 5R)-2,2-Dimethyl-5-[3-methoxy-4-(phenylmethoxy)phenyl]-1, 3 -dioxolane-4-carboxylic acid ethyl ester (**8a**) *and (4R, 5S)-2,2–dimethyl-5-[3-methoxy-4-(phenylmethoxy)phenyl]-1,3-dioxolane-4-carboxyl- ic acid ethyl ester* (**8b**). **8a**: colourless crystals, m.p. 96 °C, $[\alpha]_D^{26}$ +40.0 (c 6.0, CH_3COCH_3). **8b**: colourless crystals, m.p. 96 °C, $[\alpha]_D^{26}$ –37.0 (c 0.2, CH_3COCH_3). IR (KBr/cm^{-1}): 3032, 1753, 1378. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2 Hz, $OCH_2C\mathbf{H}_3$), 1.55 (s, 3H, CCH_3), 1.60 (s, 3H, CCH_3), 3.89 (s, 3H, OCH_3), 4.23 (q, 2H, *J* = 7.2 Hz, $OC\mathbf{H}_2CH_3$), 4.32 (d, 1H, *J* = 7.5 Hz, $CHCO_2Et$), 5.10 (d, 1H, *J* = 7.5 Hz, ArCH), 5.15 (s, 2H, OCH_2Ph), 6.86 (d, 1H, *J* = 8.4 Hz, ArH), 6.91 (d, 1H, *J* = 8.4 Hz, ArH), 6.98 (s, 1H, ArH), 7.26–7.44 (m, 5H, PhH). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.0 ($OCH_2\mathbf{C}H_3$), 25.6 ($C\mathbf{C}H_3$), 26.8 ($C\mathbf{C}H_3$), 55.8 (OCH_3), 61.3 ($O\mathbf{C}H_2CH_3$), 70.8 (OCH_2Ph), 80.5 (ArCH), 81.1 (**C**HC=O), 109.9 ($\mathbf{C}CH_3CH_3$), 111.2 (Ar), 113.7 (Ar),

* Correspondence. E-mail: houzj@lzu.edu.cn

118.9 (Ar), 127.1 (Ph), 127.7 (Ph), 128.4 (Ph), 130.5 (Ar), 136.9 (Ph), 148.2 (Ar), 149.6 (Ar), 170.3 (C=O). MS (EI): *m/z* 386 (M^+, 2), 191 (4), 165 (3), 91 (100).

(4R, 5R)-2,2-Dimethyl-5-[3-methoxy-4-(phenylmethoxy)phenyl]-1,3-dioxolane-4-methanol (**9a**) *and (4S, 5S)-2,2-Dimethyl-5-[3-methoxy -4-(phenylmethoxy)phenyl]-1,3-dioxolane-4-methanol* (**9b**). **9a**: colourless crystals, m.p. 88 °C, $[\alpha]_D^{25}$ –10.0 (c 1.8, EtOH). **9b**: colourless crystals, m.p. 88 °C, $[\alpha]_D^{25}$ +10.0 (c 0.3, EtOH). IR (KBr/cm^{-1}): 3465, 3037, 1594, 1516. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.51 (s, 3H, CCH_3), 1.57 (s, 3H, CCH_3), 2.28 (s, 1H, OH), 3.60 (dd, 1H, J = 12.3, 4.2 Hz, HC**H**OH), 3.79–3.91 (m, 2H, **H**CHOH, C**H**CH_2OH), 3.89 (s, 3H, OCH_3), 4.83 (d, 1H, J = 8.7 Hz, ArCH), 5.13 (s, 2H, OCH_2Ph), 6.85 (s, 2H, ArH), 6.95 (s, 1H, ArH), 7.25–7.43 (m, 5H, PhH). ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.0 (C**C**H_3), 27.1 (C**C**H_3), 55.9 (OCH_3), 60.3 (CH_2OH), 70.9 (OCH_2Ph), 78.4 (ArCH), 83.3 (**C**$CHCH_2$OH), 109.0 (**C**CH_3CH_3), 110.0 (Ar), 113.9 (Ar), 118.9 (Ar), 127.1 (Ph), 127.7 (Ph), 128.4 (Ph), 130.4 (Ar), 136.9 (Ph), 148.1 (Ar), 149.7 (Ar). MS (EI): *m/z* 344 (M^+, 4), 243 (7), 91 (100).

(4S, 5R)-4-Chloromethyl-2,2-dimethyl-5-[3-methoxy-4-(phenylmethoxy)phenyl]-1,3-dioxolane (**10a**) *and (4R, 5S)-4-Chloromethyl-2,2-dimethyl-5-[3-methoxy-4-(phenylmethoxy)phenyl]-1,3-dioxolane* (**10b**). **10a**: colourless oil, $[\alpha]_D^{20}$ +5.0 (c 1.4, CH_3COCH_3), **10b**: colourless oil, $[\alpha]_D^{26}$ –5.0 (c 2.6, CH_3COCH_3). IR (KBr/cm^{-1}): 3032, 1594, 1514. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.53 (s, 3H, CCH_3), 1.58 (s, 3H, CCH_3), 3.58 (dd, 1H, *J* = 11.7, 4.5 Hz, HCHCl), 3.72 (dd, 1H, *J* = 12.3, 3.6 Hz, HCHCl), 3.91 (s, 3H, OCH_3), 3.99–4.05 (m, 1H, $CHCH_2$Cl), 4.82 (d, 1H, *J* = 8.7 Hz, ArCH), 5.16 (s, 2H, OCH_2Ph), 6.86–6.95 (m, 3H, ArH), 7.30–7.44 (m, 5H, PhH). ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.2 (CCH_3), 27.5 (CCH_3), 43.3 (CH_2Cl), 56.3 (OCH_3), 71.2 (OCH_2Ph), 80.5 (ArCH), 82.4 ($CHCH_2$Cl), 109.9 (CCH_3CH_3), 110.3 (Ar), 114.1 (Ar), 119.4 (Ar), 127.5 (Ph), 128.1 (Ph), 128.8 (Ph), 130.1 (Ar), 137.2 (Ph), 148.7 (Ar), 150.1 (Ar). MS (EI): *m/z* 362 (M^+, 3), 243 (3), 137 (2), 91(100). ESI-HRMS, calcd for $C_{20}H_{27}NO_4Cl$ ($M+NH_4$): 380.1623. Found $(M+NH_4)^+$: 380.1627.

(4S, 5R)-4-Chloromethyl-2,2-dimethyl-5-(4-hydroxy-3-methyoxyphenyl)-1,3-dioxolane (**11a**) *and (4R, 5S)-4-chloromethyl-2,2-dimethyl-5-(4-hydroxy-3-methyoxyphenyl)-1,3-dioxolane* (**11b**). **11a**: colourless oil, $[\alpha]_D^{20}$ +5.0 (*c* 1.8, EtOH), **11b**: colourless oil, $[\alpha]_D^{26}$ –5.0 (c 1.5, EtOH). IR (KBr/cm^{-1}): 3432, 1609, 1517. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.54 (s, 3H, CCH_3), 1.59 (s, 3H, CCH_3), 3.59 (dd, 1H, *J* = 11.7, 4.8 Hz, **H**CHCl), 3.73 (dd, 1H, *J* = 11.7, 3.6 Hz, HC**H**Cl), 3.91 (s, 3H, OCH_3), 3.99–4.04 (m, 1H, C**H**CH_2Cl), 4.82 (d, 1H, *J* = 8.4 Hz, ArCH), 5.69 (s, 1H, OH), 6.86–6.93 (m, 3H, ArH). MS (EI): *m/z* 272 (M^+, 0.7), 179 (1), 152 (2), 85 (100).

(1R, 2S)-3-Chloro-1-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol (**1a**): To a solution of compound **11a** (0.145 g, 0.53 mmol) in MeOH (10 ml) was added 1N HCl (5 ml), and the mixture was stirred at r.t. for 8 h. It was then extracted with ethyl acetate and the combined organic layers were washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography using petroleum ether and ethyl acetate (1:1, v/v) to afford **1a** (0.105 g, 85%) as a white solid. m.p. 120 °C, $[\alpha]_D^{20}$ +3.1 (*c* 4.6, EtOH), IR (KBr/cm^{-1}): 3409, 1607, 1517. ^{1}H NMR (300MHz, $(CD_3)_2CO$): δ 3.34 (dd, 1H, *J* = 11.1, 6.4 Hz, H-3a), 3.44 (s, 3H, OH, exchangeable in D_2O), 3.59 (dd, 1H, *J* = 11.1, 4.2 Hz, H-3b), 3.81 (s, 3H, OCH_3), 3.82 (m, 1H, H-2), 4.61 (d, 1H, *J* = 5.7 Hz, H-1), 6.77 (d, 1H, *J* = 8.1 Hz, H-5'), 6.82 (dd, 1H, *J* = 8.1, 1.8 Hz, H-6'), 7.02 (d, 1H, *J* = 1.8 Hz, H-2'), ^{13}C NMR (300MHz, $(CD_3)_2CO$), δ 47.4 (C-3), 56.4 (OCH_3), 74.9 (C-1), 76.5 (C-2), 111.2 (C-2'), 115.5 (C-5'), 120.3 (C-6'), 134.0 (C-1'), 146.9 (C-4'), 148.2 (C-3'). MS (EI): *m/z* 234, 232 (M^+, 0.9, 2.7), 165 (1), 153 (100), 93 (80). ESI-HRMS, calcd for $C_{10}H_{17}NO_4Cl$ ($M + NH_4$): 250.0841. Found $(M+NH_4)^+$: 250.0842.

(1S, 2R)-3-Chloro-1-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol (**1b**): By a procedure similar to the preparation of (*1R, 2S*)-**1a**, the reaction of **11b** (0.105 g, 0.39 mmol), 1N HCl (5 ml) and MeOH (10 ml) gave (*1S, 2R*)-**1b** (0.076 g, 85%) as a white solid. mp 120 °C, $[\alpha]_D^{25}$ –3.0 (*c* 2.1, EtOH), IR (KBr/cm^{-1}): 3409, 1607, 1517. ^{1}H NMR (300MHz, $(CD_3)_2CO$): δ 3.34 (dd, 1H, *J* = 11.1, 6.4 Hz, H-3a), 3.44 (s, 3H, OH, exchangeable in D_2O), 3.59 (dd, 1H, *J* = 11.1, 4.2 Hz, H-3b), 3.81 (s, 3H, OCH_3), 3.82 (m, 1H, H-2), 4.61 (d, 1H, *J* = 5.7 Hz, H-1), 6.77 (d, 1H, *J* = 8.1 Hz, H-5'), 6.82 (dd, 1H, *J* = 8.1, 1.8 Hz, H-6'), 7.02 (d, 1H, *J* = 1.8 Hz, H-2'), ^{13}C NMR (300MHz, $(CD_3)_2CO$), δ 47.4 (C-3), 56.4 (OCH_3), 74.9 (C-1), 76.5 (C-2), 111.2 (C-2'), 115.5 (C-5'), 120.3 (C-6'), 134.0 (C-1'), 146.9 (C-4'), 148.2 (C-3'). MS (EI): *m/z* 234, 232 (M^+, 0.9, 2.7), 165 (1), 153 (100), 93 (80). ESI-HRMS, calcd for $C_{10}H_{17}NO_4Cl$ ($M+NH_4$): 250.0841. Found $(M+NH_4)^+$: 250.0842.

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