An Efficient Total Synthesis of Pedunculagin by Using a Twofold Intramolecular Double Esterification Strategy

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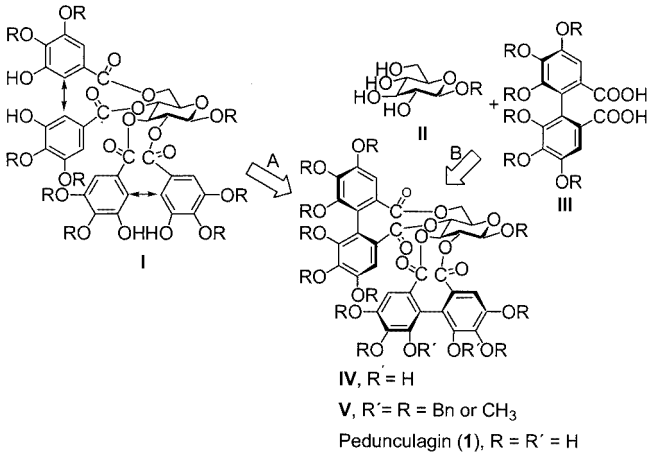
The total synthesis of naturally occurring pedunculagin (**1**) was achieved by the twofold intramolecular double esterification of enantiomerically pure (*S*)-hexabenzyloxydiphenic acid (**4**) with the D-glucose-derived sugar **2** as the key step.

Introduction

Ellagitannins, with more than 500 structurally characterized members so far, constitute one of the most important classes of tannins, and possess a variety of interesting biological activities such as anti-oxidative, anticancer, and antiviral activities. These properties, and the fact that ellagitannins are usually not toxic for humans, make them important and interesting compounds for pharmaceutical purposes. However, their broad application in pharmacy is hindered by their limited accessibility in adequate purity and quantity from natural sources. Recently some of them have become accessible through synthesis by application of the developed concepts A and/or B (Scheme 1) to the construction of their molecular skeletons.



Scheme 1. Retrosynthetic strategies for the synthesis of ellagitannins

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Pedunculagin (**1**)[1−4] is a member of the broad class of vegetable extracts known as ellagitannins. The chemical structure of pedunculagin consists of two (*S*)-**h**exa**h**ydroxy-**di**p**h**enoyl (HHDP) moieties located at the 2,3- and 4,6-positions of D-glucopyranose. Pedunculagin has been shown to inhibit the promising anticancer target enzyme DNA topoisomerase II[5] in vivo, with an IC_{100} of 500 nM.[6]

For the general synthesis of ellagitannins, two different concepts have recently been developed (Scheme 1). In the first strategy, the biaryl part of ellagitannins is constructed by the intramolecular diastereoselective oxidative coupling of phenolic aromatic systems attached to the D-glucose (concept A), which was developed by Feldman in 1994[7] and successfully applied to the synthesis of some ellagitannins.[8] The second strategy (concept B) involves an intramolecular double esterification approach, in which an appropriately protected diphenic acid **III** is esterified with the sugar derivative **II** (Scheme 1). This concept was introduced by Meyers et al. in 1994 and applied to the construction of the precursor of the natural tellimagrandin I (not shown).[9]

Recently, the naturally occurring product **1** was synthesized by Feldman et al. for the first time, based on concept A.[10] The key steps of the synthesis were the successive diastereoselective oxidative coupling of both pairs of the aryl moieties attached to the 2,3- and 4,6-positions of the D-glucosyl core. It has been shown that, for the successful synthesis of **1**, O(2)/O(3) galloyl coupling has to be done first followed by O(4)/O(6) coupling.[10] However, the large number of steps in the synthetic sequence (nine steps starting from protected gallic acid and sugar derivative) and the low overall yield of pedunculagin (2.9%) prompted us to search for a more efficient route to this important ellagitannin. Itoh at al. succeeded in the stepwise synthesis of trideca-*O*-methyl-α-pedunculagin through the double esterification approach (concept B) starting from racemic hexamethoxydiphenic acid.[11]

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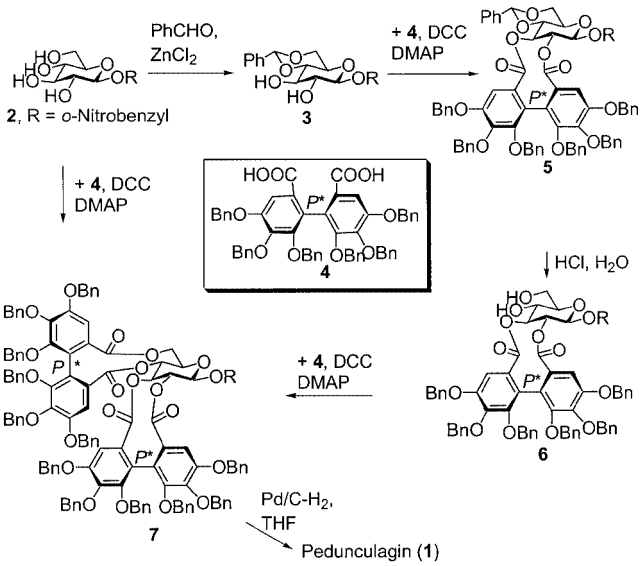
In this article we now report on both the stepwise and the two-step total synthesis of pedunculagin (**1**) in 39% overall yield, based on concept B.

Results and Discussion

Retrosynthetically, as is obvious from Scheme 1 (route B), the structurally complex target molecule **1** can be assembled using only two very simple building blocks: D-glucose **II** (R = H) and (*S*)-hexahydroxydiphenic acid **III** (R = H). However, in order to assemble the carbon framework of the target **1** in only one step, building blocks **II** and **III** have to react in a selective twofold intramolecular double esterification (Scheme 2, route B) to create **V** with four ester functions. The alternative intermolecular pathways (Scheme 2, routes A and C) would result in an undesired oligomeric mixture (not shown). It is well known that the OH groups at C6 of the anomerically protected D-glucosides are the most reactive ones. Thus, the OH groups at C6 of **II** (Scheme 2) would react first with one of the two COOH groups of the dicarboxylic acid **III** to give the corresponding monoester **VI**. The monoester **VI** itself would now be able to react in an inter- as well as in an intramolecular manner as analyzed in Scheme 2. However, from the kinetic point of view, the desired intramolecular route B was anticipated to be preferred over routes A and C.

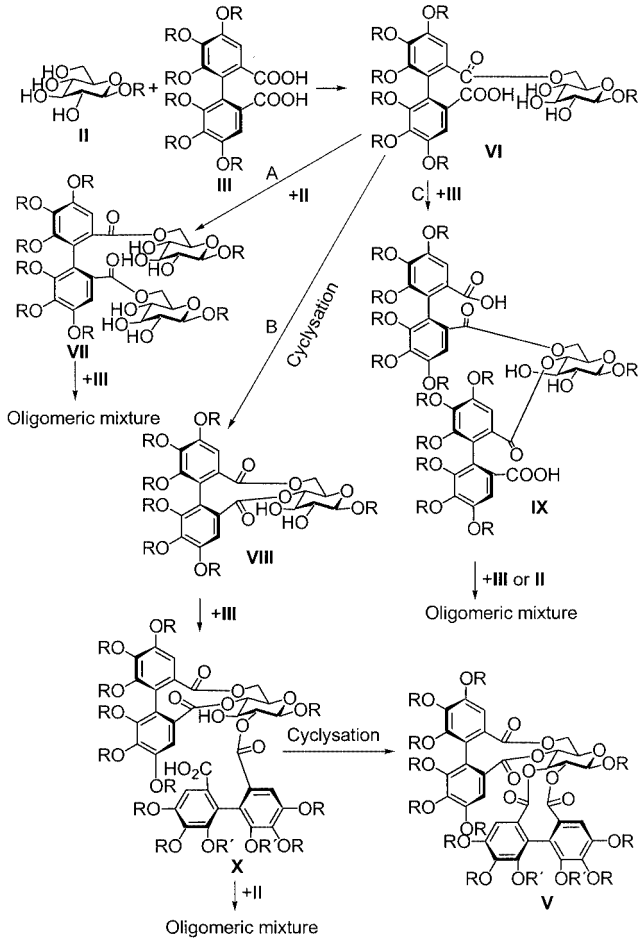
To study the intra- versus the intermolecular pathway, we first decided to synthesize **7** using a stepwise strategy starting with compound **2** (Scheme 3).



Scheme 3. Total synthesis of Pedunculagin (**1**)

Thus, sugar **2** was first protected as the benzylidene acetal and the resulting diol **3** was subsequently esterified with enantiomerically pure (*S*)-hexabenzyloxydiphenic acid (**4**)[12,13] to furnish diester **5** in excellent yield. Only a small amount of a polar side product could be detected in this reaction, and this was probably formed via the *inter*molecular version of the esterification.[14] Removal of the benzylidene acetal of diester **5** under acidic conditions then gave the corresponding diol **6** quantitatively. Diol **6** was esterified with dicarboxylic acid **4** to give a nonpolar product, which could be identified as the desired tetraester **7** by NMR spectroscopy (Scheme 3). The ^{13}C NMR spectrum of **7** showed four characteristic singlets at δ = 167.4, 167.7, 167.8, and 169.0 ppm, corresponding to the four ester functions and another characteristic singlet at δ = 100.6 ppm arising from the β-D-glucosyl moiety of tetraester **7**.

With this compound in hand, we next turned our attention to the one-step synthesis of **7** as discussed above. In fact, the esterification of sugar derivative **2** with dicarboxylic acid **4** under Steglich esterification conditions[15,16] using DCC and DMAP led to the formation of only one nonpolar product, which could easily be characterized as **7** by comparison with the compound **7** synthesized via the stepwise strategy. It should be noted that a mixture of inseparable polar products was also obtained from this reaction in 35% yield. Finally, to complete the total synthesis of pedunculagin (**1**), the main product **7** was exposed to hydrogenolysis under standard conditions using Pd/C-H_2 to remove all benzylic protective groups. From this reaction, **1**



Scheme 2. Intramolecular and intermolecular pathways

could be isolated as a brownish solid in 65% yield after purification of the crude product using preparative reversed phase thin layer chromatography.

The optically pure compound obtained was identical with **1** as shown by comparison of its specific rotation and the physical properties ($[\alpha]_D$, ^{1}H NMR, IR, MS) with those reported for pedunculagin (**1**).[10]

Conclusion

In summary, the synthesis of pedunculagin (**1**) was achieved in only two steps (39% overall yield) from the sugar derivative **2** and the dicarboxylic acid **4** by application of concept B. This methodology provides an efficient route to **1** and, potentially, its analogues. Concept B also describes a practical and rapid route for the scale-up synthesis of a variety of monomeric ellagitannins in pure form and adequate amount for further systematic biological tests and their use for pharmaceutical purposes for the first time.

Experimental Section

General Remarks: Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded using Bruker AMX 300 (300 MHz) and Bruker ARX 200 (200 MHz) spectrometers. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane as a standard (in $CDCl_3$). The degree of substitution on carbon atoms was determined by DEPT; q, t, d, and s designated primary, secondary, tertiary, and quaternary carbon atoms, respectively. HBDP stands for **h**exa**b**enzyloxy**dip**henoyl moiety and Gluc stands for the D-glucosyl core. Melting points were determined using a Gallenkamp Melting Point Apparatus and are uncorrected. Infrared (IR) spectra were obtained using a FT-IR spectral photometer Nicolet 510 P (KBr). Ultraviolet/visible (UV/Vis) spectra were recorded using a Shimadzu UV/Vis spectral photometer UV−2101 PC; λ_{max} in nm (lg ε). Elemental analyses were performed using a Perkin−Elmer Elemental Analyser 2400.

***o*-Nitrobenzyl 2,3:4,6-Bis-*O*-[(*S*)-hexabenzyloxydiphenoyl]-β-D-glucopyranoside (7):** A solution of (*S*)-hexabenzyloxydiphenic acid **4** (0.56 g, 0.63 mmol), tetrol **2** (100 mg, 0.32 mmol), DCC (300 mg), and DMAP (180 mg) in dried CH_2Cl_2 (10 mL) was refluxed for 24 h. The precipitate (dicyclohexyl urea) was then filtered off, the solution was washed twice with 1 N HCl (10 mL) and then twice with H_2O (10 mL). The solvent was evaporated and the crude product was purified by flash chromatography on silica gel with CH_2Cl_2 as eluent to give tetraester **7** (0.76 g, 0.38 mmol, 60%, m.p. 87−93 °C) as a faintly yellow powder. $[\alpha]_D^{22} = -47.1$ (c = 1.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.11−4.17 ppm (m, 2 H), 4.60 (s, 1 H), 4.62 (s, 1 H), 4.67 (d, J = 8.9 Hz, 1 H), 4.71 (d, J = 8.7 Hz, 1 H), 4.79−4.89 (m, 5 H), 4.93−5.52 (m, 22 H), 6.80 (s, 1 H, H-Ar), 6.92−7.56 (m, 64 H, H-Ar), 7.68 (t, J = 7.4 Hz, 1 H, H-Ar), 7.75 (d, J = 7.0 Hz, 1 H, H-Ar), 8.10 (d, J = 8.0 Hz, 1 H, H-Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.5 ppm (s, Gluc-*C*-6), 69.3 (s, C-7), 69.6 (t), 71.1 (s), 71.6 (s), 72.6 (s), 72.8 (t), 75.3 (s), 75.7 (s), 76.0 (s), 76.1 (t), 77.0 (t), 100.6 (t, Gluc-*C*-1), 107.7 and 108.7 (t, HBDP-*C*-5 or HBDP-*C*-5′), 122.1 (q), 122.5 (q), 124.1 (q), 124.2 (q) (HBDP-*C*-1 or HBDP-*C*-1′), 125.4 (t), 127.0 (q), 128.0 (t), 128.09 (q), 128.1 (t), 128.22 (t), 128.24 (q), 128.4 (t), 128.5 (t), 128.52 (t), 128.6 (t), 128.7 (t), 128.87 (q), 128.9 (t), 129.0 (t), 129.03 (q), 129.1 (t), 129.2 (q), 129.4 (q), 129.5 (t), 130.2 (t), 133.0 (q), 134.1 (t), 136.5 (q), 136.77 (q), 136.8 (q), 137.0 (q), 137.8 (q), 137.9 (q), 137.96 (q), 138.0 (q), 138.1 (q), 138.7 (q), 144.7 (q), 144.8 (q), 145.1 (q), 145.2 (q), 148.4 (q), 152.7 (q), 152.8 (q), 152.9 (q), 153.0 (q), 153.2 (q), 153.2 (q), 167.4 (q, *C*OOR), 167.7 (q, *C*OOR), 167.8 (q, *C*OOR), 169.0 (q, *C*OOR). IR (CCl_4): $\tilde{\nu}$ = 3095 cm^{-1}, 3069, 3038, 2940, 2872, 1755 (CO), 1533, 1455, 1414, 1367, 1341, 1176, 1098, 1010. UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 285 nm (3.92). MS (ESI, acetone): m/z (%) = 2023.9 (100) $[M + Na]^+$, 537.6 (9), 413.5 (64). $C_{125}H_{101}NO_{24}$ (2001.17): calcd. C 75.02, H 5.09, N 0.70; found C 74.30, H 5.31, N 0.80.

Synthesis of Pedunculagin (1): A suspension of tetraester **7** (323 mg, 0.16 mmol), Pd/C (350 mg, 10%) and dry THF (15 mL) was treated with hydrogen (H_2) passing slowly through the reaction mixture, which was stirred for 24 h at room temperature. The solid was filtered off through celite, and the celite was washed with acetone (150 mL). The solvent was removed under reduced pressure to give an oily residue. Purification of the crude product was carried out by reversed phase chromatography (H_2O/MeOH, 9:1 vol.%) to afford product **1** (82 mg, 0.10 mmol, 65%) as a powder. $[\alpha]_D^{20} = +60.5$ (c = 0.70, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone/D_2O): δ = 3.48−3.61 ppm (m), 4.14−4.22 (m), 4.29 (t, J = 7.0 Hz), 4.52−4.59 (m), 4.78−4.84 (m), 5.00−5.05 (m), 5.16−5.30 (m), 5.38−5.45 (m), 6.30 (s, 1 H), 6.31 (s, 1 H), 6.50 (s, 1 H), 6.54 (s, 1 H), 6.59 (s, 1 H), 6.60 (s, 1 H), 6.63 (s, 1 H), 6.64 (s, 1 H). ^{13}C NMR (75 MHz, acetone/d_6/D_2O): δ = 62.4 ppm (s, Gluc-*C*-6), 63.8 (s, Gluc-*C*-6), 67.4 (t), 69.8 (t), 70.2 (t), 72.5 (t), 75.80 (t), 76.1 (s), 77.9 (t), 78.4 (t), 91.7 (t, Gluc-*C*-1α), 95.4 (t, Gluc-*C*-1β), 107.4 (t), 107.5 (t), 107.7 (t), 107.8 (t), 108.3 (t), 114.7 (q), 115.0 (q), 115.1 (q), 116.0 (q), 116.1 (q), 116.3 (q), 125.9 (q), 126.0 (q), 126.1 (q), 126.37 (q), 126.4 (q), 126.5 (q), 126.6 (q), 126.7 (q), 136.8 (q), 136.61 (q), 136.57 (q), 136.4 (q), 136.3 (q), 144.5 (q), 144.6 (q), 144.7 (q), 145.3 (q), 145.4 (q), 145.46 (q), 145.5 (q), 168.5 (q, 2 × *C*OOR), 168.7 (q, *C*OOR), 168.8 (q, *C*OOR), 169.3 (q, *C*OOR), 169.5 (q, *C*OOR), 169.97 (q, *C*OOR), 170.0 (q, *C*OOR). IR (KBr): $\tilde{\nu}$ = 3353 cm^{-1}, 2960, 2929, 2878, 2857, 1745 (CO), 1626, 1517, 1450, 1352, 1222, 1181, 1041, 1016.

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