Supporting information

A Practical Synthesis of (±)-Nyasol

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Contents:

1. synthetic procedures of (±)-Nyasol
2. ¹H-NMR, ¹³C-NMR and Mass spectra for compounds

Experimental Section

All chemicals were obtained from commercial suppliers, and used without further purification. All solvents used for reactions were freshly distilled from proper dehydrating agent under nitrogen gas. All solvents used for chromatography were purchased and directly applied without further purification. ^1H -NMR spectra were recorded on a Bruker Avance 300 (300 MHz) and Bruker DPX 400 (400 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Peak splitting patterns are abbreviated as m (multiplet), s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), dd (doublet of doublets) and ddd (doublet of double doublet). ^{13}C -NMR spectra were recorded on a Bruker DPX 400 (100 MHz) spectrometer, fully decoupled and chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Mass spectra were recorded on a Voyager DE STR MALDI-TOF mass spectrometer. Analytical thin-layer chromatography (TLC) was performed using commercial glass plate with silica gel 60F 254 purchased from Merck.

Scheme 2. Reagents and conditions: (a) KOH, EtOH, 95%. (b) vinylmagnesium bromide, CuBr-Me₂S, HMPA, TBSCl, THF, 3 h. (c) *m*CPBA, NaHCO₃, CH₂Cl₂, then HF, MeOH, 90% (3 steps). (d) Zn(BH₄)₂, Et₂O, 92%. (e) TCDI, DIPEA, CH₂Cl₂, reflux, 2 h., 72%. (f) P(OMe)₃, reflux, 1 d, 84%, *Z/E* = 11.5. (g) MeMgI, 160 °C, 150 mbar, 1 h, 82%.

(*E*)-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (1): To a solution of 4'-methoxyacetophenone (5 g, 33.29 mmol) and *p*-anisaldehyde (4.53 g, 33.29 mmol) in EtOH (75 mL) was added 6M KOH (135 mL) dropwise. The reaction was stirred at room temperature for overnight. The solution was filtered to get compound **1** (8.48 g, 95%) as yellow solid. ^1H -NMR (300 MHz, CDCl₃) δ : 8.01~8.06 (m, 2H, C2 and C6 Ar1), 7.78 (d, 1H, *J* = 15.6 Hz, CH=CHAr), 7.58~7.63 (m, 2H, C3 and C5 Ar1), 7.43 (d, 1H, *J* = 15.6, CH=CHAr), 6.91~7.01 (m, 4H, Ar2), 3.89 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃); MS (MALDI-TOF): *m/z* [M+H]⁺ 269.57.

(1,3-bis(4-methoxyphenyl)penta-1,4-dienyloxy)(*tert*-butyl)dimethylsilane (2): To a solution of vinylmagnesium bromide (22.4 mL, 22.36 mmol) was added Copper(I) bromide dimethyl sulfide complex (184 mg, 0.89 mmol) in HMPA (3.6 mL) dropwise at -78 °C. After 0.5 h, the solution of compound **1** (2.4 g, 8.95 mmol) and TMSCl (2.3 mL, 17.90 mmol) was added dropwise respectively at the same temperature. Et₃N (10 mL) was added to quench the reaction after 3 h. The mixture was extracted with Et₂O (250 mL), washed with saturated NH₄Cl (150 mL) and dried with MgSO₄. The organic phase was evaporated to afford crude product and used directly without purification.

2-hydroxy-1,3-bis(4-methoxyphenyl)pent-4-en-1-one (3): To a mixture of compound **2** (3.20 g, 8.68 mmol) and NaHCO₃ (0.88 g, 10.42 mmol) in CH₂Cl₂ (30 mL) was added the solution of *m*CPBA (2.34 g, 10.42 mmol) in CH₂Cl₂ (30 mL) dropwise at 0 °C. The reaction was stirred at room temperature for 1 h. The solution was filtered and the filtrate was evaporated to get the crude product which was dissolved in MeOH (30 mL) to add 48 % HF (1.2 mL, 17.37 mmol) dropwise. The reaction was stirred at room temperature for 2 h. Then the mixture was neutralized by saturated NaHCO₃, extracted with EtOAc (300 mL) and dried with Mg₂SO₄. The organic layer was evaporated to get crude product, which was purified with column chromatography (hexane:EtOAc = 3:1) to afford a pair of diastereoisomers compound **3** (2.52 g, yield of 3 steps: 90%) as colorless oil. ¹H-NMR (300 MHz, CDCl₃) One isomer, δ: 7.88~7.92 (m, 2H, C2 and C6 Ar1), 7.33~7.37 (m, 2H, C2 and C6 Ar2), 6.95~7.00 (m, 2H, C3 and C5 Ar1), 6.86~6.91 (m, 2H, C3 and C5 Ar2), 5.93~6.05 (m, 1H, CH=CH₂), 5.28~5.37 (m, 2H, CH=CH₂), 5.00 (dd, 1H, *J* = 1.3, 10.2, CHOH), 4.73 (m, 1H, *J* = 1.3, 16.1, CHCH=CH₂), 3.89 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.69 (m, 1H, OH). Another isomer, δ: 7.82~7.87 (m, 2H, C2 and C6 Ar1), 6.98 (m, 2H, C2 and C6 Ar2), 6.84 (m, 2H, C3 and C5 Ar1), 6.69~6.74 (m, 2H, C3 and C5 Ar2), 6.27~6.39 (m, 1H, CH=CH₂), 5.21~5.24 (m, 2H, CH=CH₂), 3.90 (s, 3H, OCH₃), 3.87~3.90 (m, 1H, CHOH), 3.79 (m, 1H, CHCH=CH₂), 3.74 (s, 3H, OCH₃), 3.64 (d, 1H, *J* = 7.2, OH); MS (MALDI-TOF): *m/z* [M+Na]⁺ 335.61.

(±)-(1*S*,2*R*)-1,3-bis(4-methoxyphenyl)pent-4-ene-1,2-diol (4): To a solution of compound **3** (2.40 g, 7.68 mmol) in Et₂O (25 mL) was added Zn(BH₄)₂ (92 mL, 23.05 mmol, 0.25M in Et₂O) at 0 °C. The reaction was stirred at room temperature for 2 h. The reaction was quenched by ice water, extracted with EtOAc (200 mL) and dried with Mg₂SO₄. The organic layer was evaporated to get crude product, which was purified with column chromatography (hexane:EtOAc = 2:1) to afford compound **4** (2.22 g, 92%) as colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ: 7.30~7.35 (m, 2H, C2 and C6 Ar2), 7.18~7.23 (m, 2H, C2 and C6 Ar1), 6.84~6.91 (m, 4H, C3 and C5 Ar1 and Ar2), 6.04~6.16 (m, 1H, CH=CH₂), 5.04~5.14 (m, 2H, CH=CH₂), 4.48 (d, 1H, *J* = 5.9, CHOHAr), 4.12 (t, 1H, *J* = 6.0, CHOH), 3.81 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.42 (t, 1H, *J* = 7.5, CHCH=CH₂), 2.23 (bs, 1H, OH), 1.60 (bs, 1H, OH); MS (MALDI-TOF): *m/z* [M+H]⁺ 315.51.

(±)-(4*R*,5*S*)-4-(4-methoxyphenyl)-5-(1-(4-methoxyphenyl)allyl)-1,3-dioxolane-2-thione (5): To a solution of the compound **4** (2.0 g, 6.36 mmol) in CH₂Cl₂ (40 mL) were added TCDI (3.4 g, 19.08 mmol) and DIPEA (11.1 mL, 63.61 mmol). The reaction was refluxed for 2 h, the product was extracted with CH₂Cl₂ (150 mL), washed with saturated brine (100 mL x 2) and dried with Mg₂SO₄. The organic layer was evaporated to obtain the crude product, which was purified by column chromatography (hexane : EtOAc = 4:1) to afford the compound **5** (1.63 g, 72 %) as a light yellow oil. ¹H-NMR (300 MHz, CDCl₃) δ: 6.81 (m, 4H, C2 and C6 Ar1 and Ar2), 6.74 (m, 2H, C3 and C5 Ar2), 6.59 (m, 2H, C3 and C5 Ar1), 5.98~6.11 (m, 1H, CH=CH₂), 5.54 (d, 1H, *J* = 7.4, CH=CH₂), 5.35 (dd, 1H, *J* = 7.4, 10.7, CH=CH₂), 5.13 (m, 1H, CHAr), 4.90 (m, 1H, CH), 3.82 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.27 (m, 1H, CHCH=CH₂); MS (MALDI-TOF): *m/z* [M]⁺ 356.44.

(±)-(Z)-4,4'-(penta-1,4-diene-1,3-diyl)bis(methoxybenzene) (6): A solution of the compound **5** (1.50 g, 4.21 mmol) in P(OMe)₃ (2.5 mL) was refluxed for 24 h. The mixture was evaporated to obtain the crude product, which was purified by column chromatography (hexane : EtOAc = 10:1) to afford the compound **6** (994 mg, 85%) and *E*-stereoisomer (86 mg) as a light colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ: 7.21~7.24 (m, 2H, C2 and C6 Ar1), 7.14~7.18 (m, 2H, C2 and C6 Ar2), 6.83~6.88 (m, 4H, C3 and C5 Ar1 and Ar2), 6.53 (d, 1H, *J* = 11.4, ArCH=CH), 5.98~6.07 (m, 1H, CH=CH₂), 5.69 (dd, 1H, *J* = 10.0, 11.4,

ArCH=CH), 5.14~5.20 (m, 2H, CH=CH₂), 4.52 (dd, 1H, $J = 6.1, 10.0$, CHCH=CH₂), 3.79 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃); ¹³C-NMR (100 MHz, CDCl₃) δ : 159.0 (CHOCH₃), 158.6 (CHOCH₃), 141.2 (CH=CH), 135.9 (CH=CH₂), 132.1 (Ar), 130.2 (Ar), 130.1 (Ar), 129.1 (Ar), 129.0 (CH=CH), 115.4 (CH=CH₂), 114.4 (Ar), 114.1 (Ar), 55.7 (OCH₃), 55.6 (OCH₃), 47.3 (CH); HRMS (MALDI-TOF): m/z calculated [M]⁺ 280.1463, observed [M]⁺ 280.3867. *E*-stereoisomer of compound **6**: ¹H-NMR (300 MHz, CDCl₃) δ : 7.22~7.24 (m, 2H, C2 and C6 Ar1), 7.08~7.14 (m, 2H, C2 and C6 Ar2), 6.75~6.84 (m, 4H, C3 and C5 Ar1 and Ar2), 6.29 (d, 1H, $J = 16.0$, ArCH=CH), 6.12~6.20 (dd, 1H, $J = 6.6, 16.0$, ArCH=CH), 5.96~6.07 (m, 1H, CH=CH₂), 5.00~5.13 (m, 2H, CH=CH₂), 4.08 (t, 1H, $J = 6.3$, CHCH=CH₂), 3.73 (s, 6H, OCH₃).

(±)-(Z)-4,4'-(penta-1,4-diene-1,3-diyl)diphenol (7): To a solution of compound **6** (0.5 g, 1.78 mmol) in a 25 mL flask was added MeMgI (3M in Et₂O, 1.8 mL, 5.35 mmol) under N₂. The reaction was stirred at 160°C under reduced pressure (150 mbar) for 1h. The reaction was quenched by saturated NH₄Cl (50 mL), extracted by EtOAc (150 mL) and washed with saturated brine (100 mL x 2), dried with MgSO₄ and evaporated to get crude product, which was purified with column chromatography (hexane : EtOAc = 2:1) to afford compound **7** (0.37 g, 82%) as light colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ : 7.17 (m, 2H, C2 and C6 Ar1), 7.10 (m, 2H, C2 and C6 Ar2), 6.75~6.81 (m, 4H, C3 and C5 Ar1 and Ar2), 6.51 (d, 1H, $J = 11.4$, ArCH=CH), 5.95~6.09 (m, 1H, CH=CH₂), 5.67 (dd, 1H, $J = 10.0, 11.4$, ArCH=CH), 5.14~5.19 (m, 2H, CH=CH₂), 4.88 (bs, 1H, OH), 4.77 (bs, 1H, OH), 4.50 (dd, 1H, $J = 6.1, 10.0$, CHCH=CH₂); ¹³C-NMR (100 MHz, CDCl₃) δ : 154.9 (CHOH), 154.4 (CHOH), 141.1 (CH=CH), 136.0 (CH=CH₂), 132.1 (Ar), 130.4 (Ar), 130.3 (Ar), 129.3 (Ar), 129.0 (CH=CH), 115.8 (CH=CH₂), 115.5 (Ar), 115.4 (Ar), 47.2 (CH); HRMS (MALDI-TOF): m/z calculated [M]⁺ 252.1150, observed [M]⁺ 252.4411.

¹H-NMR and ¹³C-NMR spectra for compounds

¹H-NMR of compound 1

¹H-NMR of compound 3

¹H-NMR of compound 4

¹H-NMR of compound 5

Mass of compound 6

¹H-NMR of E-stereoisomer compound 6

¹H-NMR of compound 7¹³C-NMR of compound 7

Mass of compound 7