Synthesis and bioactivity of erythro-nordihydroguaiaretic acid, threo-(–)-saururenin and their analogues

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Abstract: Full details of the total syntheses of erythro-nordihydroguaiaretic acid, threo-(–)-saururenin and their analogues are presented. The syntheses were based on a unified synthetic strategy involving the Stobbe Reaction, alkylation to construct the skeleton of lignans and resolution of the threo- and erythro-isomers. The syntheses were achieved in eight to nine steps from simple aromatic precursors, and by this route 13 lignans were obtained. Among the synthesized lignans, seven lignans were natural products; moreover three of the seven natural products were synthesized for the first time. The effect of 13 lignans was examined on HIV Tat transactivation in human epithelial cells, HSV-1 gene and human leukemic, liver, prostate, stomach and breast cancer cell. Bioactivity results indicated that one product showed activity against the HIV gene and five compounds exhibited anti-HSV activity.

Keywords: synthesis; bioactivity; NDGA; saururenin

INTRODUCTION

Lignans are a class of naturally occurring plant phenols that formally arise biosynthetically from two cinnamic acid (phenylpropanoid) residues, as defined originally by Howarth in 1936.1 Lignans are found in all parts of plants, including the roots, stems, leaves, fruit and seeds, and they exhibit a wide range of biological activities, including antitumor, anti-inflammatory, immunosuppressive, cardiovascular, neuroprotective, neurotrophicm antioxidant and antiviral actions.2 There is a growing interest in lignans and their synthetic derivatives due to applications in cancer chemotherapy and anti-virus therapy.3,4

Nordihydroguaiaretic acid (NDGA) is a naturally occurring lignan from the creosote bush (Larrea tridentata). NDGA has been utilized in traditional healing practices for a wide range of ailments and was licensed for use as a topical treatment for actinic keratosis (Actinex, Chemex Pharmaceuticals, Denver CO).5,6 NDGA is a known antioxidant, a lipoygenase inhibitor, and has also been shown to inhibit P450.7–9 (–)-Saururenin is a threo-alkene, but different from erythro-NDGA, and was isolated from Saururus Cernuus L., an aquatic weed commonly found in the eastern United States.10 Saururus Cernuus L. has been used in folk medicine as a sedative and as poultice for tumors.11 More recently, much of the interest in NDGA, (–)-saururenin and their analogues centered on their role in anti-virus and anti-tumor activity. Hwu reported that NDGA and its analogues exhibited activity against HIV, and tetramethyl NDGA was a stronger anti-HIV agent.12
Cheng et al. showed that in Vero cells, NDGA and its analogues inhibited the expression of the herpes immediate early gene, which is essential for HSV replication. NDGA, (−)-saururenin and their analogues have also been shown to have cancer chemopreventive properties. 

NDGA, (−)-saururenin and their analogues have stimulated substantial synthetic efforts due to their biological activity. Lieberman et al. used the coupling of two molecules of 1-piperonyl-1-bromoethane as the key step to give the skeleton of NDGA. Son et al. developed a modified procedure for the synthesis of NDGA and related lignans. Gezginci and Timmermann reported the synthesis of meso-nordihydroguaiaretic acid from (3,4-dimethoxyphenyl)acetone using the low-valent Ti-induced carbonyl–coupling reaction of the ketone as the key step. Rao et al. described the synthesis of analogues of (−)-saururenin from Saururus cernuus, together with (−)-austrobailignan-5 by regioselective cleavage of the methylenedioxyphenyl groups. A synthetic route to NDGA and machilin A involving two Stobbe condensations to give the skeleton of lignan was reported.

In this paper, an efficient approach for the chiral synthesis of NDGA, (−)-saururenin and their analogues is presented. By this method, 13 lignans were synthesized, among them, seven lignans were natural products and moreover three of the seven natural products were synthesized for the first time. The biological effect of the 13 lignans in their pure form was examined on HIV Tat transactivation in human epithelial cells, the HSV-1 gene and human leukemic, liver, prostate, stomach, and breast cancer cells. The bioactivity results indicated that some compounds exhibited better activities against the HIV and herpes virus. Finally, it should be emphasized that the bioactivity is affected by the skeleton configuration and functional groups.

RESULTS AND DISCUSSION

Synthesis of compounds

The starting materials were piperonal 1a and veratraldehyde 1b. Condensation of 1a or 1b with diethyl succinate in EtONa/EtOH solution afforded the benzylidene half-ester, which was followed by esterification to produce the diester 2a or 2b. Treatment of 2a or 2b in THF with LDA and 3,4-methylenedioxybenzyl bromide at –78 °C afforded the diester 3a or 3b. Then the compound 3a or 3b was hydrolyzed to form the diacid. At this stage, the diacids were resolved via the quinine salt. The quinine salt of diacid (−)-4a or (−)-4b crystallized first. Concentration of the mother liquors gave a solid, which yielded the quinine salt of (−)-4a′ or (−)-4b′. The diacid 4a or 4b was esterified to produce the diester (−)-5a or (−)-5b. The diester 5a or 5b was hydrogenated under a H2 atmosphere, following by reduction with LiAlH4 in THF to produce a readily separable mixture (approximately 1:1) of diols threo-(−)-6a and erythro-7a or threo-(−)-6b and erythro-7b. 7a was a meso-compound and did not have optical rotation (Scheme 1). The spectral data were in agreement with those found in the literature.

Scheme 1

Reaction of diol threo-(−)-6a or threo-(−)-6b with equimolar amounts of TsCl in a dilute solution at room temperature gave the corresponding 8a and 8b, while diol threo-(−)-6a or threo-(−)-6b with TsCl in concentrated solution at 0 °C gave the ditoluenesulfonylesters, were reduced with LiAlH4 in THF to provide 10a, 10b. On the other hand, etherification of 6a or 6b gave the compounds 9a and 9b. The compounds 11a, 11b, 12a, 12b, 13a, and 13b were prepared in a similar manner. Compound 13a was refluxed
with PCl₅ in anhydrous CCl₄, followed by hydrolysis of the resulting dichloromethylene derivative with water to provide meso-nordihydroguaiaretic acid 14 (Scheme 2 and Scheme 3).

The compounds 6a, 6b, 7b, 10a, 10b, 13a and 14 are natural products while compounds 7b, 10b and 13a were synthesized for the first time.

Scheme 2

Scheme 3

**Spectroscopic data of the synthesized compounds**

**Diethyl-2-(3',4'-methylenedioxybenzylidene)succinate (2a):**

1H-NMR (200 MHz, CDCl₃, δ / ppm): 1.22 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.3 Hz), 3.51 (2H, s), 4.16 (2H, q, J = 7.3 Hz), 4.27 (2H, q, J = 7.3 Hz), 5.96 (2H, s), 6.76–6.87 (3H, m), 7.76 (1H, s); EI–MS (m/z, %): 306 (M⁺, 70), 261 (20), 232 (34), 203 (52), 175 (59), 159 (100).

**Diethyl-2-(3',4'-dimethoxybenzylidene)succinate (2b):**

1H-NMR (200 MHz, CDCl₃, δ / ppm): 1.33 (3H, t, J = 7.3 Hz), 1.26 (3H, t, J = 7.2 Hz), 3.58 (2H, s), 3.87 (3H, s), 3.90 (3H, s), 4.21 (2H, q, J = 7.3 Hz), 4.27 (2H, q, J = 7.3 Hz), 6.86–7.00 (3H, m), 7.84 (1H, s); EI–MS (m/z, %): 322 (M⁺, 42), 276 (14), 249 (16), 175 (100).

**2-(3',4'-Methylenedioxybenzylidene)-3-(3'',4'').**

methyleneoxynbenzyl)succinate (3a): m.p. 58–59 °C; 1H-NMR (200 MHz, CDCl₃, δ / ppm): 1.26 (3H, t, J = 7.2 Hz, CH₃), 1.34 (3H, t, J = 7.2 Hz, CH₂), 2.85 (1H, dd, J = 10.0, 14.2 Hz, H-7″α), 3.34 (1H, dd, J = 5.0, 14.2 Hz, H-7″β), 3.98 (1H, dd, J = 5.0, 10.0 Hz, H-3), 4.15–4.32 (4H, m, 2 × CH₂CH₃), 5.88 (2H, s, OCH₂O), 5.97 (2H, s, OCH₂O), 6.35–6.73 (6H, m, ArH), 7.66 (1H, s, H-7″); 13C-NMR (50 MHz, CDCl₃, δ / ppm): 14.4 (2 × CH₂CH₃), 36.0 (C-3), 45.8 (C-7″), 61.2 (2 × OCH₂CH₃), 100.9 (OCH₂O), 101.4 (OCH₂O), 108.1 (C-5″), 108.4 (C-5′″), 108.7 (C-2″), 109.7 (C-2′″), 122.4 (C-6″), 122.7 (C-6″), 129.3 (C-1″), 130.1 (C-1″′), 133.2 (C-2), 142.5 (C-7″), 146.1 (C-4″), 147.5 (C-4″′), 147.8 (C-3″, C-3′′), 166.9 (C=O), 172.9 (C=O); EI–MS (m/z, %): 440 (M⁺, 4), 395 (1), 306 (5), 231 (40), 137 (100); HRMS calcd. for C₂₄H₂₅O₈ (M+H⁺): 441.1544. Found: 441.1538.

**Diethyl-2-(3',4'-dimethoxybenzylidene)-3-(3'',4'').**

methyleneoxynbenzyl)succinate (3b): 1H-NMR (200 MHz, CDCl₃, δ / ppm): 1.26 (3H, t, J = 7.2 Hz, CH₃), 1.35 (3H, t, J = 7.2 Hz, CH₃), 2.91 (1H, dd, J = 9.8, 14.2 Hz, H-7″α), 3.34 (1H, dd, J = 5.0, 14.2 Hz, H-7″β), 3.78 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 4.10 (1H, dd, J = 5.0, 9.8 Hz, H-3), 4.18 (2H, q, J = 7.2 Hz, CH₂CH₃), 4.30 (2H, q, J = 7.2 Hz, CH₂CH₃), 5.85 (2H, s, OCH₂O), 6.35–6.80 (6H, m, ArH), 7.71 (1H, s, H-7″); 13C-NMR (50 MHz, CDCl₃, δ / ppm): 14.1 (CH₂CH₃), 14.2 (CH₂CH₃), 35.7 (C-3), 45.5 (C-7″), 55.7 (OCH₃), 55.8 (OCH₃), 60.9 (2 × CH₂CH₃), 100.7 (OCH₂O), 107.7 (C-5″), 109.4 (C-5′″), 110.7 (C-2″), 111.4 (C-2′″), 121.1 (C-6″), 122.0 (C-6″′), 127.9 (C-1″), 129.5 (C-1″′), 132.9 (C-2), 142.3 (C-7″), 145.7 (C-4″), 147.2 (C-4″′), 148.6 (C-3″), 149.1 (C-3′″), 166.7 (C=O), 172.7 (C=O); EI–MS (m/z, %): 456 (M⁺, 3), 411 (1), 382 (1), 322 (4), 247 (51), 137 (100); HRMS calcd. for C₂₅H₂₄O₈ (M+H⁺): 457.1857. Found: 457.1856.

(–)-2-(3',4'-Methylenedioxybenzylidene)-3-(3'',4'').

methyleneoxynbenzyl)succinic acid (4a): m.p. 98–99 °C; 1H-NMR (200 MHz, DMSO-d₆, δ / ppm): 2.85 (1H, dd, J = 10.2, 13.8 Hz, H-7″α), 3.25 (1H, dd, J = 4.4, 13.8 Hz, H-7″β), 3.93 (1H, dd, J = 4.4, 10.2 Hz, H-3), 5.92 (2H, s, OCH₂O), 6.04 (2H, s, OCH₂O), 6.37–6.90 (6H, m, ArH), 7.53 (1H,
(+)-2-(3',4'-Methylenedioxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinic acid (4a): m.p. 96–97 °C; [α]D16 +94.8 (c 0.8, EtOH). The 1H NMR, IR and MS data of 4a were in agreement with those of 4a.

(+)-2-(3',4'-Dimethoxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinic acid (4b): m.p. 89–91 °C; [α]D16 +142.6 (c 0.6, EtOH). The 1H-NMR, IR, MS and HRMS data of 4b were in agreement with those of 4b.

(+)-Diethyl-2-(3',4'-methylenedioxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinate (5a): [α]D16 –68.4 (c 1.0, CHCl3). The 1H-NMR, IR, MS and HRMS data of 5a were in agreement with those of 3a.

(+)-Diethyl-2-(3',4'-dimethoxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinate (5b): [α]D16 –170.1 (c 1.0, CHCl3). The 1H-NMR, IR, MS and HRMS data of 5b were in agreement with those of 3b.

(+)-Dihydrocubebin (6a): m.p. 112–113 °C; 1H-NMR (200 MHz, CDCl3, δ / ppm): 1.80–1.84 (2H, m, H-2, H-3), 2.55–2.81 (4H, m, 2 × ArCH2), 3.48 (2H, d, J = 11.2 Hz, CH2OH), 3.70–3.80 (6H, m, ArH); 13C-NMR (100 MHz, CDCl3, δ / ppm): 35.8 (C-2, C-3), 44.2 (C-7', C-7''), 59.9 (C-1, C-4), 100.7 (2 × OCH2O), 108.1 (C-5', C-5''), 109.2 (C-2', C-2''), 121.8 (C-6', C-6''), 134.3 (C-1', C-1''), 145.6 (C-4', C-4''), 147.5 (C-3', C-3''); EI–MS (m/z, %): 358 (M+, 2), 340 (0.1), 204 (0.3), 161 (3), 135 (100); HRMS calcd. for C20H26NO6 (M+NH4+): 376.1755. Found: 376.1760; [α]D16 –41.9 (c 0.8, CHCl3). The spectral data are in agreement with the literature.22

(+)-Dihydro-3',4'-dimethoxy-3'',4''-demethylenedioxycubebin (6b): 1H-NMR (200 MHz, CDCl3, δ / ppm): 1.85–1.87 (2H, m, H-2, H-3), 2.60–2.80 (4H, m, 2 × H-7', 2 × H-7''), 3.50 (2H, d, J = 11.6 Hz, CH2OH), 3.56 (2H, s, 2 × OH), 3.80 (2H, s, OCH2OH), 3.82 (3H, s, OCH3), 3.83 (3H, s, OCH3), 3.90 (2H, s, OCH2O), 6.57–6.80 (6H, m, ArH); 13C-NMR (100 MHz, CDCl3, δ / ppm): 35.7 (C-2), 35.9 (C-3), 43.9 (C-7), 44.1 (C-7''), 55.8 (OCH3), 55.9 (OCH3), 60.2 (C-1), 60.3 (C-4), 100.7 (OCH2O), 108.0 (C-5'), 109.3 (C-5''), 111.2 (C-2'), 112.1 (C-2''), 121.0 (C-6'), 121.8 (C-6''), 133.1 (C-1'), 134.3 (C-1''), 145.7 (C-4'), 147.3 (C-4''), 147.5 (C-3), 148.8 (C-3''); EI–MS (m/z, %): 374 (M+, 4), 356 (0.4), 220 (3), 203 (3), 151 (100); HRMS calcd. for C21H22NO6 (M+NH4+): 392.2068. Found: 392.2063; [α]D16 –36.8 (c 0.5, CHCl3). The spectral data are in agreement with the literature.23

Meso-2,3-bis(3',4'-methylenedioxybenzyl)butane-1,4-diol (7a): 1H-NMR (200 MHz, CDCl3, δ / ppm): 1.99–2.05 (2H, m, H-2, H-3), 2.49–2.63
(4H, m, 2 × ArCH2), 3.45–3.61 (4H, m, 2 × CH2OH), 3.71 (2H, s, 2 × OH), 5.92 (4H, s, 2 × OCH2O), 6.61–6.76 (6H, m, ArH); 13C-NMR (50 MHz, CDCl3, δ / ppm): 33.4 (C-2, C-3), 45.2 (C-7’, C-7’’), 62.9 (C-1, C-4), 100.8 (2 × OCH2O), 108.1 (C-5’, C-5’’), 109.2 (C-2’, C-2’’), 121.8 (C-6’, C-6’’), 134.1 (C-1’, C-1’’), 145.8 (C-3’, C-3’’); EI–MS (m/z, %): 358 (M+, 3), 340 (0.3), 204 (0.8), 161 (4), 135 (100); HRMS calcd. for C20H26NO6 (M+NH4+): 376.1755. Found: 376.1760.

(–)-2,3-Desmethoxy seco-isolintetralin (7b): 1H-NMR (200 MHz, CDCl3, δ / ppm): 1.84–1.86 (2H, m, 2 × H-2), 2.56–2.82 (4H, m, 2 × H-7’, 2 × H-7’’), 3.50 (2H, d, J = 11.0 Hz, CH2OH), 3.71 (2H, s, 2 × OH, CH2OH), 3.81 (3H, s, OCH3), 3.83 (3H, s, OCH3), 3.95 (2H, s, 2 × OH), 5.89 (2H, s, OCH2O), 6.56–6.78 (6H, m, ArH); 13C-NMR (100 MHz, CDCl3, δ / ppm): 33.1 (C-2), 33.4 (C-3), 45.0 (C-7’), 45.2 (C-7’’), 55.8 (OCH3), 55.9 (OCH3), 62.9 (C-1), 63.0 (C-4), 100.8 (OCH2O), 108.1 (C-5’), 109.3 (C-5’’), 111.2 (C-2’), 112.1 (C-2’’), 121.0 (C-6’), 121.8 (C-6’’), 133.0 (C-1’), 134.2 (C-1’’), 145.8 (C-4’), 147.3 (C-4’’), 147.6 (C-3’), 148.8 (C-3’’); EI–MS (m/z, %): 374 (M+, 4.7), 356 (0.23), 220 (1.8), 203 (2.5), 151 (100); HRMS calcd. for C21H30NO6 (M+NH4+): 392.2068. Found: 392.2063; [α]D16 –54.2 (c 0.8, CHCl3).

(–)-3-(3’,4’-Dimethoxybenzyl)-4-(3”,4”-methylenedioxybenzyl)tetrahydrofuran (8b): 1H-NMR (200 MHz, CDCl3, δ / ppm): 2.15–2.18 (2H, m, 2 × ArCH2), 3.46–3.54 (2H, m, 2 × H-2), 3.84 (3H, s, OCH3), 3.85 (3H, s, OCH3), 3.89–3.93 (2H, m, 2 × H-5), 5.91 (2H, s, 2 × OCH2O), 6.51–6.75 (6H, m, ArH); 13C-NMR (100 MHz, CDCl3, δ / ppm): 39.1 (C-3), 39.2 (C-4), 46.4 (C-7’, C-7’’), 73.2 (C-2), 73.3 (C-5), 100.7 (2 × OCH2O), 107.9 (C-5’), 108.9 (C-2’), 121.4 (C-6’), 134.0 (C-1’), 147.5 (C-4’), 147.7 (C-4’’), 147.9 (C-3’), 151 (100); [α]D16 –54.2 (c 0.8, CHCl3). The spectral data were in agreement with the literature.24

(+)-2,3-Bis(3’,4’-methyleneoxybenzyl)butane-1,4-dimethoxybutane (9a): 1H-NMR (300 MHz, CDCl3, δ / ppm): 2.00–2.03 (2H, m, H-2, H-3), 2.52–2.69 (4H, m, 2 × ArCH2), 3.28 (10H, s, 2 × OCH3, 2 × H-1, 2 × H-4), 5.92 (4H, s, 2 × OCH2O), 6.55–6.71 (6H, m, ArH); 13C-NMR (75 MHz, CDCl3, δ / ppm): 35.1 (C-2, C-3), 41.2 (C-7’, C-7’’), 58.9 (C-5’, C-5’’), 72.7 (C-1, C-4), 100.9 (2 × OCH2O), 108.2 (C-5’), 109.7 (C-2’, C-2’’), 122.1 (C-6’, C-6’’), 135.1 (C-1’), 145.8 (C-4’, C-4’’), 147.7 (C-3’, C-3’’); EI–MS (m/z, %): 376 (M+, 11), 204 (2), 187 (3), 161 (2), 136 (100); [α]D16 –104.7 (c 0.6, CHCl3).
MS, (m/z, %): 386 (M⁺, 5), 354 (7), 218 (9), 187 (19), 161 (8), 135 (100); 
[α]D16 +12.3 (c 0.5, CHCl₃).

(−)-2-(3',4'-Dimethoxybenzyl)-3-(3'',4''-methyleneoxybenzyl)-1,4-dimethoxybutane (9b): ¹H-NMR (300 MHz, CDCl₃, δ / ppm): 2.00–2.03 (2H, m, H-2, H-3), 2.61–2.64 (4H, m, 2 × ArCH₂), 3.29 (10H, s, 2 × OCH₃, 2 ×H-1, 2 ×H-4), 3.82 (3H, s, ArOCH₃), 3.86 (3H, s, ArOCH₃), 5.92 (2H, s, 2 × OCH₂O), 6.55–6.78 (6H, m, ArH); ¹³C-NMR (75 MHz, CDCl₃, δ / ppm): 34.8 (C-2), 34.9 (C-3), 40.7 (C-7'), 40.9 (C-7''), 55.7 (OCH₃), 55.9 (OCH₃), 58.7 (ArOCH₃), 58.8 (ArOCH₃), 72.4 (C-1), 72.6 (C-4), 100.7 (OCH₂O), 107.9 (C-5'), 109.4 (C-5''), 110.9 (C-2'), 111.9 (C-2''), 121.1 (C-6'), 121.9 (C-6''), 133.5 (C-1'), 134.9 (C-1''), 145.5 (C-4'), 147.1 (C-4''), 147.4 (C-3'), 148.7 (C-3''); EI–MS (m/z, %): 402 (M⁺, 21), 370 (6), 203 (17), 151 (100); [α]D16 +14.8 (c 0.6, CHCl₃).

(−)-Austrobaileignan-5 (10a): m.p. 44–45 °C; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 0.81 (6H, d, J = 6.8 Hz, 2 × CH₃), 1.67–1.77 (2H, m, H-2, H-3), 2.33 (2H, dd, J = 8.2, 13.6 Hz, ArCH₂), 2.55 (2H, dd, J = 6.0, 13.6 Hz, ArCH₂), 5.92 (4H, s, 2 × OCH₂O), 6.52–6.75 (6H, m, ArH); ¹³C-NMR (100 MHz, CDCl₃, δ / ppm): 13.7 (C-1), 13.8 (C-4), 37.7 (C-2), 37.9 (C-3), 40.9 (C-7'), 41.1 (C-7''), 55.7 (OCH₃), 55.8 (OCH₃), 100.6 (OCH₂O), 107.8 (C-5'), 109.2 (C-5''), 111.0 (C-2'), 112.0 (C-2''), 120.8 (C-6'), 121.7 (C-6''), 134.1 (C-1'), 135.4 (C-1''), 145.4 (C-4'), 147.0 (C-4''), 147.3 (C-3'), 148.7 (C-3''); EI–MS (m/z, %): 326 (M⁺, 1), 135 (20), 123 (100); [α]D16 −36.3 (c 0.5, CHCl₃). The spectral data are in agreement with the literature.²⁵

(−)-Saururevin (10b): ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 0.82 (6H, d, J = 6.6 Hz, 2 × CH₃), 1.71–1.77 (2H, m, H-2, H-3), 2.30–2.42 (2H, m, ArCH₂), 2.49–2.59 (2H, m, ArCH₂), 3.83 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 5.90 (2H, s, OCH₂O), 6.51–6.78 (6H, m, ArH); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 13.7 (C-1), 13.8 (C-4), 37.7 (C-2), 37.9 (C-3), 40.9 (C-7'), 41.1 (C-7''), 55.7 (OCH₃), 55.8 (OCH₃), 100.6 (OCH₂O), 107.8 (C-5'), 109.2 (C-5''), 111.0 (C-2'), 112.0 (C-2''), 120.8 (C-6'), 121.7 (C-6''), 134.1 (C-1'), 135.4 (C-1''), 145.4 (C-4'), 147.0 (C-4''), 147.3 (C-3'), 148.7 (C-3''); EI–MS (m/z, %): 342 (M⁺, 8), 206(2), 151 (100); [α]D16 −33.0 (c 0.8, CHCl₃). The spectral data were in agreement with the literature.¹⁰

Meso-3,4-bis(3',4'-methylenedioxybenzyl)tetrathydrofuran (11a): ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 2.49–2.53 (4H, m, H-3, H-4, ArCH₂), 2.75–2.84 (2H, m, ArCH₂), 3.62 (2H, dd, J = 5.6, 8.2 Hz, 2 × H-2), 3.79 (2H, dd, J = 5.6, 8.2 Hz, 2 × H-2), 3.79 (2H, dd, J = 5.6, 8.2 Hz, 2 × H-2), 5.95 (4H, s, 2 × OCH₂O), 6.57–6.78 (6H, m, ArH); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 33.2 (C-3, C-4), 43.6 (C-7', C-7''), 71.9 (C-2, C-5), 100.8 (2 × OCH₂O), 108.2 (C-5', C-5''), 108.9 (C-2', C-2''), 121.5 (C-6', C-6''), 134.3 (C-1', C-1''), 145.8 (C-4', C-4''), 147.7 (C-3', C-3''); EI–MS (m/z, %): 340 (M⁺, 9), 204 (5), 187(2), 161 (5), 136 (100). HRMS calcd. for C₂₀H₂₄NO₅ (M+NH₄⁺): 358.1649. Found: 358.1648; [α]D16 0 (c 0.8, CHCl₃).

(+)-3-(3',4'-Dimethoxybenzyl)-4-(3'',4''-methyleneoxybenzyl)tetrathydrofuran (11b): ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 2.15–2.18 (2H, m, H-3, H-4), 2.45–2.59 (4H, m, 2 × ArCH₂), 3.46–3.54 (2H, m, 2 × H-2), 3.84 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 3.89–3.93 (2H, m, 2 × H-5), 5.91 (2H, s, OCH₂O), 6.51–6.78 (6H, m, ArH); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 39.0 (C-3), 39.1 (C-4), 46.5 (C-7'),
46.6 (C-7''), 55.7 (OCH3), 55.8 (OCH3), 73.2 (C-2), 73.3 (C-5), 100.8 (OCH2O), 108.0 (C-5'), 108.9 (C-5''), 111.1 (C-2'), 111.8 (C-2''), 120.5 (C-6'), 121.4 (C-6''), 132.9 (C-1'), 134.1 (C-1''), 145.8 (C-4'), 147.4 (C-4''), 147.6 (C-3'), 148.8 (C-3''); EI–MS (m/z, %): 356 (M +, 15), 220 (3), 177 (6), 151 (100); HRMS calcd. for C21H25O5 (M+H +): 357.1697. Found: 357.1695; [α]D16 +2.5 (c 0.8, CHCl3).

Meso-2,3-Bis(3',4'-methylenedioxybenzyl)-1,4-dimethoxybutane (12a): 1H-NMR (300 MHz, CDCl3, δ / ppm): 2.04–2.08 (2H, m, H-2, H-3), 2.51–2.69 (4H, m, 2 × ArCH2), 3.26 (6H, s, 2 × OCH3), 3.26–3.38 (4H, m, H-1, H-4), 5.92 (4H, s, 2 × OCH2O), 6.58–6.74 (6H, m, ArH); 13C-NMR (75 MHz, CDCl3, δ / ppm): 34.4 (C-2, C-3), 40.9 (C-7', C-7''), 58.6 (C-7', C-7''), 72.7 (C-1, C-4), 100.7 (2 × OCH2O), 107.9 (C-5', C-5''), 109.3 (C-2', C-2''), 121.8 (C-6', C-6''), 134.9 (C-1', C-1''), 145.6 (C-4', C-4''), 147.5 (C-3', C-3''); EI–MS, (m/z, %): 386 (M+, 5), 354 (5), 322 (3), 218 (11), 187 (21), 173 (12), 135 (100). HRMS calcd. for C22H27O6 (M+H +): 387.1802. Found: 387.1812; [α]D16 0 (c 0.4, CHCl3).

(+)-2-(3',4'-Dimethoxybenzyl)-3-(3'',4''-methylenedioxybenzyl)-1,4-dimethoxybutane (12b): 1H-NMR (300 MHz, CDCl3, δ / ppm): 2.07–2.11 (2H, m, H-2, H-3), 2.58–2.66 (4H, m, 2 × ArCH2), 3.29 (6H, s, 2 × OCH3), 3.26–3.38 (4H, m, ArCH2), 3.85 (3H, s, ArOCH3), 3.86 (3H, s, ArOCH3), 5.92 (4H, s, 2 × OCH2O), 6.58–6.74 (6H, m, ArH); 13C-NMR (75 MHz, CDCl3, δ / ppm): 34.8 (C-2), 34.9 (C-3), 40.7 (C-7'), 40.8 (C-7''), 55.6 (OCH3), 55.8 (OCH3), 58.7 (ArOCH3), 58.8 (ArOCH3), 72.4 (C-1), 72.6 (C-4), 100.7 (OCH2O), 107.8 (C-5'), 109.4 (C-5''), 110.9 (C-2'), 120.0 (C-2''), 121.0 (C-6'), 121.9 (C-6''), 133.5 (C-1'), 134.8 (C-1''), 145.5 (C-4'), 147.1 (C-4''), 147.4 (C-3'), 148.7 (C-3''); HRMS calcd. for C23H34NO6 (M+NH4+): 420.2381. Found: 420.2384; [α]D16 +2.7 (c 0.8, CHCl3).

Meso-machilin A (13a): m.p. 47–48 °C; 1H-NMR (200 MHz, CDCl3, δ / ppm): 0.83 (6H, d, J = 6.6 Hz, 2 × CH3), 1.72–1.76 (2H, m, H-2, H-3), 2.26 (2H, dd, J = 9.4, 13.4 Hz, ArCH2), 2.72 (2H, dd, J = 4.8, 13.4 Hz, ArCH2), 5.93 (4H, s, 2 × OCH2O), 6.58–6.76 (6H, m, ArH); 13C-NMR (100 MHz, CDCl3, δ / ppm): 16.1 (C-1, C-4), 39.0 (C-2, C-3), 39.3 (C-7', C-7''), 100.6 (2 × OCH2O), 107.9 (C-5', C-5''), 109.2 (C-2', C-2''), 121.8 (C-6', C-6''), 135.6 (C-1', C-1''), 145.4 (C-4', C-4''), 147.4 (C-3', C-3''); EI–MS, (m/z, %): 326 (M +, 3), 135(58), 123 (100); [α]D16 0 (c 0.4, CHCl3). The spectral data are in agreement with the literature.26

(–)-Isaururenin (13b): 1H-NMR (200 MHz, CDCl3, δ / ppm): 0.82 (6H, d, J = 6.6 Hz, CH3), 0.85 (3H, d, J = 6.6 Hz, CH3), 1.72–1.76 (2H, m, H-2, H-3), 2.26 (2H, dd, J = 9.4, 13.4 Hz, ArCH2), 2.72 (2H, dd, J = 4.8, 13.4 Hz, ArCH2), 5.93 (4H, s, 2 × OCH2O), 6.58–6.76 (6H, m, ArH); 13C-NMR (100 MHz, CDCl3, δ / ppm): 16.1 (C-1, C-4), 39.0 (C-2, C-3), 39.3 (C-7', C-7''), 100.6 (2 × OCH2O), 107.9 (C-5', C-5''), 109.2 (C-2', C-2''), 121.8 (C-6', C-6''), 135.6 (C-1', C-1''), 145.4 (C-4', C-4''), 147.4 (C-3', C-3''); EI–MS, (m/z, %): 326 (M +, 3), 135(58), 123 (100); [α]D16 0 (c 0.4, CHCl3). The spectral data are in agreement with the literature.26

Meso-nordihydroguaiaretic acid (14): m.p. 184–185 °C; 1H-NMR (300 MHz, acetone-d6, δ / ppm): 0.86 (6H, d, J = 6.3 Hz, 2 × CH3), 1.80–1.85
Bioactivity

**Antitumor activity:** NDGA 14, (−)-saururenin 10b and their analogues 8a, 8b, 9a, 9b, 10a, 11a, 11b, 12a, 12b, 13a and 13b were evaluated *in vitro* against HL-60 human leukemic cells, PC-3MIE8 human prostatic carcinoma cells, BGC-823 human stomach cancer cells and MDA-MB-435 human breast cancer cell, and the assays of the lignans have been previously published.27 The antitumor test indicated the inhibitory rates of tumor cell were less than 30 %, and the synthesized compounds showed no obvious antitumor activity.

**Anti-HIV activity:** The synthesized compounds were evaluated for their anti-HIV activity by determining their ability to inhibit the HIV Tat transactivation in *vitro*. The assay method was described previously.28 The compounds 8a, 8b, 9a, 9b, 10a, 10b, 11a, 11b, 12a, 12b, 13a, 13b and 14 were tested for their activities against the HIV and herpes viruses. The results showed that 9a has activity against HIV-RT (IC50 = 160 μg ml–1), while the other tested compounds exhibited no obvious activity.

**Anti-HSV activity:** The activity of the HSV-1 gene inhibitor was examined by measuring the extent of the process of Vero cells transfected with HSV-1 in *vitro*. The assays of the compounds NDGA, (−)-Saururenin and their analogues reported here were in agreement with those previously reported.29 The results are given in Table I. The compounds 10a, 12a, 12b, 13a and 14 showed activity against the herpes virus. The IC50 values of 10a and 12b were less than 100 μg ml–1, and compound 14 with an IC50 value of 4.12 μg ml–1 exhibited better bioactivity against the herpes virus. The results showed that the erythro-structure was good for antiviral activity; however, the compounds with tetrahydrofuran ring did not exhibit activity, which showed that the tetrahydrofuran ring appears suitable for lowering the cytotoxicity. On the other hand, the results showed that the data of SI was much lower. Thus, SI should be enhanced in a later study on structure-function relationships in order to increase the selectivity of the activity.

EXPERIMENTAL

The melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The optical rotation values were determined on a Perkin-Elmer 341 polarimeter. Infrared spectra were recorded on a Nicolet NEXUS 670 FT–IR. The 1H-NMR and 13C-NMR spectra were recorded on Brucker AM–400, Mercury Plus–300 and Avance–200 spectrometers. The mass spectra were recorded on a ZAB–HS spectrometer. The HRMS were obtained on a Bruker Daltonics APEXII47e spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh) and TLC inspections on silica gel GF254 plates.

**Diethyl 2-(3',4'-methylenedioxybenzylidene)succinate (2a)**

Piperonal (1a) (15.0 g, 100 mmol) and diethyl succinate (17.4 g, 100 mmol) were added to a solution of NaOEt (13.6 g, 200 mmol) in EtOH (200 ml). After refluxing for 4 h, the EtOH was removed. The residue was cooled and acidified with HCl (5 M). The mixture was extracted with AcOEt (3 × 80 ml). The AcOEt layer was then re-extracted with a saturated NaHCO3 solution (100 ml). The NaHCO3 extract was acidified with
HCl and the pH value was adjusted to 2. Then the obtained oily layer was again extracted with AcOEt (3 × 100 ml). The combined organic layer was dried and concentrated in vacuo. This residue was then added to a mixture of EtOH (250 ml), benzene (100 ml), and H$_2$SO$_4$ (2 ml), then refluxed in a Dean Stark apparatus for 24 h. The mixture was concentrated in vacuo and extracted with AcOEt (200 ml), then washed with a saturated NaHCO$_3$ solution (3 × 50 ml). The extract was dried over MgSO$_4$ and concentrated in vacuo. Flash column chromatography of the residue afforded compound 2a as a yellow oil (28.2 g). Yield: 92%.

**Diethyl 2-3',4'-dimethoxybenzylidene)succinate (2b)**

Following the procedure described for the preparation of 2a but starting with veratraldehyde (1b) (16.6 g, 100 mmol), compound 2b was obtained as a yellow oil (29.6 g). Yield: 92%.

2-(3',4'-methylenedioxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinate (3a)

To a well-stirred solution of 2a (24.5 g, 80 mmol) in THF (100 ml) was added dropwise a solution of LDA (80 mmol, 2 M) in THF at –78 °C under a N$_2$ atmosphere. The mixture was stirred at this temperature for 20 min, then 3,4-methylenedioxybenzyl bromide (17.2 g, 80 mmol) in THF (50 ml) was added. The mixture was stirred at –78 °C for 2 h. The mixture was quenched with a saturated NH$_4$Cl solution (100 ml). After warming to room temperature, the mixture was extracted with CH$_2$Cl$_2$ (3 × 80 ml) and the organic layer was dried over MgSO$_4$ and concentrated in vacuo. Flash chromatography of the residue over silica gel gave compound 3a as white crystals (31.6 g). Yield: 90%.

**Diethyl-2-(3',4'-dimethoxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinate (3b)**

Following the procedure described for the preparation of 3a but starting with 2b (25.8 g, 80 mmol), compound 3b was obtained as a yellowish oil (31.7 g). Yield: 87%.

(–)-2-(3',4'-methylenedioxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinic acid (4a)

Diester 3a (26.4 g, 60 mmol) was added to a 20 % aqueous solution of NaOH (250 ml) and refluxed for 3 h. After cooling to room temperature, the mixture was washed with EtOAc (3 × 30 ml). After decolorizing with active carbon, the mixture was acidified with HCl (2 M) whereby white solids were obtained. The crude product was crystallized from HOAc to give the (±)-diacid 4a. The (±)-diacid 4a and (–)-quinine (38.9 g, 120 mmol) in ethanol (120 ml) were refluxed for 1 h. The reaction mixture was allowed to cool slowly to room temperature, whereby fine white crystals were obtained. After two recrystallizations from ethanol, the solid was added to a solution of HCl (2 M, 100 ml) and stirred for 1 h. The mixture was extracted with EtOAc (3 × 80 ml) and the extract was dried over MgSO$_4$ and the solvent evaporated. The white solid was recrystallized from EtOAc to yield the (–)-diacid 4a as white crystals (10.1 g). Yield: 44 %.

The white solids obtained by concentrating the mother liquors were recrystallized twice from methanol and water to yield the (–)-diacid 4a' as white crystals (9.0 g). Yield: 39%.

(--)-2-(3',4'-Dimethoxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinic acid (4b)

Following the procedure described for the preparation of 4a but starting with the diester 3b (27.4 g, 60 mmol), the (–)-diacid 4b was obtained as white crystals (10.8 g). Yield: 45%.

(–)-Dihydrocubebin (6a) and meso-2,3-Bis(3',4'-methylenedioxybenzyl)butane-1,4-diol (7a)

To 151 ml of a mixture of EtOH : benzene : H$_2$SO$_4$ (100 : 50 : 1) was added 4a (7.7 g, 20 mmol). The mixture was refluxed in a Dean Stark apparatus for 36 h to remove the water. The reaction mixture was concentrated in vacuo, extracted with EtOAc (100 ml) and then neutralized with a saturated NaHCO$_3$ solution (3 × 30 ml). The extract was dried over MgSO$_4$ and concentrated in vacuo. Flash column chromatography of the residue gave the (–)-diester 5a as a colorless oil (8.0 g). Yield: 91%.

(–)-Dihydrocubebin (6a) and meso-2,3-Bis(3',4'-methylenedioxybenzyl)butane-1,4-diol (7a)
The (–)-diester 5a (7.1 g, 16 mmol) in ethyl acetate (200 ml) was stirred under a hydrogen atmosphere for 12 h in the presence of 10 % Pd/C (0.7 g). The reaction mixture was filtered through a pad of Celite and the solvent was removed in vacuo to give a white solid. The solid was dissolved in dry THF (80 ml) and added to a stirred suspension of LiAlH₄ (1.4 g, 36 mmol). The mixture was stirred for 10 h. Then the reaction was quenched by ice water and filtered. The filtrate was dried over MgSO₄ and concentrated in vacuo. Flash column chromatography of the residue gave threo-(–)-6a (2.7 g, yield: 47 %) as white crystals and erythro-7a (2.6 g, yield: 46 %) as a colorless oil.

(–)-Dihydro-3',4'-dimethoxy-3'',4''-demethylenedioxycubebin (6b) and (–)-2,3-desmethoxy seco-isolintetralin (7b)

Following the procedure described for the preparation of 6a and 7a but starting with the diester 5b (7.3 g, 16 mmol), 6b (2.6 g, yield: 44 %) and 7b (2.9 g, yield: 48 %) were obtained as colorless oils.

(–)-Dehydroxycubebin (8a)

To a solution of (–)-diol 6a (0.36 g, 1 mmol) and pyridine (0.08 g, 1 mmol) in CH₂Cl₂ (25 ml) was added TsCl (0.19 g, 1 mmol) in CH₂Cl₂ (20 ml) at room temperature. The mixture was stirred for 24 h, quenched with HCl (2 M) and extracted with CH₂Cl₂ (3 × 20 ml). The organic layer was dried over MgSO₄ and concentrated in vacuo. Flash column chromatography of the residue gave (–)-dehydroxycubebin (8a) as a colorless oil (0.26 g). Yield: 76 %.

(–)-3-(3',4'-Dimethoxybenzyl)-4-(3'',4''-methylenedioxybenzyl)tetrahydrofuran (8b)

Following the procedure described for the preparation of (–)-dehydroxycubebin (8a) but starting with 6b (0.37 g, 1 mmol), compound 8b was obtained as a colorless oil (0.27 g). Yield: 75 %.

(+)-2,3-Bis(3',4'-methylenedioxybenzyl)butane-1,4-dimethoxybutane (9a)

To a mixture of NaH (1 mmol) and 6a (0.36 g, 1 mmol) in THF (30 ml) was added CH₃I (2 mmol). The mixture was stirred for 7 h at room temperature, quenched with a saturated NH₄Cl solution (20 ml) and then extracted with CH₂Cl₂ (3 × 20 ml). The organic layer was washed with saturated NaCl solution (20 ml) and then concentrated in vacuo. Flash column chromatography of the residue gave 9a as a colorless oil (0.33 g). Yield: 85 %.

(+)-2-(3',4'-Dimethoxybenzyl)-3-(3'',4''-methylenedioxybenzyl)-1,4-dimethoxybutane (9b)

Following the procedure described for the preparation of 9a but starting with 6b (0.37 g, 1 mmol), compound 9b was obtained as a colorless oil (0.35 g). Yield: 88 %.

(–)-Austrobailignan-5 (10a)

To a solution of (–)-diol 6a (0.72 g, 2 mmol) in pyridine (2.5 ml) was added TsCl (0.76 g, 4 mmol) at 0 °C. The mixture was stirred at this temperature for 4 h, acidified with HCl (2 M, 20 ml) and extracted with EtOAc (3 × 20 ml). The organic layer was washed with a saturated NaCl solution (20 ml), dried over MgSO₄ and concentrated in vacuo. Flash column chromatography of the residue gave 10a as white crystals (0.56 g). Yield: 86 %.

(–)-Saururenin (10b)

Following the procedure described for the preparation of 10a but starting with the diester 6b (0.75 g, 2 mmol), compound 10b was obtained as a colorless oil (0.6 g). Yield: 87 %.

Meso-3,4-bis(3',4'-methylenedioxybenzyl)tetrahydrofuran (11a)

Following the procedure described for the preparation of 8a, compound 7a (0.36 g, 1 mmol) was used as the starting material to give compound 11a as a colorless oil (0.25 g). Yield: 74 %.

(+)-3-(3',4'-Dimethoxybenzyl)-4-(3'',4''-methylenedioxybenzyl)tetrahydrofuran (11b)

Following the procedure described for the preparation of 8a but starting with 7b (0.37 g, 1 mmol), compound 11b was obtained as a colorless oil (0.26 g). Yield: 72 %.

Meso-2,3-bis(3',4'-methylenedioxybenzyl)-1,4-dimethoxybutane (12a)

Following the procedure described for the preparation of 9a but starting with 7a (0.36 g, 1 mmol), compound 12a was obtained as a colorless oil (0.32 g). Yield: 82 %.

(+)-2-(3',4'-Dimethoxybenzyl)-3-(3'',4''-methylenedioxybenzyl)-1,4-dimethoxybutane (12b)

Following the procedure described for the preparation of 9a but starting with 7b (0.37 g, 1 mmol), compound 12b was obtained as a colorless oil (0.34 g). Yield: 85 %.

Meso-machilin A (13a)
Following the procedure described for the preparation of 10a, compound 7a (1.07 g, 3 mmol) was used as starting material to give meso-machilin A (4) as white crystals (0.87 g). Yield: 89 %.

(–)-Isaururenin (13b)

Following the procedure described for the preparation of 10a but starting with 7b (0.75 g, 2 mmol), compound 13b was obtained as a colorless oil (0.55 g). Yield: 81 %.

Meso-nordihydroguaiaretic acid (14)

Compound 13a (0.65 g, 2 mmol) was dissolved in dry CCl4 (50 ml), PCl5 (2.50 g, 12 mmol) was then added. The mixture was refluxed for 10 h under a nitrogen atmosphere. The amber-colored solution was concentrated in vacuo and then ice water (15 ml) was added slowly into the residue and refluxed for 5 h under a nitrogen atmosphere. A white solid appeared slowly in the solution, which was collected, washed with water and crystallized from ethanol to give meso-nordihydroguaiaretic acid (14) as white crystals (0.51 g). Yield: 85 %.

CONCLUSIONS

In summary, an efficient chiral synthetic method was developed to give NDGA, (–)-saururenin and their analogues. With cheap materials, short experimental procedures, mild conditions and simple operations, the route will exhibit more potential value in the future.

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REFERENCES
TABLE I Anti-herpes virus activity of some of the synthesized compounds

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1) Acyclovir
SCHEME CAPTIONS

Scheme 1. Synthesis route of the compounds 2–7. The starting materials were piperonal (1a) and veratraldehyde (1b). Condensation of 1a or 1b with diethyl succinate in EtONa/EtOH solution afforded the benzyldiene half-ester, which was followed by esterification to produce the diester 2a or 2b. Treatment of 2a or 2b in THF with LDA and 3, 4-methylenedioxybenzyl bromide at –78 °C afforded the diester 3a or 3b. Then compound 3a or 3b was hydrolyzed to form the diacid. At this stage, the diacids were resolved via the quinine salt. The quinine salt of diacid (–)-4a or (–)-4b crystallized first. Concentration of the mother liquors gave a solid, which yielded the quinine salt of (+)-4a’ or (+)-4b’. The diacid 4a or 4b was esterified to produce diester (–)-5a or (–)-5b. The diester 5a or 5b was hydrogenated under an H2 atmosphere, followed by reduction with LiAlH4 in THF to produce a readily separable mixture (approximately 1:1) of diols threo-(–)-6a and erythro-7a or threo-(–)-6b and erythro-7b.

Scheme 2. Synthesis route of the compounds 8–10. Reaction of diol threo-(–)-6a or threo-(–)-6b with an equimolar amount of TsCl in dilute solution at room temperature gave the corresponding 8a and 8b, while diol threo-(–)-6a or threo-(–)-6b with TsCl in concentrated solution at 0 °C gave the ditoluenesulfonyl ester, which were reduced with LiAlH4 in THF to provide 10a or 10b.

Scheme 3. Synthesis route of the compounds 11–14. Etherification of 6a or 6b gave the compounds 9a or 9b. Compounds 11a, 11b, 12a, 12b, 13a and 13b were prepared similarly. Compound 13a was refluxed with PCl5 in anhydrous CCl4, followed by hydrolysis of the resulting dichloromethylene derivative with water to provide meso-nordihydroguaiaretic acid (14).
Scheme 1:
Scheme 2:

1) TsCl, pyridine, 0°C
2) THF, reflux

a: $R^1, R^2$: OCH$_2$O
b: $R^1 = R^2$: OCH$_3$
Scheme 3