Asymmetric Synthesis of (+)-Hinokinin, (+)-Dihydrocubebin and Cubebin Dimethyl Ether, a New Lignan from *Phyllanthus niruri*

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The asymmetric synthesis of the new lignan cubebin dimethyl ether was accomplished in eight steps with an overall yield of 40 %. In addition, the known lignans (+)-hinokinin and (+)-dihydrocubebin were synthesized by this route. Our approach involves the highly diastereoselective and enantioselective ($de \geq 98$ %, $ee \geq 98$ %) construction of a *trans*-substituted 2,3-dibenzylbutyrolactone through an asymmetric Michael addition of an enantiopure lithiated aminonitrile to 5*H*-furan-2-one.

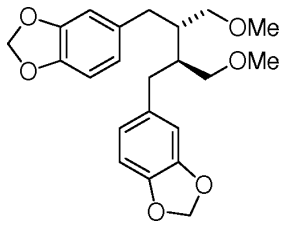
Key words: Lignans, Nucleophilic Acylation, α-Aminonitrile, Michael Addition, Asymmetric Synthesis

Introduction

Cubebin dimethyl ether (**1**) is a new lignan which was recently isolated from cell suspension cultures of *Phyllanthus niruri (euphorbiaceae)* [1]. This plant is well-known in folk medicine as a remedy against different diseases like jaundice, asthma and bronchial infections [2]. Other lignans which were isolated from this plant also exhibited biological activities. Phyllanthin and hypophyllanthin show a moderately inhibitive effect on Gram-positive and Gram-negative bacteria and *anti*-oxidant activities [3]. (–)-*trans*-2-(3,4-Dimethoxybenzyl)-3-(3′,4′-methylenedioxybenzyl)butyrolactone, also isolated from *Bursera schlechtendalii* [4], showed *anti*-tumor activities and nirtetralin and niranthin are known for their *anti*-human hepatitis B virus activity [5].

The structure of cubebin dimethyl ether (**1**) was assigned on the basis of mass spectrometric combined with ^{1}H and ^{13}C NMR data and supported by a H,H-COSY, HMQC, and HMBC NMR-spectroscopic analysis. The researchers who isolated this lignan assume the (8*S*,8′*S*) *trans*-configuration due to the biogenesis of cubebin dimethyl ether [1]. Up to now exists only one report on the synthesis of (8*R*,8′*R*)-cubebin dimethyl ether, starting from (–)-dihydrocubebin lignan and converting it in (8*R*,8′*R*)-cubebin dimethyl ether [6].

We now wish to report the first asymmetric synthesis of cubebin dimethyl ether (**1**) employing our asymmetric nucleophilic acylation methodology based on



Cubebin dimethyl ether (**1**)

lithiated α-aminonitriles [7a – h]. We first synthesized the enantiopure *trans*-configurated 2,3-disubstituted γ-butyrolactone **6** [7i – j], which can be easily transformed to (+)-hinokinin (**8**), (+)-dihydrocubebin (**9**) and (8*S*,8′*S*)-cubebin dimethyl ether (**1**) in diastereo- and enantiomerically pure form. Needless to say that employing the enantiomer of the auxiliary amine **2** should give rise to the (8*R*,8′*R*) enantiomer of **1**.

Results and Discussion

As depicted in Scheme 1, the α-aminonitrile (*S*,*S*,*R*/*S*)-**3** was obtained from the enantiomerically pure secondary amine (*S*,*S*)-**2**, piperonal and potassium cyanide in HOAc/methanol [7k]. The aminonitrile was isolated in 81 % yield as a mixture of α-epimers. Deprotonation of **3** with LDA in THF and reaction with 5*H*-furan-2-one at −78 °C afforded the Michael adduct (*S*,*S*,*R*,*R*)-**4** in high yield (79 %) and diastereoselectivity ($de \geq 88$ %, after chromatography $de \geq 98$ %).

The second stereogenic centre of the natural compound was introduced by subsequent metalation of

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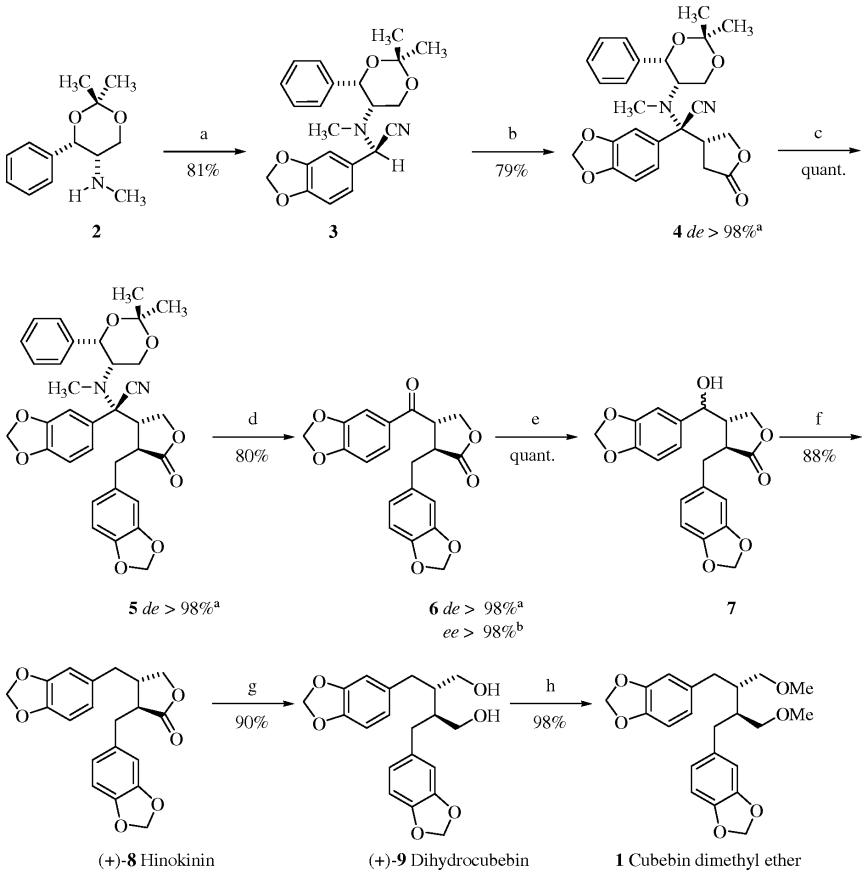

Scheme 1. Reagents and conditions: (a) piperonal, MeOH, CH_3CO_2H, KCN; (b) 1. LDA, THF, −78 °C, 90 min; 2. 5*H*-furan-2-one, −78 °C; (c) 1. 1.2 eq. *t*-BuLi, THF, −78 °C, 90 min; 2. $ArCH_2Br$, −90 to 0 °C; (d) $AgNO_3$, H_2O, THF, 25 °C; (e) $NaBH_4$, $MeOH/CH_2Cl_2$; (f) H_2, Pd/C, $HClO_4$, MeOH, 4 atm, rt; (g) $LiAlH_4$, THF; (h) NaH (2.2 eq.), THF, MeI (8 eq.), 3 h.

[a] After chromatography, determined by ^1H and ^{13}C NMR. [b] Determined by ^1H NMR-shift reagent (Pirkle alcohol) [8].

the Michael adduct **4** with 1.2 equivalents of *t*-BuLi in THF at −100 °C and trapping of the enolate with 3,4-methylenedioxybenzyl bromide at this temperature. The resulting aminonitrile (*S*,*S*,*R*,*R*,*S*)-**5** was obtained in quantitative yield and high diastereomeric purity ($de \geq 98\,\%$). The silver nitrate mediated cleavage of the auxiliary provided the enantiopure *trans*-2,3-disubstituted γ-butyrolactone (*S*,*S*)-**6** with excellent asymmetric induction ($de \geq 98\,\%$, $ee \geq 98\,\%$) [7g–i]. First the reduction of the ketone **6** with sodium borohydride in methanol quantitatively gave the corresponding alcohol **7** as an epimeric mixture. The second step, catalytic hydrogenolysis with Pd/C at 4 atm, furnished (+)-hinokinin (**8**) in very good yield (88 %) and excellent stereoisomeric purity $de \geq 98\,\%$, $[\alpha]_D^{22} = +33.0$ (c = 1.6, $CHCl_3$) (lit. [9]: $[\alpha]_D^{24} = +32.8$ (c = 1.88, $CHCl_3$)). The subsequent reduction step with lithium aluminium hydride opened the butyrolactone ring and afforded the known lignan (+)-dihydrocubebin (**9**) in excellent yield (90 %) with an optical rotation of $[\alpha]_D^{22} = +34.0$ (c = 0.1, $CHCl_3$) in accordance with the literature (lit. [10]: $[\alpha]_D^{20} = -32.4$ (c = 3.3, $CHCl_3$)). Finally, deprotonation of (+)-dihydrocubebin with NaH (2.2 eq.) and methylation with MeI (8 equiv.) provided the title cubebin dimethyl ether (**1**) in 98 % yield. The spectroscopic data (NMR, IR, MS) were in accordance with the literature, but the optical rotations of (*S*,*S*)-**1** differed $[\alpha]_D^{22} = -3.1$ (c = 0.1, $CHCl_3$) from those given for (*R*,*R*)-**1** (lit. [6]: $[\alpha]_D = -7.7°$).

Conclusion

In conclusion, we have reported the first asymmetric synthesis of the new lignan cubebin dimethyl ether isolated from *Phyllanthus niruri Linn. (euphorbiaceae*) based on our conjugate asymmetric nucleophilic acylation methodology.

Experimental Section

All products were characterized by comparison of their spectroscopic data with those of the listed literature. All moisture-sensitive reactions were carried out by using stan-

dard Schlenk techniques. The chiral auxiliary (*S,S*)-**2** was prepared according to the literature procedure [7b]. Optical rotation values were measured on a Perkin-Elmer P241 polarimeter; solvents used were of Merck UVASOL quality. Microanalyses were obtained with a Heraeus CHN-O-RAPID or Vario EL element analyzer. Mass spectra were acquired on a Varian MAT 212 (EI, 70 eV, 1 mA) or Finnigan MAT SSQ 7000 (CI 100 eV) spectrometer. High resolution mass spectra were recorded on a Finnigan MAT 95 spectrometer. IR spectra were recorded on a Perkin-Elmer FT/IR 1760. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded on Gemini 300 or Varian Inova 400 spectrometers with $CDCl_3$ as a solvent and TMS as an internal standard.

Compounds **3**, **4**, **5**, and **6** were prepared following the same procedure and experimental conditions as described previously [7k, 7g, 7i].

*(+)-Hinokinin (**8**)*

To a solution of ketone **6** (354 mg, 0.96 mmol) in CH_2Cl_2 (30 mL) was added $NaBH_4$ (0.12 g, 3.04 mmol) and MeOH (15 mL). After 2 h the reaction mixture was diluted with CH_2Cl_2 (30 mL) and water (10 mL). The aqueous phase was extracted three times with CH_2Cl_2 (15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuum. The crude product was directly used for the next step. The epimeric mixture of alcohol **7** (356 mg, 0.96 mmol) was dissolved in dry ethanol (60 mL) and two drops of aqueous $HClO_4$ were added. The mixture was hydrogenated using Pd/C (60 mg) as a catalyst at 4 atm H_2 pressure. After 48 h, the solution was neutralized with Na_2CO_3 and the catalyst was filtered off. The solvent was evaporated in vacuum and the crude product was purified by column chromatography (Et_2O : pentane = 1 : 1) to give 299 mg (88 %) of (+)-hinokinin (**8**) as a colourless syrup. – IR ($CHCl_3$): ν = 2903 (s), 2362 (m), 1768 (s, C=O), 1492 (s), 1443 (s), 1247 (s), 1191 (s), 1038 (s), 928 (s), 811 (m), 756 (m), 668 (m). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 – 2.62 (m, 4H, OCH_2CHCH_2, OCH_2CHCH_2, $OCCHCH_2$), 2.84 (dd, J = 14.0, 7.1 Hz, 1H, OCCHCHH), 2.98 (dd, J = 14.0, 4.9 Hz, 1H, OCCHCHH), 3.85 (dd, J = 9.0, 7.4 Hz, 1H, OCHHCH), 4.12 (dd, J = 9.0, 7.1 Hz, 1H, OCHHCH), 5.93 (s, 4H, 2 × OCH_2O), 6.46 (m, 2H, arom. CH), 6.60 (dd, J = 7.9, 1.6 Hz, 1H, arom. CH), 6.62 (d, J = 1.6 Hz, 1H, arom. CH), 6.69 (d, J = 8.2 Hz, 1H, arom. CH), 6.73 (d, J = 7.7 Hz, 1H, arom. CH) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.76 (CH_2CHCO), 38.29 (CH_2CHCH_2O), 41.22 (CH_2CHCH_2), 46.40 (CH_2CHCO), 71.02 ($CHCH_2O$), 100.86 (OCH_2O), 108.10, 108.17, 108.64, 109.26, 121.35, 122.03 (arom. CH), 131.13, 131.41, 146.12, 146.24, 147.63, 147.66 (arom. C), 178.14 (CO) ppm. – MS (EI, 70 eV): *m/z* (%) = 355 (15) $[M+1]^+$, 354 (67) M^+, 219 (6), 217 (16), 172 (6), 161 (8), 160 (7), 135 (33), 134 (100), 130 (7), 105 (5), 77 (15). – $C_{20}H_{18}O_6$ (354.35): calcd. C 67.79, H 5.12; found C 68.05, H 5.23.

*(+)-Dihydrocubebin (**9**)*

To a suspension of $LiAlH_4$ (28 mg, 0.74 mmol) in dry THF (5 mL) at 0 °C under Ar, a solution of (+)-hinokinin (130 mg, 0.37 mmol) in dry THF (5 mL) was slowly added *via* syringe. The reaction mixture was stirred at 0 °C for 0.5 h and then at r. t. for further 0.5 h. After addition of EtOAc (20 mL) the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and water (5 mL). The water phase was separated and extracted three times with EtOAc (10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuum. The crude product was purified by column chromatography (Et_2O) to give (+)-dihydrocubebin (**9**) (119 mg, 90 %) as colourless cubes. – M. p. 102 °C (lit. [11]: 103 – 104 °C). – IR (KBr): ν = 3852 (s), 3742 (s), 3681 (m), 3430 (m), 3337 (m), 2361 (s), 2339 (s), 1700 (s), 1650 (s), 1505 (s), 1246 (s), 1036 (s), 669 (m). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (m, 2H, 2 × CH_2CHCH_2), 2.60 (dd, J = 13.6, 5.6 Hz, 2H, 2 × CCHH), 2.73 (dd, J = 13.6, 8.6 Hz, 2H, 2 × CCHH), 3.48 (dd, J = 11.1, 3.9 Hz, 2H, 2 × CHHOH), 3.76 (d, J = 11.1 Hz, 2H, 2 × CHHOH), 3.83 (s, 2H, 2 × CH_2OH), 5.90 (s, 4H, 2 × OCH_2O), 6.59 (d, J = 7.9 Hz, 2H, arom. CH), 6.63 (s, 2H, arom. CH), 6.70 (d, J = 7.9 Hz, 2H, arom. CH) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.89 (CCH_2), 44.26 (CH_2CHCH_2), 60.02 (CH_2OH), 100.77 (OCH_2O), 108.09, 109.33, 121.86 (arom. CH), 134.36, 145.69, 147.55 (arom. C) ppm. – MS (EI, 70 eV): *m/z* (%) = 359 (7) $[M+1]^+$, 358 (38) M^+, 340 (14), 203 (22), 191 (10), 187 (14), 174 (5), 172 (8), 160 (6), 136 (34), 135 (100), 130 (5), 77 (10). – $C_{20}H_{22}O_6$ (358.39): calcd. C 67.03, H 6.19; found C 67.27, H 6.12.

*Cubebin dimethyl ether (**1**)*

To a stirred solution of (+)-dihydrocubebin (**9**) (60 mg, 0.20 mmol) in dry THF (5 mL) methyl iodide (123 mg, 0.86 mmol), sodium hydride (370 mg, 9.20 mmol, 60 % dispersion in oil) and a second portion of methyl iodide (68 mg, 0.48 mmol) were added. After 2.5 h at r. t., the mixture was cooled to 0 °C and methanol (5 mL) was added. Concentration under reduced pressure and flash chromatography of the crude compound (Et_2O : pentane = 1 : 3) afforded 76 mg (98 %) of cubebin dimethyl ether (**1**) as a colourless oil. – IR ($CHCl_3$): ν = 2889 (s), 2356 (s), 1493 (s), 1477 (s), 1246 (s), 1195 (m), 1111 (s), 1040 (s), 933 (m), 866 (s), 808 (m), 758 (s). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (m, 2H, 2 × CH_2CHCH_2), 2.56 (dd, J = 13.7, 8.2 Hz, 2H, 2 × CCHH), 2.65 (dd, J = 13.7, 6.0 Hz, 2H, 2 × CCHH), 3.28 (s, 6H, 2 × CH_3O), 3.28 (dd, J = 9.9, 4.9 Hz, 4H, 2 × CH_3OCH_2), 5.91 (s, 4H, 2 × OCH_2O), 6.56 (dd, J = 7.9, 1.6 Hz, 4H, arom. CH), 6.70 (d, J = 7.9 Hz, 2H, arom. CH) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.81 (CCH_2), 40.89

(CH_2CHCH_2), 58.60 (CH_3O), 72.39 (CH_3OCH_2), 100.54 (OCH_2O), 107.76, 109.25, 121.70 (arom. *C*H), 134.67, 145.31, 147.22 (arom. *C*) ppm. – MS (EI, 70 eV): *m/z* (%) = 387 (19) $[M+1]^+$, 386 (78) M^+, 355 (12), 354 (54), 322 (19), 219 (8), 217 (14), 206 (5), 204 (5), 188 (5), 186 (43), 185 (8), 173 (15). – HRMS: calcd. 386.172938; found 386.172940.

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