Synthesis, anti-virus and anti-tumour activities of dibenzylbutyrolactone lignans and their analogues

Yamu Xia*, Jia You, Yuanyuan Zhang and Zhongliang Su

College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042, P.R. China

An efficient synthesis of dibenzylbutyrolactone lignans and their analogues has been developed. Based on a Stobbe condensation of piperonal or veratraldehyde with diethylsuccinate and alkylation with 3,4-methylenedioxybenzyl bromide to give the skeleton of the lignan. The (±)-diacid was resolved with quinine and the functional groups were transformed to obtain three benzylbutyrolactone lignans and seven analogues. Four natural lignans were prepared by this method, and five lignans were synthesised for the first time. The synthesised compounds were evaluated for anti-HIV, anti-HSV, and anti-tumour activities. Results showed that the dibenzylbutyrolactone lignans and their analogues were inactive against HIV Tat transactivation and HSV-1 *in vitro*, but some compounds displayed significant activity against MDA-MB-435 human breast cancer cell.

Keywords: dibenzylbutyrolactone lignan, biological activity

Lignans are a class of secondary plant metabolites produced by the oxidative dimerisation of two phenylpropanoid units. They are widely distributed in the plant kingdom. Lignans are found in all parts of the plants, including the roots, stems, leaves, fruit, and seeds and they exhibit a wide range of biological activities.[1-3] Different families of lignans include dibenzylbutanes, dibenzocyclooctadienes and a diverse family of dibenzylbutyrolactone.[4]

Many dibenzylbutyrolactone lignans and their analogues have interesting antitubercular, anti-inflammatory and insecticidal activities.[5-7] More particularly some, such as retrojusticidin B, exhibit differential inhibition of HIV-1 RT and human DNA polymerase-α.[8] Some display strong activity as potent anti-HIV agents.[9,10] Other dibenzylbutyrolactone lignans and their analogues have been shown to have a beneficial anti-tumour effect throughout the early promotional phase of carcinogenesis, and useful drugs have been developed from the well-known lignan podophyllotoxin for the treatment of cancer and other ailments. Their activities are greatly reduced when the lignan skeleton or ester and lactone groups are not present.[11-13]

The synthesis of dibenzylbutyrolactone lignans and their analogues continue to play a central role in the asymmetric synthesis of lignans. Fischer has reported total syntheses of (–)-arctigenin, (–)-matairesinol and (–)-α-conidendrin, by way of a highly stereoselective domino radical sequence.[14] Ferrie *et al*. have developed a short synthetic route of lactonic lignans. This method exploited a three-component coupling strategy using a novel Lewis acid catalysed ring-opening/cyclisation reaction of 2-methoxytetrahydrofuran derivatives leading to γ–butyrolactones as a key step.[15] The asymmetric synthesis of a series of (7'*S*,8*R*,8'*R*)-7'-hydroxylignano-9,9'-lactones was described by Raffaelli, among them the mammalian lignan (7'*S*)-hydroxyenterolactone and (7'*S*)-parabenzlactone, allowing the stereochemistry of natural occurring (–)-parabenzlactone to be re-assigned.[16]

In order to elucidate further the structural specificity of dibenzylbutyrolactone lignans and analogues underlying HIV, HSV and tumour cell suppression, we now describe an efficient approach to the asymmetric synthesis of dibenzylbutyrolactone lignans and analogues. Furthermore, we report the first synthesis of five lignans. The effect of 10 dibenzylbutyrolactone lignans and analogues in their pure form was examined on HIV Tat transactivation in human epithelial cells, HSV-1 gene and human leukaemia, liver, prostate, stomach, and breast cancer cell.

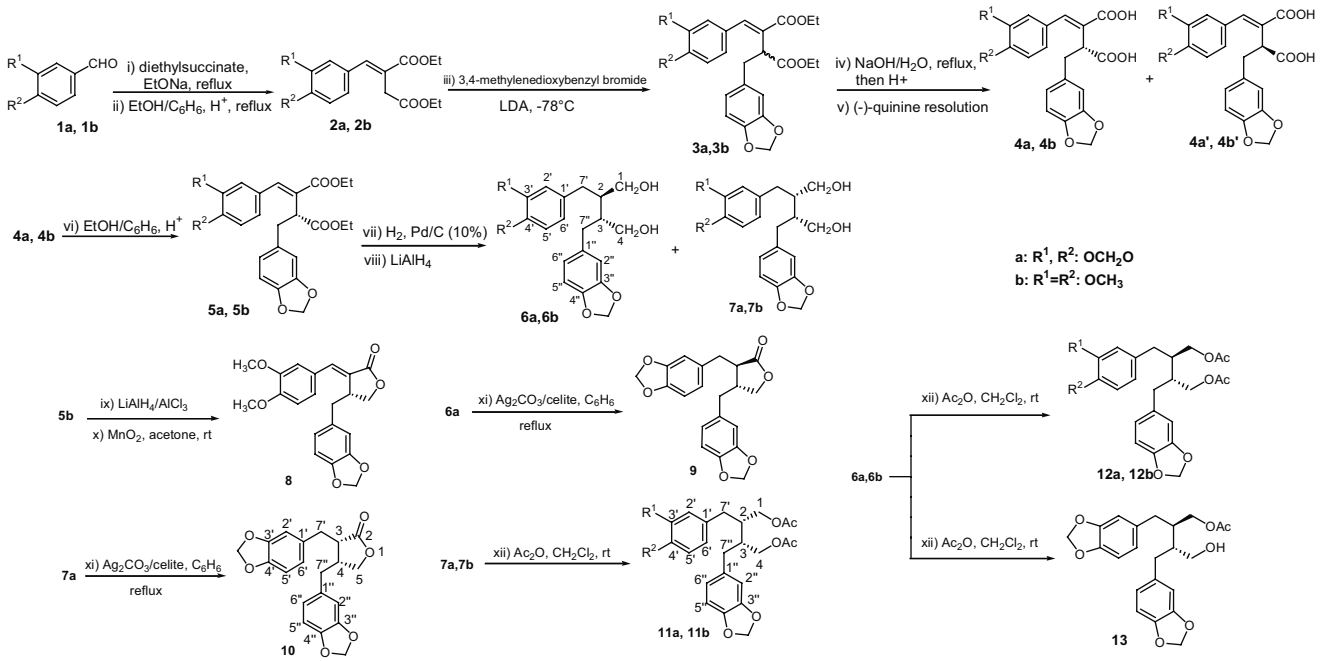
* Correspondent. E-mail: xiaym@qust.edu.cn

Results and discussion

Synthesis of compounds

In order to construct the skeleton of dibenzylbutyrolactone lignans and their analogues, we report a route involving a Stobbe condensation and alkylation. As shown in Scheme 1, we first used cheap piperonal (heliotropin) (**1a**) and veratraldehyde (**1b**) as raw materials, to obtain the *trans*-(*E*)-unsaturated diester **2a** or **2b** by a Stobbe condensation and esterification reaction. The *trans*-(*E*)-configuration of the olefinic double bond was evident from the appearance of the deshielded vinylic proton at δ7.76/7.84 in the ^{1}H NMR spectrum.[17,18] When ester **2a** or **2b** was treated with LDA at –78 °C, it was alkylated with 3,4-methylenedioxybenzyl bromide to produce the compounds **3a** or **3b**. Saponification of **3a** or **3b** gave the diacid **4a** or **4b**. Then, the diacids were resolved via their quinine salts. The quinine salt of diacid (–)-**4a** or (–)-**4b** crystallised first. Concentration of the mother liquors gave a solid which yielded the quinine salt of (+)-diacid **4a'** or **4b'**. The diacid (–)-**4a** or (–)-**4b** was esterified with EtOH to produce diester (–)-**5a** or (–)-**5b**. Treatment of (–)-**5b** with $LiAlH_4/AlCl_3$ afforded the unsaturated diol, followed by oxidation with MnO_2 to give (–)-Kaerophyllin **8**. Compounds (–)-**5a** or (–)-**5b** were hydrogenated using a 10% palladium on charcoal catalyst, following by reduction with $LiAlH_4$ in THF to produce a readily separable mixture (approximate 1 : 1) of the *threo*-(–)-**6a** and *erythro*-**7a** or *threo*-(–)-**6b** and *erythro*-**7b**. diols *Threo*-**6a** and **6b** had consistently larger Rf values than those of the corresponding *erythro*-**7a** and **7b**, and each pair was easily separated by flash column chromatography over silica gel. The absolute configuration of *threo*-(–)-**6a** and *erythro*-**7a** or *threo*-(–)-**6b** and *erythro*-**7b** were agreement with those reported in the literature. Subjecting the diol **6a** to Ag_2CO_3/celite oxidation afforded (–)-hinokinin **9** in 92% yield. Similarly, oxidation of the diol **7a** with Ag_2CO_3/celite produced (±)-isohinokinin **10** in 94% yield. Compounds (–)-**6a** and (–)-**6b** or **7a** and **7b** were allowed to react with excess Ac_2O, which after usual work-up gave the diacetate (–)-**12a** and (–)-**12b** or **11a** and **11b**. When (–)-**6a** reacted with equimolar Ac_2O, compound **13** was obtained.

In summary, we have developed an efficient stereoselective synthetic route to the dibenzylbutyrolactone lignans and their analogues. By this method, three dibenzylbutyrolactone lignans **8, 9** and **10** and seven analogues **5a**, **5b**, **11a**, **11b, 12a, 12b** and **13** were prepared. Compounds **8**, **9**, **10** and **12b** were natural products and their spectroscopic data were in agreement with those reported in the literature. Compounds **11a**, **11b**, **12a**, **12b** and **13** were synthesised for the first time.



Scheme 1 Synthetic route for the compounds **2–13.**

Biological activity

Inhibition of HIV Tat transactivation: The HIV Tat protein, a potent transactivator of HIV proviral transcription, is required for HIV replication. The synthetic compounds were evaluated for anti-HIV activity by determining their ability to inhibit the HIV Tat transactivation *in vitro*. The assay has been described previously.[19] This test for anti-HIV activity indicated the dibenzylbutyrolactone lignans and their analogues showed no obvious inhibition of HIV Tat transactivation *in vitro*.

Inhibition of HSV-1 gene promoter activity: The activity of the HSV-1 gene inhibitor was examined by measuring the extent of Vero cells transfected with HSV-1 *in vitro*. The assays for all the dibenzylbutyrolactone lignans and their analogues reported here were in agreement with the methods previously reported.[20] We examined the effect of the dibenzylbutyrolactone lignans and their analogues, and compared this effect with that of Acyclovir. Results showed that the dibenzylbutyrolactone lignans and their analogues were inactive against HSV-1 *in vitro.*

Inhibition of tumor cell: The assays of the some lignans containing the ester function have been previously published.[21] All dibenzylbutyrolactone lignans and their analogues reported here were tested in the same assay. A series of our dibenzylbutyrolactone lignans and related analogues were evaluated against HL-60 human leukemic cell, PC-3MIE8 human prostatic carcinoma cell, BGC-823 human stomach cancer cell, MDA-MB-435 human breast cancer cell. The results are shown in Table 1.

We observed that all of the compounds at 10^{-5}M, 10^{-6}M and 10^{-7}M concentrations inhibited HL-60 cell, PC-3MIE8 cell, BGC-823 cell and Bel-7402 cell lines to below 30%. The most interesting activities, however, were displayed against MDA-MB-435 human breast cancer cell. In a screen against MDA-MB-435 human breast cancer cell we observed that the pair of **11a**, **11b**, **12b** and **13** having an acetyl group possessed good activity. Furthermore, **11a** the **13** having two methylenedioxy units showed inhibition ratio above 55% at 10^{-5}M. Compounds **11a** and **13** were not regioisomers, and had a different configuration. Thus we concluded that the acetyl group and methyleneoxy unit significantly influenced the biological activity for dibenzylbutyrolactone lignans and related analogues.

Experimental

Melting points were measured on a Kofler apparatus and were uncorrected. Optical rotations were determined on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Nicolet NEXUS 670 FT−IR and Nicolet AVATAR 360 FT−IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AM−400 MHz, Mercury Plus−300 MHz and Avance–200 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS as internal standard. Mass spectra were recorded on a ZAB−HS spectrometer. HRMS were

Table 1 Anti-tumour activities of compounds

	HL-60 (inhibitory rate %)			PC-3MIE8 (inhibitory rate %)			BGC-823 (inhibitory rate %)			MDA-MB-435 (inhibitory rate %)		
	10^{-5}M	10^{-6}M	10^{-7}M	10^{-5}M	10^{-6}M	10^{-7}M	10^{-5}M	10^{-6}M	10^{-7}M	10^{-5}M	10^{-6}M	10^{-7}M
5a	–	–	–	14.3	–	–	14.2	4.2	4.2	–	–	–
5b	16.0	5.9	–	13.8	–	–	14.5	–	–	14.9	3.0	–
8	5.4	–	–	–	–	–	–	–	–	–	–	–
9	7.3	3.3	–	–	–	–	–	–	–	–	–	–
10	10.4	9.0	4.3	13.1	2.0	–	3.4	2.5	1.4	–	–	–
11a	1.8	1.9	–	3.4	–	–	–	–	–	**59.5**	**35.9**	–
11b	8.4	7.3	–	25.9	–	–	1.6	–	–	**30.8**	27.9	12.4
12a	8.2	7.4	14.0	6.6	–	–	–	–	–	–	–	–
12b	7.3	2.7	–	11.0	–	–	–	–	–	**36.1**	27.6	14.1
13	–	–	–	–	–	–	–	–	–	**55.9**	17.4	14.2

obtained on a Bruker Daltonics APEXII47e spectrometer. Elemental analysis was performed by an Elementar Vario EL analyser. Flash column chromatography was performed on silica gel (200–300 mesh) and TLC inspections on silica gel GF_{254} plates, unless noted specially below.

Diethyl 2-(3',4'-methylenedioxybenzylidene) succinate (**2a**): Piperonal **1a** (15.0 g, 100 mmol) and diethylsuccinate (17.4 g, 100 mmol) were added to a solution of NaOEt (13.6 g, 200 mmol) in EtOH (200 mL). After heating under reflux for 4 h, ethanol was removed. The residue was cooled and acidified with HCl (5 N). The mixture was extracted with EtOAc (3 × 80 mL). The EtOAc layer was then washed with a saturated solution of $NaHCO_3$ (100 mL). Acidification of the $NaHCO_3$ extract with HCl (2 N) provided an oily layer, which was again extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. This residue was then added to the mixture of EtOH (250 mL), benzene (100 mL), and H_2SO_4 (2 mL), then heated at reflux with a Dean and Stark apparatus for 24 h to remove water. The reaction mixture was concentrated *in vacuo* and extracted with EtOAc (200 mL), then washed with a $NaHCO_3$ saturated 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, 92%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.22 (t, *J* = 7.3 Hz, 3H), 1.29 (t, *J* = 7.3 Hz, 3H), 3.51 (s, 2H), 4.16 (q, *J* = 7.3 Hz, 2H), 4.27 (q, *J* = 7.3 Hz, 2H), 5.96 (s, 2H), 6.76−6.87 (m, 3H), 7.76 (s, 1H). Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.55; H, 5.78%. EI−MS (*m/z*,%): 306 (M^+, 70), 261 (20), 232 (34), 203 (52), 175 (59), 159 (100).

Diethyl 2-(3',4'-dimethoxybenzylidene) succinate (**2b**): Following the procedure described for the preparation of **2a**, and starting with the veratraldehyde **1b** (16.6 g, 100 mmol), compound **2b** was obtained as a yellow oil (29.6 g, 92%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.33 (t, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 3.58 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 4.21 (q, *J* = 7.3 Hz, 2H), 4.27 (q, *J* = 7.3 Hz, 2H), 6.86−7.00 (m, 3H), 7.84 (s, 1H). Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.21; H, 6.64%. EI−MS (*m/z*,%): 322 (M^+, 42), 276 (14), 249 (16), 175 (100).

Diethyl 2-(3',4'-methylenedioxybenzylidene)-3- (3'',4''-methylenedioxybenzyl)succinate (**3a**): A solution of LDA (80 mmol, 2 M in THF) in THF at −78 °C was added dropwise under nitrogen atmosphere to a well-stirred solution of compound **2a** (24.5 g, 80 mmol) in THF (100 mL). 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 NH_4Cl saturated 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 a white solid (31.6 g, 90%). M.p. 58–59 °C. IR (KBr, cm^{-1}) ν_{max}: 3410, 2981, 1736, 1490, 1246, 1039, 930, 809, 770. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.26 (t, *J* = 7.2 Hz, 3H, CH_3), 1.34 (t, *J* = 7.2 Hz, 3H, CH_3), 2.85 (dd, *J* = 10.0 Hz, *J* = 14.2 Hz, 1H, H-7''α), 3.34 (dd, *J* = 5.0 Hz, *J* = 14.2 Hz, 1H, H-7''β), 3.98 (dd, *J* = 5.0 Hz, *J* = 10.0 Hz, 1H, H-3), 4.15−4.32 (m, 4H, 2 × CH_2CH_3), 5.88 (s, 2H, OCH_2O), 5.97 (s, 2H, OCH_2O), 6.35−6.73 (m, 6H, ArH), 7.66 (s, 1H, H-7'). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.4 (2 × CH_2CH_3), 36.0 (C-3), 45.8 (C-7''), 61.2 (2 × OCH_2CH_3), 100.9 (OCH_2O), 101.4 (OCH_2O), 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). Anal. Calcd for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.21; H, 5.68%. HRMS Calcd for $C_{24}H_{25}O_8$ (M + H^+): 441.1544. Found: 441.1538. EI-MS (*m/z*,%): 440 (M^+, 4), 395 (1), 306 (5), 231 (40), 137 (100).

Diethyl 2-(3',4'-dimethoxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinate (**3b**): Following the procedure described for the preparation of **3a**, and starting with **2b** (25.8 g, 80 mmol), compound **3b** was obtained as a yellowish oil (31.7 g, 87%). IR (KBr, cm^{-1}) ν_{max}: 2958, 2839, 1741, 1517, 918, 810, 760. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.26 (t, *J* = 7.2 Hz, 3H, CH_3), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3), 2.91 (dd, *J* = 9.8 Hz, *J* = 14.2 Hz, 1H, H-7''α), 3.34 (dd, *J* = 5.0 Hz, *J* = 14.2 Hz, 1H, H-7''β), 3.78 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.10 (dd, *J* = 5.0 Hz, *J* = 9.8 Hz, 1H, H-3), 4.18 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 4.30 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 5.85 (s, 2H, OCH_2O), 6.35−6.80 (m, 6H, ArH), 7.71 (s, 1H, H-7'). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.1 (CH_2CH_3), 14.2 (CH_2CH_3), 35.7 (C-3), 45.5 (C-7''), 55.7 (OCH_3), 55.8 (OCH_3), 60.9 (2 × CH_2CH_3), 100.7 (OCH_2O), 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). Anal. Calcd for $C_{25}H_{28}O_8$: C, 65.78; H, 6.18. Found: C, 65.61; H, 6.29%. HRMS Calcd for $C_{25}H_{29}O_8$ (M + H^+): 457.1857. Found: 457.1856. EI−MS (*m/z*,%): 456 (M^+, 3), 411 (1), 382 (1), 322 (4), 247 (51), 137 (100).

(−)-2-(3',4'-Methylenedioxybenzylidene)-3-(3'',4''-methylenedioxybenzyl) succinic acid (**4a**): Diester **3a** (26.4 g, 60 mmol) was added to a solution of 20% aqueous NaOH (250 mL) and heated at reflux for 3 h. After cooling to room temperature, the mixture was washed with EtOAc (3 × 30 mL). After being discoloured with activated carbon, the mixture was acidified with HCl (2 N), and a white solid was obtained. The crude product was crystallised from HOAc to give the (±)-diacid **4a**. The (±)-diacid **4a** and (–)-quinine (38.9 g, 120 mmol) in ethanol (120 mL) was heated at reflux for 1 h. The reaction mixture was allowed to cool to room temperature slowly and fine white crystals were obtained. After two recrystallisations from ethanol it was added to a solution of HCl (2 N, 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 evaporated. The white solids were recrystallised in EtOAc to yield the (–)-diacid **4a** as white crystals (10.1 g, 44%). M.p. 98–99 °C. $[\alpha]_D^{16}$ –95.3 (*c* 1.0, EtOH). IR (KBr, cm^{-1}) ν_{max}: 3385, 2898, 1703, 1498, 1242, 1040, 928, 813, 620. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.85 (dd, *J* = 10.2 Hz, *J* = 13.8 Hz, 1H, H-7''α), 3.25 (dd, *J* = 4.4 Hz, *J* = 13.8 Hz, 1H, H-7''β), 3.93 (dd, *J* = 4.4 Hz, *J* = 10.2 Hz, 1H, H-3), 5.92 (d, *J* = 7.6 Hz, 2H, OCH_2O), 6.04 (s, 2H, OCH_2O), 6.37−6.90 (m, 6H, ArH), 7.53 (s, 1H, H-7'). Anal. Calcd for $C_{20}H_{16}O_8$: C, 62.50; H, 4.20. Found: C, 65.39; H, 4.33%. EI−MS (*m/z*,%): 384 (M^+, 1), 366 (1), 244 (1), 203 (3), 159 (2), 135 (100). The white solids from evaporated solution were recrystallised twice in methanol and water to yield the (+)-diacid **4a'** as white crystals (9.0 g, 39%). M.p. 96–97 °C. $[\alpha]_D^{16}$ + 94.8 (c 0.8, EtOH). ^{1}H NMR, IR, and MS of **4a'** are in agreement with **4a**.

(−)-2-(3',4'-Dimethoxybenzylidene)-3-(3'',4''-methylenedioxybenzyl) succinic acid (**4b**): Following the procedure described for the preparation of **4a**, and starting with the diester **3b** (27.4 g, 60 mmol), (–)-diacid **4b** was obtained as white crystals (10.8 g, 45%). M.p. 90−91 °C. $[\alpha]_D^{16}$ –143.2 (c 0.7, EtOH). IR (KBr, cm^{-1}) ν_{max}: 3522, 2943, 1714, 1516, 1255, 1142, 925. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.83 (dd, *J* = 10.2 Hz, *J* = 14.0 Hz, 1H, H-7''α), 3.18 (dd, *J* = 4.8 Hz, *J* = 14.0 Hz, 1H, H-7''β), 3.64 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.95 (dd, *J* = 4.8 Hz, *J* = 10.2 Hz, 1H, H-3), 5.87 (d, *J* = 8.2 Hz, 2H, OCH_2O), 6.35−6.89 (m, 6H, ArH), 7.52 (s, 1H, H-7'). Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.03. Found: C, 62.91; H, 5.18%. HRMS Calcd for $C_{21}H_{21}O_8$ (M + H^+): 401.1231. Found: 401.1239. EI-MS (*m/z*,%): 400 (M^+, 1), 382 (17), 260 (5), 219 (12), 175 (26), 135 (100). (+)-diacid **4b'** was obtained as white crystals (9.2 g, 38%). M.p. 89–91 °C. $[\alpha]_D^{16}$ + 142.6 (c 0.6, EtOH). ^{1}H NMR, IR, MS and HRMS of **4b'** are in agreement with **4b**.

(−)-Diethyl 2-(3',4'-methylenedioxybenzylidene)-3-(3'',4''-methylenedioxybenzyl)succinate (**5a**): **4a** (7.7 g, 20 mmol) was added to a 100 mL mixture of EtOH: benzene: H_2SO_4 (100: 50: 1). The mixture was heated under reflux with a Dean and Stark apparatus to remove water for 36 h. The reaction mixture was concentrated *in vacuo* and extracted with EtOAc (100 mL), and then neutralised with a $NaHCO_3$ saturated solution (3 × 30 mL). The extract was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography of the residue gave (R)-(–)-diester **5a** as colourless oil (8.0 g, 91%). $[\alpha]_D^{16}$ –68.4 (c 1.0, $CHCl_3$). ^{1}H NMR, IR, MS and HRMS of **5a** are in agreement with **3a**.

(−)-Diethyl2-(3',4'-dimethoxybenzylidene)-3-(3'',4''-methylenedioxybenzyl) succinate (**5b**): Following the procedure described for the preparation of **5a**, and starting with the diester **4b** (8.0 g, 20 mmol), diacid **5b** was obtained as a colourless oil (8.2 g, 90%). $[\alpha]_D^{16}$ –170.1 (c 1.0, $CHCl_3$). ^{1}H NMR, IR, MS and HRMS of **5b** are in agreement with **3b**.

(−)-Dihydrocubebin (**6a**) *and meso-2,3-bis(3',4'-methylenedioxybenzyl)butane-1,4-diol* (**7a**): (R)-(–)-Diester **5a** (7.1 g, 16 mmol) in ethyl acetate (200 mL) was stirred under 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) and *erythro*-**7a** (2.6 g).

(–)-*Dihydrocubebin* (**6a**). Yield 47%. White crystals. M.p. 112–113 °C. $[\alpha]_D^{16}$ –41.9 (*c* 0.8, $CHCl_3$). (Lit.[22] m.p. 112 °C. $[\alpha]_D$ –42). IR (KBr, cm^{-1}) ν_{max}: 3382, 2921, 1514, 1242, 1032, 928, 809, 764. ^{1}H

NMR (200 MHz, $CDCl_3$) δ: 1.80−1.84 (m, 2H, H-2, H-3), 2.55−2.81 (m, 4H, 2 × $ArCH_2$), 3.48 (d, *J* = 11.2 Hz, 2H, CH_2OH), 3.72 (s, 2H, 2 × OH), 3.74 (d, *J* = 11.2 Hz, 2H, CH_2OH), 5.91 (s, 4H, 2 × OCH_2O), 6.58−6.73 (m, 6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.8 (C-2, C-3), 44.2 (C-7', C-7"), 59.9 (C-1, C-4), 100.7 (2 × OCH_2O), 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"). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.21; H, 6.33%. HRMS Calcd for $C_{20}H_{26}NO_6$ (M + NH_4^+): 376.1755. Found: 376.1760. EI−MS (*m/z*,%): 358 (M^+, 2), 340 (0.1), 204 (0.3), 161 (3), 135 (100).

Meso-2,3-Bis(3',4'-methylenedioxybenzyl) butane-1,4-diol (**7a**): Yield 46%. Colourless oil. $[\alpha]_D^{16}$ 0 (*c* 0.7, $CHCl_3$). IR (KBr, cm^{-1}) ν_{max}: 3293, 2920, 1488, 1246, 1037, 928, 811, 731. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.99−2.05 (m, 2H, H-2, H-3), 2.49−2.63 (m, 4H, 2 × $ArCH_2$), 3.45−3.61 (m, 4H, 2 × CH_2OH), 3.71 (s, 2H, 2 × OH), 5.92 (s, 4H, 2 × OCH_2O), 6.61−6.76 (m, 6H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 33.4 (C-2, C-3), 45.2 (C-7', C-7"), 62.9 (C-1, C-4), 100.8 (2 × OCH_2O), 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-4', C-4"), 147.6 (C-3', C-3"). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.16; H, 6.41%. HRMS Calcd for $C_{20}H_{26}NO_6$ (M + NH_4^+): 376.1755. Found: 376.1760. EI-MS (*m/z*,%): 358 (M^+, 3), 340 (0.3), 204 (0.8), 161 (4), 135 (100).

(−)-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**, and starting with the diester **5b** (7.3 g, 16 mmol), **3b** (2.6 g) and **7b** (2.9 g) were obtained.

(−)-Dihydro-3',4'-dimethoxy-3",4"-demethylenedioxycubebin (**6b**): Yield 44%. Colourless oil. $[\alpha]_D^{16}$ −36.8 (*c* 0.5, $CHCl_3$). (Lit.[23] $[\alpha]_D$ −9.9) IR (KBr, cm^{-1}) ν_{max}: 3374, 1593, 1515, 1488, 1442, 928. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.85−1.87 (m, 2H, H-2, H-3), 2.60−2.80 (m, 4H, 2 × H-7', 2 × H-7"), 3.50 (d, *J* = 11.6 Hz, 2H, CH_2OH), 3.56 (s, 2H, 2 × OH), 3.80 (d, *J* = 11.6 Hz, 2H, CH_2OH), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.90 (s, 2H, OCH_2O), 6.57−6.80 (m, 6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.7 (C-2), 35.9 (C-3), 43.9 (C-7'), 44.1 (C-7"), 55.8 (OCH_3), 55.9 (OCH_3), 60.2 (C-1), 60.3 (C-4), 100.7 (OCH_2O), 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"). Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.19; H, 6.79%. HRMS Calcd for $C_{21}H_{30}NO_6$ (M + NH_4^+): 392.2068. Found: 392.2063. EI-MS (*m/z*,%): 374 (M^+, 4), 356 (0.4), 220 (3), 203 (3), 151 (100).

(−)-2,3-Desmethoxy seco-isolintetralin (**7b**): Yield 48%. Colourless oil. $[\alpha]_D^{16}$ −1.7 (*c* 0.3, $CHCl_3$). (Lit.[24] $[\alpha]_D$ −1.6). IR (KBr, cm^{-1}) ν_{max}: 3365, 2919, 1514, 1241, 1032, 727, 643. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.84−1.86 (m, 2H, H-2, H-3), 2.56−2.82 (m, 4H, 2 × H-7', 2 × H-7"), 3.50 (d, *J* = 11.0 Hz, 2H, CH_2OH), 3.75 (d, *J* = 11.0 Hz, 2H, CH_2OH), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.95 (s, 2H, 2 × OH), 5.89 (s, 2H, OCH_2O), 6.56−6.78 (m, 6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.1 (C-2), 33.4 (C-3), 45.0 (C-7'), 45.2 (C-7"), 55.8 (OCH_3), 55.9 (OCH_3), 62.9 (C-1), 63.0 (C-4), 100.8 (OCH_2O), 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"). Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.11; H, 6.84%. HRMS Calcd for $C_{21}H_{30}NO_6$ (M + NH_4^+): 392.2068. Found: 392.2063. EI-MS (*m/z*,%): 374 (M^+, 4.7), 356 (0.23), 220 (1.8), 203 (2.5), 151 (100).

(−)-Kaerophyllin (**8**): $LiAlH_4$ (0.076 g, 2 mmol) was added to dry THF at 0 °C and the mixture was stirred at this temperature for 10 min, then anhydr-$AlCl_3$ (0.082 g, 0.6 mmol) was added. After stirring for 20 min compound **5b** (0.90 g, 2 mmol) was added. The mixture was stirred for 10 h. Then the reaction was quenched by water and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in acetone. Then freshly-prepared MnO_2 (0.54 g, 6 mmol) was added. After stirring for 36 h, the mixture was filtered and the filtrate was concentrated *in vacuo*. Flash column chromatography of the residue gave **8** as a colourless solid (0.60 g, 82%). M.p. 146–147 °C. $[\alpha]_D^{20}$ −67.7 (*c* 1.2, $CHCl_3$). (Lit.[25] m.p. 148 °C. $[\alpha]_D$ −66.9). IR (KBr, cm^{-1}) ν_{max}: 2913, 1745, 1644, 1596, 1515, 1249, 1185, 1035, 927, 807. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.61 (dd, *J* = 10.4 Hz, *J* = 14.4 Hz, 1H, H-6'a), 3.04 (dd, *J* = 4.2 Hz, *J* = 14.4 Hz, 1H, H-6'b), 3.75−3.92 (m, 1H, H-4), 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.27 (d, *J* = 4.0 Hz, 2H, 2 × H-5), 5.94 (s, 2H, OCH_2O), 6.61−7.25 (m, 6H, ArH), 7.54 (d, *J* = 1.8 Hz, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 37.4 (C-6'), 39.6 (C-4), 55.9 (2 × OCH_3), 69.4 (C-5), 101.1 (OCH_2O), 108.4, 109.0, 111.2, 112.9, 121.9, 123.5, 125.6, 126.8, 131.4 (C-3), 137.4 (C-6), 146.5, 147.9, 149.0, 150.6, 172.6 (C-2). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.25; H, 5.26%. EI-MS (*m/z*,%): 368 (M^+, 9), 306 (0.3), 233 (69), 135 (100).

(−)-Hinokinin (**9**): Freshly-prepared Ag_2CO_3/Celite (2 mmol) and compound **6a** (0.36 g, 1 mmol) was added to 30 mL of anhydrous benzene. The solution was heated at reflux for 16 h, cooled and filtered. The filtrate was concentrated *in vacuo*. Flash column chromatography of the residue gave compound **9** as a colourless solid (0.33 g, 93%). M.p. 63–64 °C. $[\alpha]_D^{20}$ −34.2 (*c* 1.3, $CHCl_3$). (Lit.[26] $[\alpha]_D$ −36). IR (KBr, cm^{-1}) ν_{max}: 2916, 1767, 1494, 1430, 1247, 1037, 928. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.42−2.60 (m, 4H, 2 × $ArCH_2$), 2.83 (dd, *J* = 7.2 Hz, *J* = 14.1 Hz, 1H, H-4), 2.98 (dd, *J* = 4.5 Hz, *J* = 14.1 Hz, 1H, H-3), 3.86 (dd, *J* = 7.2 Hz, *J* = 9.3 Hz, 1H, H-5a), 4.13 (dd, *J* = 6.9 Hz, *J* = 9.3 Hz, 1H, H-5b), 5.93 (s, 2H, OCH_2O), 5.94 (s, 2H, OCH_2O), 6.50−6.75 (m, 6H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.7 (C-6'), 38.3 (C-6), 41.2 (C-4), 46.4 (C-3), 71.1 (C-5), 101.0 (2 × OCH_2O), 108.2, 108.3, 108.7, 109.3, 121.5, 122.2, 131.2, 131.5, 146.2, 146.4, 147.8 (C-α, C-α'), 178.4 (C-2). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.93; H, 5.31%. EI-MS (*m/z*,%): 354 (M^+, 14), 218 (4), 192 (3), 135 (100).

(±)-Isohinokinin (**10**): Freshly-prepared Ag_2CO_3/Celite (2 mmol) and compound **7a** (0.36 g, 1 mmol) was added to 30 mL of anhydrous benzene. The solution was heated at reflux for 16 h, cooled and filtered. The filtrate was concentrated *in vacuo*. Flash column chromatography of the residue gave **(±)-**Isohinokinin **10** as a colourless solid (0.33 g, 93%). M.p. 115–116 °C. (Lit.[27] m.p. 115 °C). $[\alpha]_D^{20}$ 0 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}) ν_{max}: 2902, 1771, 1490, 1443, 1248, 1038, 927, 809. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.29 (t, *J* = 13.5 Hz, 1H, H-6'a), 2.53−2.75 (m, 1H, H-4), 2.73 (dd, *J* = 10.5 Hz, *J* = 14.7 Hz, 1H, H-6a), 2.88 (dd, *J* = 3.0 Hz, *J* = 13.5 Hz, 1H, H-6'b), 3.01−3.15 (m, 1H, H-3), 3.22 (dd, *J* = 4.2 Hz, *J* = 14.7 Hz, 1H, H-6b), 4.01−4.11 (m, 2H, 2 × H-5), 5.92 (s, 2H, OCH_2O), 5.96 (s, 2H, OCH_2O), 6.51−6.54 (m, 2H, ArH), 6.71−6.81 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.5 (C-6'), 32.5 (C-6), 39.9 (C-4), 45.2 (C-3), 69.3 (C-5), 101.0 (2 × OCH_2O), 108.4 (C-γ, C-γ'), 108.6, 109.0, 121.2, 121.9, 132.0, 132.1, 146.2 (C-β, C-β'), 147.9 (C-α, C-α'), 177.8 (C-2). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.63; H, 5.39%. EI-MS (*m/z*,%): 354 (M^+, 12), 218 (7), 192 (5), 135 (100).

Meso-2,3-bis(3',4'-methylenedioxybenzyl)-1,4-butanediol diacetates (**11a**): The minimum amount of pyridine was added to a mixture of **7a** (0.36 g, 1 mmol) in CH_2Cl_2 (30 mL). Then Ac_2O was added dropwise. The mixture was stirred at room temperature for 10 h. The solution was concentrated. Flash column chromatography of the residue gave **11a** as a colourless oil (0.40 g, 90%). $[\alpha]_D^{20}$ 0 (*c* 0.4, $CHCl_3$). IR (KBr, cm^{-1}) ν_{max}: 3450, 2899, 1737, 1494, 1245, 1038, 930, 812, 775. ^1H NMR (300 MHz,$CDCl_3$) δ: 2.04 (s, 6H, 2 × $COCH_3$), 2.14−2.17 (m, 2H, H-2, H-3), 2.53 (dd, *J* = 7.2 Hz, *J* = 14.1 Hz, 2H, $ArCH_2$), 2.70 (dd, *J* = 9.0 Hz, *J* = 13.8 Hz, 2H, $ArCH_2$), 4.01−4.13 (m, 4H, 2 × CH_2OMe), 5.93 (s, 4H, 2 × OCH_2O), 6.54−6.75 (m, 6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8 (2 × CH_3), 34.1 (C-2, C-3), 39.8 (C-7', C-7"), 64.5 (C-1, C-4), 100.8 (2 × OCH_2O), 108.2 (C-5', C-5"), 108.9 (C-2', C-2"), 121.7 (C-6', C-6"), 133.3 (C-1', C-1"), 145.9 (C-4', C-4"), 147.7 (C-3', C-3"), 170.8 (2 × C=O). Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.31; H, 5.67%. HRMS Calcd for $C_{24}H_{30}NO_8$ (M + NH_4^+): 460.1966. Found 460.1964. EI-MS (*m/z*,%): 442 (M^+, 5), 322 (1), 281 (1), 187 (13), 135 (100).

Erythro-(−)-2-(3',4'-methylenedioxybenzyl)-3-(3",4"-dimethoxybenzyl)-1,4-butanediol diacetates (**11b**): Following the procedure described for the preparation of **11a**, and starting with **7b** (0.37 g, 1 mmol), compound (−)-**11b** was obtained as a colourless oil (0.43 g, 93%). $[\alpha]_D^{20}$ −1.3 (*c* 0.8, $CHCl_3$). IR (KBr, cm^{-1}) ν_{max}: 2926, 1717, 1511, 1243, 1036, 913. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.00 (s, 6H, 2 × $COCH_3$), 2.05−2.25 (m, 2H, H-2, H-3), 2.50−2.74 (m, 4H, 2 × $ArCH_2$), 3.82 (s, 6H, 2 × OCH_3), 3.96−4.10 (m, 4H, H-1, H-4), 5.89 (s, 2H, OCH_2O), 6.55−6.78 (m, 6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8 (2 × CH_3), 33.7 (C-3), 34.1 (C-2), 39.7 (C-7', C-7"), 55.6 (OCH_3), 55.7 (OCH_3), 64.6 (C-4), 64.7 (C-1), 100.8 (OCH_2O), 108.1 (C-5"), 108.9 (C-5"), 111.1 (C-2"), 111.7 (C-2'), 120.8 (C-6"), 121.7 (C-6'), 132.1 (C-1"), 133.3 (C-1'), 145.9 (C-4"), 147.3 (C-4'), 147.6 (C-3"), 148.8 (C-3'), 170.9 (2 × C=O). Anal. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.59. Found: C, 65.33; H, 6.67%. HRMS Calcd for $C_{25}H_{34}NO_8$ (M + NH_4^+): 476.2279. Found 476.2279. EI-MS (*m/z*,%): 458 (M^+, 19), 398 (1), 203 (13), 187 (8), 151 (100), 135 (64).

Threo-(−)-2,3-bis(3',4'-methylenedioxybenzyl)-1,4-butanediol diacetates (**12a**): Following the procedure described for the preparation of **11a**, and starting with **6a** (0.36 g, 1 mmol), compound (−)-**12a** was obtained as a colourless oil (0.41 g, 92%). $[\alpha]_D^{20}$ −37.2 (*c* 0.5, $CHCl_3$). IR (KBr, cm^{-1}) ν_{max}: 2898, 1737, 1494, 1245, 1037, 930, 811, 775. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.07 (s, 6H, 2 × $COCH_3$), 2.07−2.17 (m, 2H, H-2, H-3), 2.56 (dd, *J* = 7.2 Hz, *J* = 14.1 Hz, 2H, $ArCH_2$), 2.66 (dd, *J* = 7.2 Hz, *J* = 14.1 Hz, 2H, $ArCH_2$), 4.00 (dd, *J* = 5.1 Hz, *J* = 11.1 Hz, 2H, CH_2OMe), 4.10 (dd, *J* = 5.1 Hz,

J = 11.1 Hz, 2H, CH_2OMe), 5.93 (s, 4H, 2 × OCH_2O), 6.51−6.72 (m, 6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9 (2 × CH_3), 34.8 (C-2, C-3), 39.9 (C-7', C-7"), 64.1 (C-1, C-4), 100.8 (2 × OCH_2O), 108.1 (C-5', C-5"), 109.1 (C-2', C-2"), 121.8 (C-6', C-6"), 133.3 (C-1', C-1"), 145.9 (C-4', C-4"), 147.6 (C-3', C-3"), 170.9 (2 × C=O). Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.37; H, 5.77%. EI-MS (*m/z*,%): 442 (M^+, 6), 322 (2), 281 (1), 187 (19), 135 (100).

Threo-(–)-2-(3',4'-methylenedioxybenzyl)-3-(3",4"-dimethoxybenzyl)-1,4-butanediol diacetates (**12b**): Following the procedure described for the preparation of **11a**, and starting with **6b** (0.37 g, 1 mmol), compound (–)-**12b** was obtained as a colourless oil (0.42 g, 92%). $[\alpha]_D^{20}$ –32.6 (*c* 0.6, $CHCl_3$). IR (KBr, cm^{-1}) ν_{max}: 2937, 1736, 1512, 1240, 1034, 929. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.07 (s, 6H, 2 × $COCH_3$), 2.07−2.13 (m, 2H, H-2, H-3), 2.56−2.70 (m, 4H, 2 × $ArCH_2$), 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.00−4.11 (m, 2H, H-1), 4.05−4.15 (m, 2H, H-4), 5.93 (s, 2H, OCH_2O), 6.51−6.79 (m, 6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9 (2 × CH_3), 34.8 (C-3), 34.9 (C-2), 39.7 (C-7"), 39.8 (C-7'), 55.7 (OCH_3), 55.9 (OCH_3), 64.2 (C-4), 64.3 (C-1), 100.8 (OCH_2O), 108.1 (C-5"), 109.1 (C-5"), 111.1 (C-2"), 111.7 (C-2'), 120.9 (C-6"), 121.8 (C-6'), 132.1 (C-1"), 133.3 (C-1'), 145.9 (C-4"), 147.4 (C-4'), 147.6 (C-3"), 148.8 (C-3'), 170.9 (2 × C=O). Anal. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.59. Found: C, 65.66; H, 6.37%. EI-MS (*m/z*,%): 458 (M^+, 19), 398 (1), 203 (13), 187 (8), 151 (100), 135 (64).

Threo-(–)-2,3-bis(3',4'-methylenedioxybenzyl)-1,4-butanediol monoacetate (**13**): Starting with **6a** (0.36 g, 1 mmol) and Ac_2O (0.06 g, 1 mmol), and following the procedure described for the preparation of **11a**, **13** was obtained as a colourless oil (0.29 g, 72%). $[\alpha]_D^{20}$ –44.6 (*c* 0.1, $CHCl_3$). IR (KBr, cm^{-1}) ν_{max}: 3453, 2894, 1733, 1495, 1247, 1038, 929, 811, 732. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.79−1.89 (m, 1H, H-3), 2.07 (s, 3H, $COCH_3$), 2.06−2.26 (m, 1H, H-2), 2.50−2.73 (m, 4H, 2 × $ArCH_2$), 3.60 (s, 2H, H-4), 4.01−4.14 (m, 2H, H-1), 5.91 (s, 4H, 2 × OCH_2O), 6.53−6.71 (m, 6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2 (CH_3), 34.9 (C-3), 35.2 (C-2), 40.2 (C-7"), 43.4 (C-7'), 62.4 (C-4), 64.9 (C-1), 101.1 (2 × OCH_2O), 108.3 (C-5', C-5"), 109.5 (C-2', C-2"), 122.1 (C-6', C-6"), 134.1 (C-1"), 134.4 (C-1'), 146.0 (C-4', C-4"), 147.9 (C-3', C-3"), 171.4 (C=O). Anal. Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 65.73; H, 6.26%. EI-MS (*m/z*, %): 400 (M^+, 5), 382 (1), 340 (2), 187 (6), 135 (100).

This work was financially supported by the Open Foundation of Chemical Engineering Subject, Qingdao University of Science and Technology, China 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 Centre for Drug Screening is acknowledged for the anti-HIV, ant-HSV assay of our compound.

Received 19 June 2009; accepted 10 August 2009
Paper 09/0648 doi: 10.3184/030823409X12506792542747
Published online: 8 September 2009

References

1 D. Su, W. Tang, Y. Hu, Y. Liu, S. Yu, S. Ma, J. Qu and D. Yu, *J. Nat. Prod.*, 2008, **71**, 784.
2 M.A. Ouyang, Y.S. Wein, Z.K. Zhang and Y.H. Kuo, *J. Agric. Food. Chem.*, 2007, **55**, 6460.
3 N. Li, J.L. Wu, J.I. Sakai and M. Ando, *J. Nat. Prod.*, 2003, **66**, 1421.
4 R.S. Ward. *Nat. Prod. Rep.*, 1999, **16**, 75.
5 J.J. Chen, C.S. Yang, C.F. Peng, I.S. Chen and C.L. Miaw, *J. Nat. Prod.*, 2008, **71**, 1016.
6 J.J. Chen, T.Y. Wang and T.L. Hwang, *J. Nat. Prod.*, 2008, **71**, 212.
7 G.B. Messiano, L. Vieira, M.B. Machado, L.M.X. Lopes, S.A. de Bortoli and J. Zukerman-Schpector, *J. Agric. Food. Chem.*, 2008, **56**, 2655.
8 K.C.S.C. Liu, S.S Lee., M.T. Lin, C.W. Chang, C.L. Liu, J.Y. Lin, F.L. Hsu, S. Ren and E. Lien, *J. Med. Chem. Res.*, 1997, **7**, 168.
9 G.L. Zhang, Y.H. Wang, Y.T. Zheng, Z. Zhen and M.W. Wang, *J. Nat. Prod.*, 2007, **70,** 662.
10 E. Eich, H. Pertz, M. Kaloga, J. Schula, M.R. Fesen, A. Mazumder and Y. Pommier, *J. Med. Chem.*, 1996, **39**, 86.
11 N. Li, J.L. Wu, T. Hasegawa, J. Sakai, L.M. Bai, L.Y. Wang, S. Kakuta, Y. Furuya, H. Ogura, T. Kataoka, A. Tomida, T. Tsuruo and M. Ando, *J. Nat. Prod.*, 2007, **70**, 544.
12 R.W. Jiang, J.R. Zhou, P.M. Hon, S.L. Li, Y. Zhou, L.L. Li, W.C. Ye, H.X. Xu, P.C. Shaw and P.P.H. But, *J. Nat. Prod.*, 2007, **70**, 283.
13 M.S. Kurzer and X. Xu, *Annu. Rev. Nutr.*, 1997, **17**, 353.
14 J. Fischer, A.J. Reynolds, L.A. Sharp and M.S. Sherburn, *Org. Lett.*, 2004, **6**, 1345.
15 L. Ferrie, K. Bouyssi and G. Balme, *Org. Lett.*, 2005, **15**, 3143.
16 B. Raffaelli, K. Wahala and T. Hase, *Org. Biomolec. Chem.*, 2006, **4**, 331.
17 R.J. Hart and H.G. Heller, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1321-1324.
18 J. Liu and N.R. Brooks, *Org. Lett.,* 2002, **4**, 3521.
19 G.T. Tan, J.M. Pezzuto, A.D. Kinghorn and S.H. Hughes, *J. Nat. Prod.*, 1990, **54**, 143.
20 R. Dulbeccok, *Proc. Natl. Acad. Sci. U.S.A.*, 1952, **38**, 747.
21 P. Papadia, N. Margiotta, A. Bergamo, G. Sava and G. Natile, *J. Med. Chem.*, 2005, **48**, 3364.
22 A.S.R. Anjaneyulu, P.A. Ramaiah, L.R. Row, R. Venkateswarlu, A. Pelter and R.S. Wardet, *Tetrahedron*, 1981, **37**, 3641.
23 M.J. Kato, M. Yoshida and O.R. Gottlieb, *Phytochemistry*, 1992, **31**, 283.
24 P. Satyanarayana and S. Venkateswarlu, *Tetrahedron*, 1991, **47**, 8931.
25 G.A. Mikaya, D.G. Turabelidae and E.P. Kemertelidze, *Planta Med.*, 1981, **43**, 378.
26 A. Van Oeveren, J.F.G.A. Jansen and B.L. Feringa, *J. Org. Chem.*, 1994, **59**, 5999.
27 X. Lu and G. Zhu, *Synlett.*, 1993, 68.