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 5H-furan-2-one.

Key words: Lignans, Nucleophilic Acylation, $\alpha$-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 (8S,8′S) trans-configuration due to the biogenesis of cubebin dimethyl ether [1]. Up to now exists only one report on the synthesis of (8R,8′R)-cubebin dimethyl ether, starting from (−)-dihydrocubebin lignan and converting it in (8R,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 lithiated $\alpha$-aminonitriles [7a–h]. We first synthesized the enantiopure trans-configurated 2,3-disubstituted $\gamma$-butyrolactone 6 [7i–j], which can be easily transformed to (+)-hinokinin (8), (+)-dihydrocubebin (9) and (8S,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 (8R,8′R) enantiomer of 1.

Results and Discussion

As depicted in Scheme 1, the $\alpha$-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 $\alpha$-epimers. Deprotonation of 3 with LDA in THF and reaction with 5H-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...
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 ≥ 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 ≥ 98%, ee ≥ 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 ≥ 98%, \[ \alpha_D^{22} = +33.0 \ (c = 1.6, \text{CHCl}_3) \] (lit. [9]: \[ \alpha_D^{24} = +32.8 \ (c = 1.88, \text{CHCl}_3) \]). 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 \[ \alpha_D^{22} = +34.0 \ (c = 0.1, \text{CHCl}_3) \] in accordance with the literature (lit. [10]: \[ \alpha_D^{20} = -32.4 \ (c = 3.3, \text{CHCl}_3) \]). 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 \[ \alpha_D^{22} = -3.1 \ (c = 0.1, \text{CHCl}_3) \] from those given for (R,R)-1 (lit. [6]: \[ \alpha_D^{19} = -7.7^\circ \]).

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-
to standard 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 (KBr) or Varian Inova 400 spectrometers with CDCl₃ 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 CH₂Cl₂ (30 mL) was added NaBH₄ (0.12 g, 3.04 mmol) and MeOH (15 mL). After 2 h the reaction mixture was diluted with CH₂Cl₂ (30 mL) and water (10 mL). The aqueous phase was extracted three times with CH₂Cl₂ (15 mL). After 2 h 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 NH₄Cl (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 MgSO₄ and evaporated in vacuum. The crude product was purified by column chromatography (Et₂O) 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), 2362 (s), 1748 (s, C = O), 1350 (m), 1247 (s), 1191 (s), 1034 (m), 1029 (s), 928 (m), 811 (m), 756 (m), 718 (s), 704 (s), 699 (m). – ¹H NMR (300 MHz, CDCl₃): δ = 1.83 (m, 2H, 2 × CH₂CH₂H), 2.50 (dd, δ = 13.6, 5.6 Hz, 2H, 2 × CH₂OH), 2.73 (dd, δ = 13.6, 8.6 Hz, 2H, 2 × CH₂OH), 3.48 (dd, δ = 11.1, 3.9 Hz, 2H, 2 × CH₂OH), 3.76 (dd, δ = 11.1, 1.1 Hz, 2H, 2 × CH₂OH), 5.90 (s, 4H, 2 × OCH₂O), 6.59 (d, δ = 7.9 Hz, 2H, arom. CH), 6.63 (s, 2H, arom. CH), 6.70 (d, δ = 7.9 Hz, 2H, arom. CH) ppm. – ¹³C NMR (75 MHz, CDCl₃): δ = 35.89 (C = O), 44.26 (CH₂CH₂H), 60.02 (CH₂OH), 100.77 (OCH₂O), 108.09, 109.33, 121.86 (arom. CH), 134.36, 145.69, 147.55 (arom. C) ppm. – MS (El, 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). – C₂₀H₁₉O₆ (354.35): calc. C 67.79, H 5.12; found C 68.05, H 5.23.

(+)-Dihydrocubebin (9)

To a suspension of LiAlH₄ (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 NH₄Cl (10 mL) and water (5 mL). The water phase was evaporated in vacuum and the crude product was purified by column chromatography (Et₂O) 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), 2362 (s), 1748 (s, C = O), 1350 (m), 1247 (s), 1191 (s), 1034 (m), 1029 (s), 928 (m), 811 (m), 756 (m), 718 (s), 704 (s), 699 (m). – ¹H NMR (300 MHz, CDCl₃): δ = 1.83 (m, 2H, 2 × CH₂CH₂H), 2.50 (dd, δ = 13.6, 5.6 Hz, 2H, 2 × CH₂OH), 2.73 (dd, δ = 13.6, 8.6 Hz, 2H, 2 × CH₂OH), 3.48 (dd, δ = 11.1, 3.9 Hz, 2H, 2 × CH₂OH), 3.76 (dd, δ = 11.1, 1.1 Hz, 2H, 2 × CH₂OH), 5.90 (s, 4H, 2 × OCH₂O), 6.59 (d, δ = 7.9 Hz, 2H, arom. CH), 6.63 (s, 2H, arom. CH), 6.70 (d, δ = 7.9 Hz, 2H, arom. CH) ppm. – ¹³C NMR (75 MHz, CDCl₃): δ = 35.89 (C = O), 44.26 (CH₂CH₂H), 60.02 (CH₂OH), 100.77 (OCH₂O), 108.09, 109.33, 121.86 (arom. CH), 134.36, 145.69, 147.55 (arom. C) ppm. – MS (El, 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). – C₂₀H₁₉O₆ (354.35): calc. C 67.79, H 5.12; found C 68.05, H 5.23.

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 (Et₂O: pentane = 1: 3) afforded 76 mg (98 %) of cubebin dimethyl ether (1) as a colourless oil. – IR (CHCl₃): ν = 2889 (s), 2356 (s), 1493 (s), 1477 (s), 1340 (14), 203 (22), 191 (10), 187 (14), 174 (5), 172 (8), 160 (6), 136 (34), 135 (100), 130 (5), 77 (10). – C₂₀H₂₂O₆ (358.39): calc. C 67.03, H 6.19; found C 67.27, H 6.12.
A New Lignan from *Phyllanthus niruri* (CH₂CH₂O), 58.60 (CH₂O), 72.39 (CH₂OCH₂), 100.54 (OCH₃), 107.76, 109.25, 121.70 (arom. CH), 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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