Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *75* (10) 1325–1335 (2010)
JSCS–4055
UDC 542.913+57–188:547.474.4
Original scientific paper

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

YAMU XIA[1]*, YUANYUAN ZHANG[1], WEI WANG[1], YINING DING[1] and RUI HE[2]

[1]*College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042 and* [2]*College of Mathematics and Physics, Qingdao University of Science and Technology, Qingdao 266042, P. R. China*

(Received 10 April, revised 11 June 2010)

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, neurotrophic, 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

* Corresponding author. E-mail: xiaym@qust.edu.cn
doi: 10.2298/JSC090410108X

treatment for actinic keratosis (Actinex, Chemex Pharmaceuticals, Denver, CO).[5,6] NDGA is a known antioxidant, a lipoxygenase 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.[13] NDGA, (–)-saururenin and their analogues have also been shown to have cancer chemopreventive properties.[14–16]

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.[17] Son *et al.* developed a modified procedure for the synthesis of NDGA and related lignans.[18] 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.[19] Rao *et al.* described the synthesis of analogues of (–)-saururenin from *Saururus cernuus*, together with (–)-austrobailignan-5 by regioselective cleavage of the methylenedioxyphenyl groups.[20] A synthetic route to NDGA and machilin A involving two Stobbe condensations to give the skeleton of lignan was reported.[21]

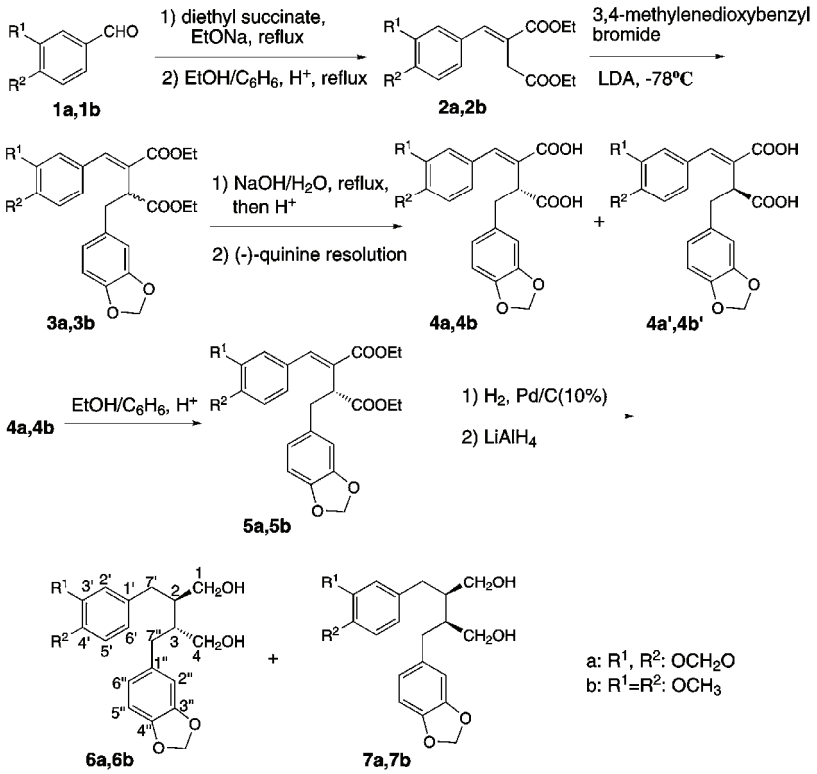
In this paper, an efficient approach for the chiral synthesis of NDGA, (–)-saururenin and their analogues is presented. By this method, 13 lignans were synthesized, among them, seven lignans were natural products and moreover three of the seven natural products were synthesized for the first time. The 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

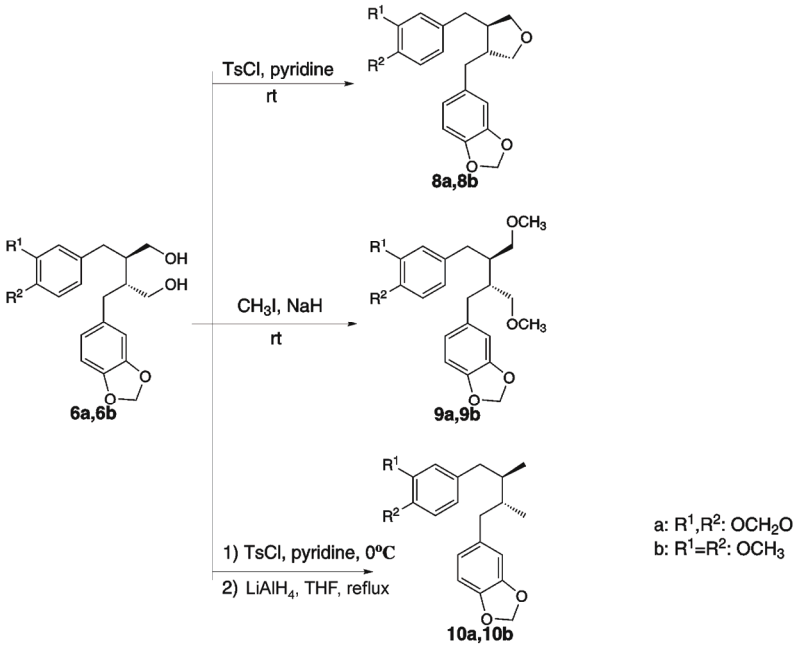
The starting materials were piperonal **1a** and veratraldehyde **1b**. Condensation of **1a** or **1b** with diethyl succinate in EtONa/EtOH solution afforded the benzylidene half-ester, which was followed by esterification to produce the diester **2a** or **2b**. Treatment of **2a** or **2b** in THF 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 H_2 atmosphere, following by reduction with $LiAlH_4$ 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. 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 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 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 H_2 atmosphere, followed by reduction with $LiAlH_4$ in THF to produce a readily separable mixture (approximately 1:1) of diols *threo*-(–)-**6a** and *erythro*-**7a** or *threo*-(–)-**6b** and *erythro*-(–)-**7b**.

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 ditoluenesulfonyl esters, which were reduced with $LiAlH_4$ in THF to provide **10a** and **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 PCl_5 in anhydrous CCl_4, followed by hydrolysis of the resulting dichloromethylene derivative with water to provide *meso*-nordihydroguaiaretic acid **14** (Schemes 2 and 3).

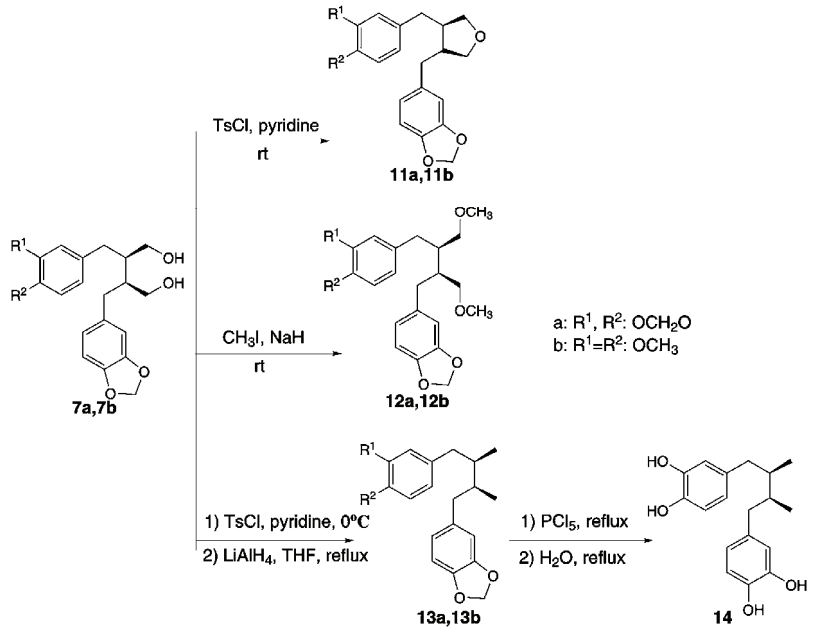


Scheme 2. Synthesis route of the compounds **8**–**10**. Reaction of diol *threo*-(–)-**6a** or *threo*-(–)-**6b** with an equimolar amount of TsCl in dilute solution at room temperature gave the corresponding **8a** and **8b**, while diol *threo*-(–)-**6a** or *threo*-(–)-**6b** with TsCl in concentrated solution at 0 °C gave the ditoluenesulfonyl esters, which were reduced with $LiAlH_4$ in THF to provide **10a** or **10b**. Etherification of **6a** or **6b** gave the compounds **9a** or **9b**.

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.

Spectroscopic data of the synthesized compounds

The spectral data (Supplementary material) are in agreement with those already reported.[19]



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**).

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 (IC_{50} = 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.

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

Sample code	TC_{50} / μg ml^{-1}	IC_{50} / μg ml^{-1}	*SI*
10a	143.17	68.71	2.08
12a	231.12	143.10	1.61
12b	192.45	53.42	3.6
13a	111.11	111.10	1.0
14	12.35	4.12	3.0
Acyclovir	>250	1.66	>150.6

The compounds **10a**, **12a**, **12b**, **13a** and **14** showed activity against the herpes virus. The IC_{50} values of **10a** and **12b** were less than 100 μg ml^{-1}, and compound **14** with an IC_{50} 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 ^{1}H-NMR and ^{13}C-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 EtOAc (3×80 ml). The EtOAc layer was then re-extracted with a saturated $NaHCO_3$ solution (100 ml). The $NaHCO_3$ 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_2SO_4 (2 ml), then refluxed in a Dean Stark apparatus for 24 h. The mixture was concentrated *in vacuo* and extracted with EtOAc (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 %.

*Diethyl 2-(3,4-methylenedioxybenzyl)-3-(3,4-methylenedioxybenzylidene)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_4Cl solution (100 ml). After warming to room temperature, the mixture was extracted with CH_2Cl_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-Methylenedioxybenzyl)-3-(3,4-methylenedioxybenzylidene)succi-nic 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%.

The (+)-diacid **4b'** was obtained as white crystals (9.2 g). Yield: 38 %.

*(–)-Diethyl 2-(3,4-methylenedioxybenzyl)-3-(3,4-methylenedioxybenzylidene)succinate (**5a**)*

To 151 ml of a mixture of EtOH:benzene:H_2SO_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 %.

*(–)-Diethyl 2-(3,4-methylenedioxybenzyl)-3-(3,4-dimethoxybenzylidene)succinate (**5b**)*

Following the procedure described for the preparation of **5a** but starting with the diester **4b** (8.0 g, 20 mmol), the diacid **5b** was obtained as a colorless oil (8.2 g). Yield: 90 %.

*(–)-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 $LiAlH_4$ (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 $MgSO_4$ 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.

*(2*R*,3*R*)-2-(3,4-Dimethoxybenzyl)-3-(3,4-methylenedioxybenzyl)-1,4-butanediol (**6b**) and (2*R*,3*S*)-2-(3,4-Dimethoxybenzyl)-3-(3,4-methylenedioxybenzyl)-1,4-butanediol (**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 CH_2Cl_2 (25 ml) was added TsCl (0.19 g, 1 mmol) in CH_2Cl_2 (20 ml) at room temperature. The mixture was stirred for 24 h, quenched with HCl (2 M) and extracted with CH_2Cl_2 (3×20 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromategraphy of the residue gave (–)-dehydroxycubebin **(8a)** as a colorless oil (0.26 g). Yield: 76 %.

*(–)-5-{[(3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-tetrahydro-3-furanyl]methyl}-1,3-benzodioxole (**8b**)*

Following the procedure described for the preparation of (–)-dehydroxycubebin (**8a**) but starting with **6b** (0.37 g, 1.0 mmol), compound **8b** was obtained as a colorless oil (0.27 g). Yield: 75 %.

*(+)-5.5'-[(2*R*,3*R*)-2,3-Bis(methoxymethyl)-1,4-butanediyl]bis(1,3-dioxole) (**9a**)*

To a mixture of NaH (1 mmol) and **6a** (0.36g, 1 mmol) in THF (30 ml) was added CH_3I (2 mmol). The mixture was stirred for 7 h at room temperature, quenched with a saturated NH_4Cl solution (20 ml) and then extracted with CH_2Cl_2 (3×20 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography of the residue gave **9a** as a colorless oil (0.33 g). Yield: 85 %;

*(+)-5-[(2-(2*R*,3*R*)-4-(3,4-Dimethoxybenzyl)-2,3-bis(methoxymethyl)-butyl]-1,3-benzodioxole (**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, 2.0 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 $MgSO_4$ and concentrated *in vacuo* to give the crude ditoluenesulfonyl ester. A mixture of this ditoluenesulfonyl ester and $LiAlH_4$ (0.20 g, 5.0 mmol) in dry THF (30 ml) was refluxed for 6 h, the mixture quenched with ice-water, filtered and then 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-*5,5'-[(Tetrahydro-3,4-furandiyl)bis(methylene)]bis(1,3-benzodioxole) (**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 %.

*(+)-5-{[(3*S*,4*R*)-4-[(3,4-Dimethoxyphenyl)methyl]tetrahydro-3-furanyl]methyl}-1,3--benzodioxole (**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-*5,5'-[Bis(methoxymethyl)-1,4-butanediyl]bis(1,3-benzodioxole) (**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 %.

*(+)-5-{[(3*S*,4*R*)-4-[(3,4-Dimethoxyphenyl)-2,3-bis(methoxymetyl)butyl]-1,3-benzodioxole (**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 %.

*(–)-Isosaururenin (**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 CCl_4 (50 ml), PCl_5 (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.

SUPPLEMENTARY MATERIAL

Spectroscopic data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgements. This work was financially supported by the foundation of State Key Laboratory of Applied Organic Chemistry of China (No. 200708) and the National Natural

Science Foundation of Shandong (No. 2006Q02). Peking University School of Pharmaceutical Sciences is kindly acknowledged for evaluation of our compounds in their human tumor cell line screening panel and The National Center for Drug Screening is acknowledged for the anti-HIV and anti-HSV assay of the compounds.

ИЗВОД

СИНТЕЗА И БИОЛОШКА АКТИВНОСТ *erythro*-НОРДИХИДРОГВАЈАРЕТИЧНЕ КИСЕЛИНЕ, *threo*-САУРУРЕНИНА И ЊИХОВИХ АНАЛОГА

YAMU XIA[1], YUANYUAN ZHANG[1], WEI WANG[1], YINING DING[1] и RUI HE[2]

[1]*College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042 и* [2]*College of Mathematics and Physics, Qingdao University of Science and Technology, Qingdao 266042, P. R. China*

У раду је дат детаљан приказ тоталне синтезе *erythro*-нордихидрогвајаретичне киселине, *threo*-(–)-саууренина и њихових аналога. Општа синтетичка стратегија која је примењена заснива се на Stobbe-овој реакцији, алкиловању у циљу изградње лигнанског скелета и раздвајању *threo*- и *erythro*-изомера. Синтеза 13 лигнана је остварена у 8–9 синтетичких фаза коришћењем једноставних ароматичних прекурсора. Од добијених лигнана седам су природни производи од којих је за три урађена прва синтеза у овом раду. Испитан је утицај свих добијених лигнана на HIV Tat трансактивацију у хуманим епителним ћелијама, HSV-1 ген и ћелије хумане леукемије, рака јетре, простате, желуца и дојке. Резултати биолошких испитивања указују да један производ показује активност према HIV-у а пет једињења поседују анти-HSV активност.

(Примљено 10. априла, ревидирано 11. јуна 2010)

REFERENCES

1. R. D. Howarth, *Annu. Rep. Prog. Chem.* **33** (1936) 266
2. M. Saleem, H. J. Kim, M. S. Ali, Y. S. Lee, *Nat. Prod. Rep.* **22** (2005) 696
3. N. Li, J. Wu, T. Hasegawa, J. Sakai, L. Bai, L. Wang, S. Kakuta, Y. Furuya, H. Ogura, T. Kataoka, A. Tomida, T. M. Tsuruo, *J. Nat. Prod.* **70** (2007) 544
4. G. Zhang, N. Li, Y. Wang, Y. Zheng, Z. Zhang, M. Wang, *J. Nat. Prod.* **70** (2007) 662
5. S. Arteaga, A. Andrade-Cetto, R. Cardenas, *J. Ethnopharmacol.* **98** (2005) 231
6. J. D. Lambert, R. T. Dorr, B. N. Timmermann, *Pharm. Biol.* **42** (2004) 149
7. J. L. Billinsky, E. S. Krol, *J. Nat. Prod.* **71** (2008) 1612
8. W. Tong, X. Ding, T. E. Adrian, *Biochem. Biophys. Res. Commun.* **296** (2002) 942
9. R. Agarwal, Z. Y. Wang, D. P. Bik, H. Mukhtar, *Drug Metab. Dispos.* **19** (1991) 620
10. K. V. Rao, N. S. P. Rao, *J. Nat. Prod.* **53** (1990) 212
11. K. V. Rao, F. M. Alvarez, *J. Nat. Prod.* **45** (1982) 393
12. J. R. Hwu, W. N. Tseng, J. Gnabre, P. Giza, R. C. C. Huang, *J. Med. Chem.* **41** (1998) 2994
13. H. S. Cheng, L. Teng, J. N. Li, R. Park, D. E. Mold, J. Gnabre, J. R. Hwu, W. N. Tseng, R. C. C. Huang, *J. Med. Chem.* **41** (1998) 3001
14. S. Whitman, M. Gezginci, B. N. Timmermann, T. R. Holman, *J. Med. Chem.* **45** (2002) 2659
15. T. W. Moody, J. Leyton, A. Martinez, S. Hong, A. Mallkinson, J. L. Mulshine, *Exp. Lung Res.* **24** (1998) 617
16. J. Chang, J. Reiner, J. X. Xie, *Chem. Rev.* **105** (2005) 4581

17. S. V. Lieberman, G. P. Mueller, E. T. Stiller, *J. Am. Chem. Soc.* **69** (1947) 1540
18. J. K. Son, S. H. Lee, L. Nagarapu, Y. Jahng, *Bull. Korean Chem. Soc.* **26** (2005) 1117
19. M. H. Gezginci, B. N. Timmermann, *Tetrahedron Lett.* **42** (2001) 6083
20. K. V. Rao, S. K. Chattopadhyay, *J. Org. Chem.* **55** (1990) 1427
21. Y. M. Xia, Q. Wang, Y. N. Din, F. K. Yang, X. P. Cao, *Chin. J. Org. Chem.* **28** (2008) 1040
22. A. S. R. Anjaneyulu, P. A. Ramaiah, L. R. Row, R. Venkateswarlu, A. Pelter, R. S. Ward, *Tetrahedron* **37** (1981) 3641
23. M. J. Kato, M. Yoshida, O. R. Gottlieb, *Phytochemistry* **31** (1992) 283
24. P. Satyanarayana, S. Venkateswarlu, *Tetrahedron* **47** (1991) 8931
25. S. T. Murphy, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **28** (1975) 81
26. H. Shimomura, Y. Sashida, M. Oohara, *Phytochemistry* **26** (1987) 1513
27. J. L. Wu, N. Li, T. Hasegawa, J. Sakai, S. Kakuta, W. Tang, S. Oka, M. Kiuchi, H. Ogura, T. Kataoka, A. Tomida, T. Tsuruo, M. Ando, *J. Nat. Prod.* **68** (2005) 1656
28. G. T. Tan, J. M. Pezzuto, A. D. Kinghorn, S. H. Hughes, *J. Nat. Prod.* **54** (1991) 143
29. R. Dulbeccok, *Proc. Natl. Acad. Sci. U.S.A.* **38** (1952) 747.