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Synthesis of picropodophyllin homolactone

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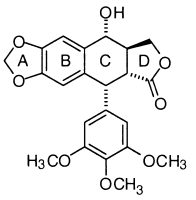
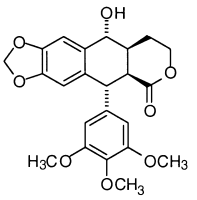
Abstract

Based on a Wittig olefination strategy, the first synthesis of picropodophyllin homolactone **2** is described in nine steps and 30% overall yield from podophyllotoxine **1**. The relative configuration of **2** was unambiguously determined using 2D NOESY NMR and a Monte Carlo search protocol. This work corrects the literature on the synthesis of **2**.

We have been engaged in activities[1] in the area of podophyllotoxin **1**,[2] a natural product endowed with potent antimitotic activity. The *trans*-fused lactone moiety is being considered as an important factor for displaying significant cytotoxic activity,[3] the *cis* analogues being less potent. Less is known concerning six-membered ring lactone analogues. In 1985, Anjanamurthy and Lokanatha Rai[4] reported the synthesis of picropodophyllin homolactone **2**. However, it appeared to us that the IR absorption at 1760 cm^{-1} was not consistent with a δ-lactone functionality. In this communication, we describe the first synthesis of picropodophyllin homolactone **2** via a route which would accomodate a good degree of flexibility with respect to the size and nature of the D-ring.



1



2

The synthesis of picropodophyllin homolactone **2** began with podophyllotoxin **1**, which was transformed into **3**[5] (97%) through silylation (TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C) of the benzylic

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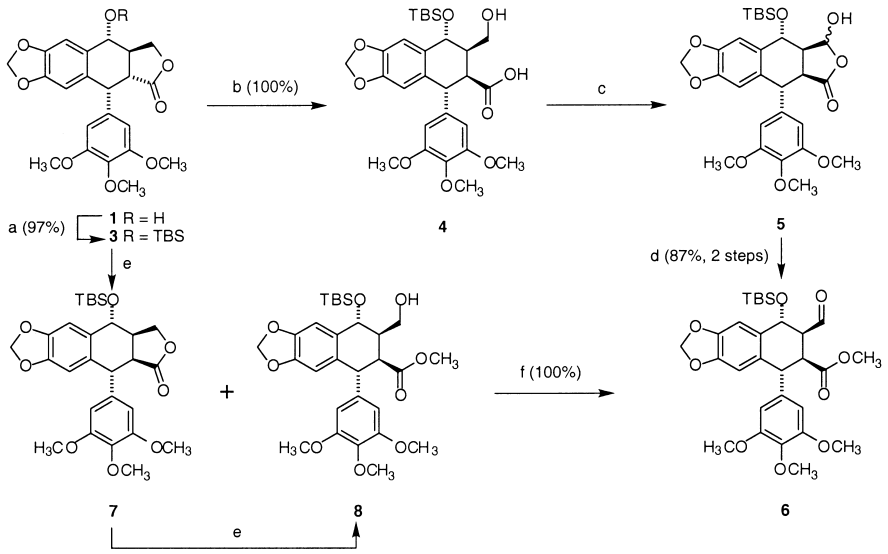
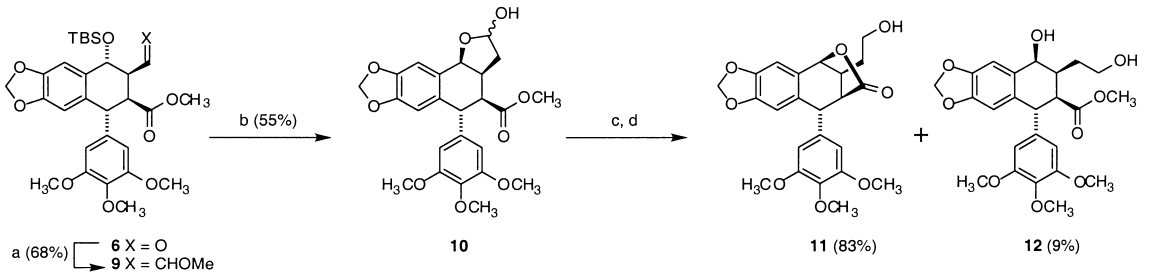
alcohol (Scheme 1). Subsequent hydrolysis of the γ-lactone (2N NaOH, THF, 0°C) afforded the resulting hydroxy-acid **4** (quantitative yield) with epimerization at the C_2 stereocenter. Oxidation of **4** to the low soluble lactols **5** (Dess–Martin periodinane, CH_2Cl_2, 25°C) followed by esterification (CH_3I, K_2CO_3, acetone, 25°C) provided the desired aldehyde **6** (87% yield for the two steps). Similar lactol compounds have been used in the asymmetrical total synthesis of (–)-podophyllotoxin reported by Bush and Jones.[6] Alternatively, according to earlier observations,[7] transesterification of **3** under equilibrating conditions (K_2CO_3 cat., MeOH, 25°C) resulted in a mixture of picropodophyllin derivative **7**[5] (43%) and methyl picropodophyllate derivative **8** (57%). Usefully, the overall yield of **8** was improved to 86%, since it was possible to recycle (three cycles) the undesired lactone **7** by conversion into the methyl ester **8** using the same procedure. A Swern oxidation of the resulting alcohol also afforded the subgoal **6**. The one-carbon homologation and the completion of the synthesis were then addressed (Scheme 2).

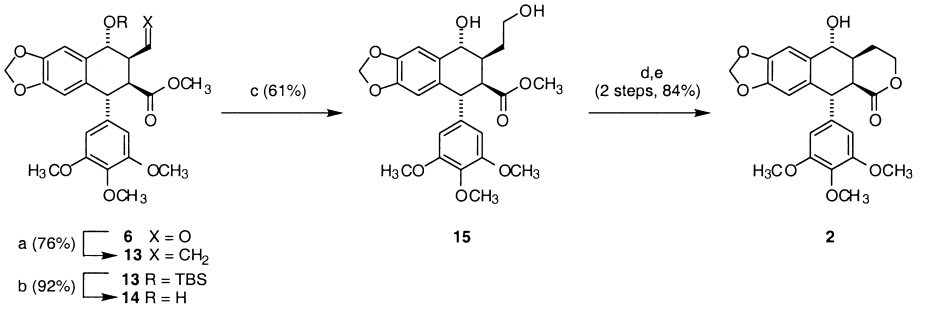


Scheme 1. (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C. (b) NaOH, THF/H_2O, 0°C. (c) Dess–Martin periodinane, CH_2Cl_2, 25°C. (d) CH_3I, K_2CO_3, acetone, 25°C. (e) K_2CO_3 cat., MeOH, 25°C. (f) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, –78 to 25°C



Scheme 2. (a) $Ph_3P^+CH_2OCH_3$ Cl^-, *n*-BuLi, THF, –40 to 25°C. (b) 30% $HClO_4/H_2O$, Et_2O, 25°C. (c) $NaBH_4$, MeOH, 25°C. (d) SiO_2, MeOH, reflux

The enol ether functionality of **9** was stereoselectivity incorporated (84% overall yield, *E*:*Z* ratio = 60:40 by ^{1}H NMR analysis) by treating **6** with methoxymethylenetriphenylphosphonium chloride and *n*-BuLi.[8] A subsequent hydrolysis of **9** (30% $HClO_4/H_2O$, Et_2O, 25°C) afforded an inseparable 1:5 mixture of the stable γ-lactols **10** (55%). This transformation accomplished not only the two deprotection operations, but also the unwanted epimerization at C_4. Attempts to avoid the acidic removal of the TBS ether protecting group by the method of Yamamoto[9] (TBAF, BF_3–Et_2O) also led to **10**, but in low yield. Sequential reduction ($NaBH_4$, MeOH, 25°C) of **10** and acidic treatment of the resultant diol gave a mixture of the anticipated[10] γ-lactone **11** (83%), encompassing a neopodophyllotoxin-like structure,[11] and hydroxy-ester **12** (9%). The utility of **11**[12] as a viable intermediate in the synthesis of **2** was not examined. Consequently, we chose to subject aldehyde **6** to a Wittig methylenation (76%) in order to suppress the problematic acidic hydrolysis of the enol ether **9** (Scheme 3).



Scheme 3. (a) $Ph_3P^+CH_3\ I^-$, *n*-BuLi, THF, –78°C. (b) TBAF, THF, 25°C. (c) 9-BBN, THF then 30% H_2O_2/H_2O, phosphate buffer, pH 7, MeOH, 25°C. (d) NaOH, THF/H_2O, 0°C. (e) DCC, 4-DMAP, THF, 25°C

Attempted direct alkene hydroboration of **13** by means of conventional reagents (9-BBN, BH_3/SMe_2) failed to provide the desired TBS ether analogue of **15**. However, diol **15** was conveniently prepared in 56% overall yield by deprotection of the sterically hindered TBS ether and subsequent hydroboration (9-BBN, THF, 25°C) of the olefin **14**. The coupling constants of **15** ($J_{1,2} = 8.9$, $J_{2,3} = 3.5$ and $J_{3,4} = 4.4$ Hz) were similar to those found for methyl picropodophyllate.[13]

The synthesis was then completed by saponification of **15**, giving the crude δ-hydroxy-acid, which was immediately treated with DCC and 4-DMAP to afford the desired δ-lactone **2**[14] in 84% overall yield. The structure of **2** was established unambiguously on the basis of a spectroscopic analysis (^{1}H NMR (400 MHz), 1D, 2D NOESY; ^{13}C NMR (100 MHz); IR) and molecular modeling. This product was clearly different from that described earlier[4] by comparison of their melting points and spectroscopic data (^{1}H NMR, IR). The IR absorption at 1741 cm^{-1} indicated the presence of a δ-lactone functionality. A Monte Carlo search (SYBYL 6.5/Tripos force field) gave the lowest energy conformations as **A** and **B** respectively, for the *cis*-lactone **2** and the *trans*-isomer **16** (Fig. 1). The vicinal coupling constants (H-1, H-2, H-3, H-4) and the observed NOESY (absence of H-2/H-4 and H-3/H-12a interactions, strong H-2/H-12a NOESY) confirm structure **2** for the synthesized lactone, in good agreement with a conformation such as **A**. These data allow us to exclude structure **16**.

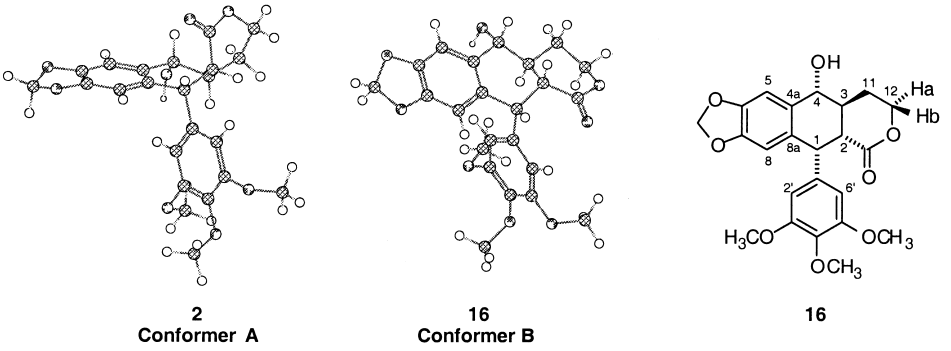


Figure 1.

Compounds **10**, **11** and **2** displayed low activities in vitro against L1210 (IC_{50} values in μM: **10**, 23.5; **11**, 21; **2**, 1.3; **1**, 0.007).

In summary, the first synthesis of **2** has been achieved from podophyllotoxin **1** in nine steps and 30% overall yield. Moreover, our route should allow the construction of podophyllotoxin analogues including D-rings of various sizes and degrees of substitution, from the key intermediate **6**. Such an approach is currently under investigation.

Acknowledgements

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12. Analytical data for compound **11**. Mp: 88–90°C; $[\alpha]_D^{25}$ +42 (*c* 0.4; $CHCl_3$); IR ($CDCl_3$) 3628, 2938, 1769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, 1H, $J=4.7$ Hz, OH), 1.62 (m, 1H, H-11a), 1.81 (m, 1H, H-11b), 2.78 (d, 1H,

$J = 1.1$ Hz, H-2), 2.86 (t, 1H, $J = 7.3$ Hz, H-3), 3.72 (m, 2H, H-12a, H-12b), 3.78 (s, 6H, OMe), 3.84 (s, 3H, OMe), 4.41 (d, 1H, $J = 1.1$ Hz, H-1), 5.10 (d, 1H, $J = 1.0$ Hz, H-4), 5.94 (d, 1H, $J = 1.2$ Hz, OCH_2O), 5.99 (d, 1H, $J = 1.2$ Hz, OCH_2O), 6.31 (s, 2H, H-2′, H-6′), 6.49 (s, 1H, H-8), 6.75 (s, 1H, H-5); MS (DCI/NH_3) m/z 429 $[M+H]^+$, 446 $[M+NH_4]^+$.

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14. Analytical data for compound **2**. Mp: 197–198°C (hexane/EtOAc), lit.:[4] 144–146°C; $[\alpha]_D^{25}$ –114 (c 0.1; $CHCl_3$); IR ($CDCl_3$) 3800–3400, 2932, 1741, 1591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09–2.19 (m, 2H, H-11a, H-11b), 2.43 (bs, 1H, OH), 2.53 (m, 1H, H-3), 3.01 (dd, 1H, $J = 6.4$, 2.9 Hz, H-2), 3.79 (s, 6H, OMe), 3.84 (s, 3H, OMe), 4.26–4.35 (m, 1H, H-12a), 4.38 (d, 1H, $J = 9.6$ Hz, H-4), 4.43–4.51 (m, 1H, H-12b), 4.64 (d, 1H, $J = 2.9$ Hz, H-1), 5.91–5.94 (degenerated m, 2H, OCH_2O), 6.30 (s, 2H, H-2′, H-6′), 6.43 (s, 1H, H-8), 7.00 (s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) quaternary carbons not specifically assigned δ 24.9 (C-11), 34.2 (C-3), 43.6 (C-1), 46 (C-2), 56 (2C, OMe), 60.7 (1C, OMe), 66 (C-12), 71.4 (C-4), 101 (OCH_2O), 105.8 (C-5), 105.9 (2C, C-2′, C-6′), 109.4 (C-8), 128, 131.5, 137, 136.8 (quaternary carbons C-1′, C-4′, C-4a, C-8a), 146.9, 147.4 (quaternary carbons C-6, C-7), 153.2 (2C, C-3′, C-5′), 173 (C=O); MS (DCI/NH_3) m/z 446 $[M+NH_4]^+$.