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A New and Efficient Strategy for the Synthesis of Podophyllotoxin and Its Analogues

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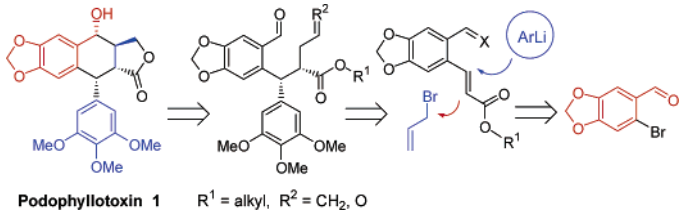
ABSTRACT



An efficient and stereoselective strategy for the total synthesis of podophyllotoxin was developed. This route leads to podophyllotoxin 1 in only 12 steps with 29% overall yield. A notable feature of this synthetic strategy is the use of the cascade addition–alkylation to ensure the key C1–C2 stereochemistry that is pivotal for the synthesis of podophyllotoxin.

The natural product podophyllotoxin (**1**), a potent inhibitor of microtubule assembly, is the major constituent of the podophyllum family.[1] Podophyllotoxin is currently used for the treatment of venereal warts and also has served as an important precursor for the preparation of clinical anti-tumor drugs etoposide and teniposide.[2] A recent report also raised the possibility of using podophyllotoxin derivatives as anti-HIV agents.[3] Owing to its significant clinical role, the synthesis and biological studies of podophyllotoxin and its analogues have been an important topic in medicinal chemistry.[4] The structure of podophyllotoxin is shown in Figure 1.

The important biological activities as well as the intriguing structure (four contiguous chiral centers, rigid *trans* lactone, pseudoaxial ring E, and facile epimerization at C2 and C4) of podophyllotoxin have long attracted the attention of numerous research groups. Synthetic efforts directed toward those aryl tetrahydronaphthalene lignan lactones have generated a great deal of creative methodologies.[5] Although there are numerous documented strategies for the syntheses of

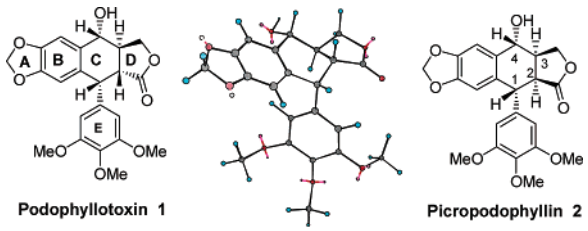


Figure 1. Podophyllotoxin and picropodophyllin.

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(2) (a) Hande, K. R. *Eur. J. Cancer* **1998**, *34*, 1514. (b) Damayanthi, Y.; Lown, J. W. *Curr. Med. Chem.* **1998**, *5*, 205. (c) Silverberg, L. J.; Dillon, J. L.; Vemishetti, P.; Sleezer, P. D.; Discordia, R. P.; Hartung, K. B.; Gao, Q. *Org. Process Res. Dev.* **2000**, *4*, 34 and references therein.

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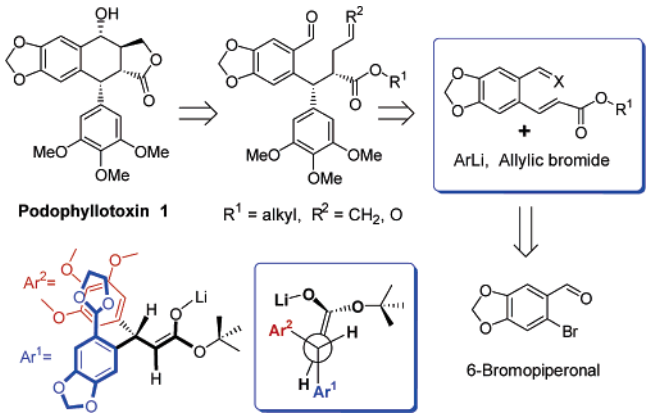
podophyllotoxin, many unfortunately fail to meet adequate measures of efficiency, stereoselectivity, and/or flexibility. Furthermore, only a few proceed through tactics that do not involve epimerization of thermodynamically more stable picropodophyllin **2** to **1**, via kinetic protonation of ester enolates of **2** at a later stage in the synthetic routes.[6]

In seeking a more efficient and flexible synthetic strategy toward aryltetralin lactone podophyllotoxin **1** and its analogues, we have designed a new route outlined in Scheme 1

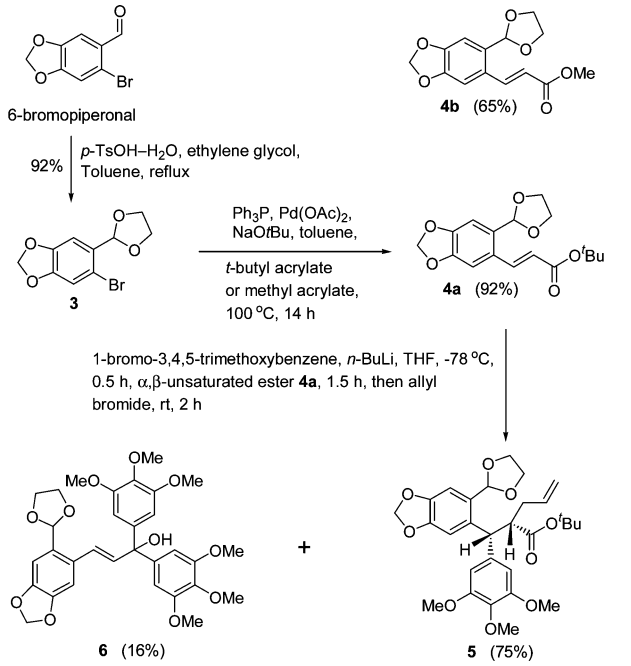
Scheme 1. Retrosynthetic Analysis of Podophyllotoxin



that should require fewer steps and result in high stereoselectivities. Key to the success of our new approach was a tandem process that was initiated by aryl lithium and quenched with allyl bromide, a conjugate addition followed by enolate alkylation. We anticipated that a desired anti stereochemistry would be ensured at this step.

We started our research with the protection of the carbonyl group in 6-bromopiperonal, a commercially available material. After a successful Heck reaction, we obtained α,β-unsaturated ester **4** (**4a** and **4b**). The next conjugate addition/enolate alkylation toward **4a** was carried out initially with organocupurate. Unfortunately, we did not obtain the desired tandem process, with mainly starting material being obtained. Utilization of aryl lithium generated in situ finally promoted the cascade reaction. As expected, only one diastereoisomer was obtained in 75% yield together with minor 1,2-addition product **6**. Although the relative stereochemistry might be predicted by the model shown in Scheme 1, it was not confirmed at this stage. No attempt was made to determine the stereochemistry, because this issue could be addressed in a later stage of our synthesis. It was worthwhile to note that when the reaction was conducted with the methyl ester of unsaturated carbonyl compound **4b**, the same operation resulted in mainly 1,2-addition with no desired 1,4-addition product being obtained. A bulky *tert*-butyl ester group is necessary for the initial Michael addition (Scheme 2).

Scheme 2. Key Conjugate Addition−Alkylation



After deprotection of the ketal moiety, the resulting aldehyde **7** was submitted to an oxidative cleavage process. Dihydroxylation of aldehyde **7** with osmium tetroxide followed by treatment with $NaIO_4$ afforded dialdehyde **8** in 94% yield over two steps (Scheme 3). Although chromatography could be conducted, the liable dialdehyde **8** was better used in the next aldol reaction without further purification. In the presence of potassium carbonate in methanol, the aldol condensation afforded high yield (99%) of unsaturated aldehyde **9**. The relative stereochemistry for C2 and C3 was established by a ROESY spectrum and could also be deduced by the coupling constant (4.8 Hz) between the proton in C2 and the proton in C3. Although compound **9** could be utilized for the synthesis of podophyllotoxin and its analogues, a better intermediate was sought. To our delight, treatment of dialdehyde **8** with L-proline resulted in only one pair of diastereisomers at the C4 position.[7] Chromatography of the aldol product was problematic and led to conjugate aldehyde **9**; a silica gel mediated dehydration process might occur in column chromatography. This issue was finally solved by direct reduction of the aldol product with sodium borohydride to 1,3-diol **10** (see Scheme 4). An

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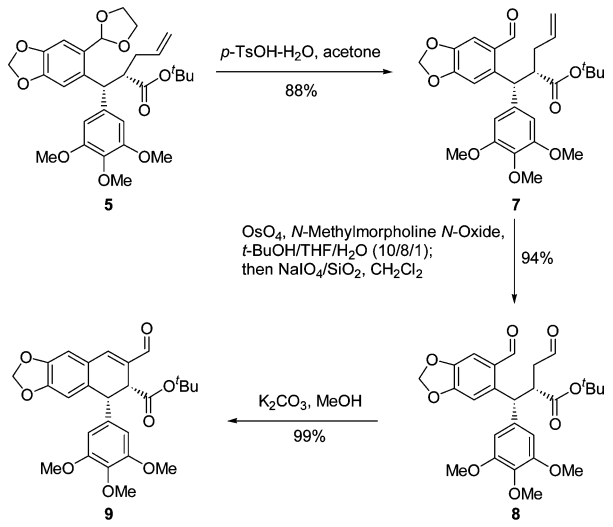
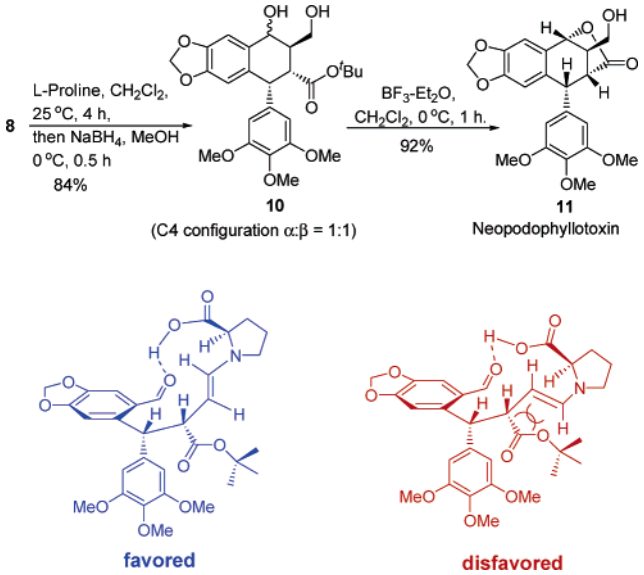
(6) (a) Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.* **1989**, *54*, 4280 and epimerization of C3 required. (b) Kraus, G. A.; Wu, Y. *J. Org. Chem.* **1992**, *57*, 2922. (c) Charlton, J. L.; Koh, K. *J. Org. Chem.* **1992**, *57*, 1514. (d) Bush, E. J.; Jones, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 151.

Scheme 3. Synthesis of Dialdehyde **8** and Related Aldol Reaction



anti relative stereochemistry was observed between the ester group at C2 and the methylene-hydroxyl group at C3. The relative stereochemistry is shown in Scheme 4.

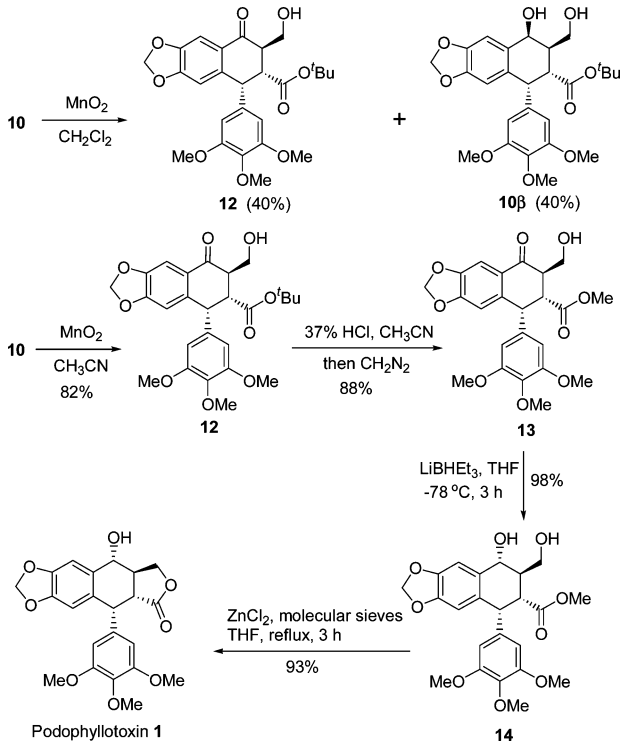
Scheme 4. Proline-Promoted Aldol Reaction



In our initial synthetic plan, treatment of 1,3-diol **10** with acid or Lewis acid would lead to podophyllotoxin **1**, a deprotection and lactonization process. Unfortunately, treatment of **10** with trifluoroacetic acid or BF_3·Et_2O led to neopodophyllotoxin in nearly quantitative yield, probably via a carbon cation (C4) pathway. This transformation provided a further evidence for the relative stereochemistry of 1,3-diol **10**.

Although neopodophyllotoxin has been transformed to podophyllotoxin and a formal synthesis could be claimed,[6c] we still decided to convert the 1,3-diol to the ketone by a regioselective oxidation. Similar oxidation of 1,3-diol **10** to the ketone was reported in the literature; unfortunately, oxidation with MnO_2 provided the desired transformation in low yield (40%).[8] We conducted an oxidation with activated MnO_2 in dichloromethane and found that 40% yield of ketone **12** was formed together with recovery of pure 1,3-diol *cis*-isomer **10**β (C4-hydroxyl group in β orientation) (Scheme 5). This observation suggested that an intra-

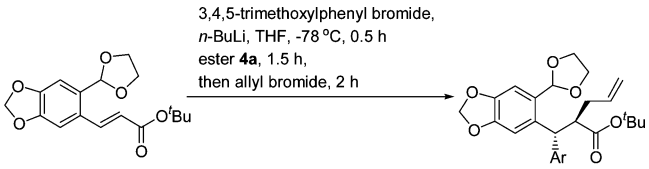
Scheme 5. Final Stage of the Total Synthesis of (±)-Podophyllotoxin



molecular hydrogen bond might be formed in the 1,3-diol *cis*-isomer thus rendering it resistant to oxidation and only

(7) In principle, two new stereogenic centers were formed and four diastereisomers were expected. Due to steric effect as depicted in Scheme 4, only one pair of diasteroisomers were obtained. Spectra date for key intermediates follow. Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.06 (1H, s), 6.93 (1H, s), 6.67 (2H, s), 6.24 (1H, s), 5.92 (1H, d, J = 1.2Hz), 5.86 (1H, d, J = 1.2 Hz), 5.85−5.68 (1H, m), 5.03 (1H, d, J = 10.1 Hz), 4.98 (1H, d, J = 3.0 Hz), 4.37 (1H, d, J = 11.7 Hz), 4.21−4.12 (1H, m), 4.12−4.03 (3H, m), 3.84 (6H, s), 3.79 (3H, s), 3.09 (1H, ddd, J = 7.1, 7.2, 11.7 Hz), 2.28 (2H, t, J = 7.1 Hz), 1.17 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.47, 153.58, 148.31, 146.43, 137.61, 137.04, 135.94, 135.58, 129.33, 117.04, 108.21, 106.39, 105.88, 101.45, 101.26, 81.02, 65.74, 65.31, 61.18, 56.50, 52.09, 47.81, 36.41, 28.10. Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.58 (1H, s), 7.29 (1H, s), 6.87 (1H, s), 6.62 (1H, s), 6.24 (2H, s), 5.99 (2H, s), 4.51 (1H, d, J = 4.8 Hz), 3.87 (1H, d, J = 4.8 Hz), 3.78 (3H, s), 3.74 (6H, s), 1.31 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 191.31, 171.02, 153.31, 150.39, 147.32, 145.10, 137.37, 134.30, 134.21, 125.33, 109.99, 108.89, 105.29, 101.84, 81.54, 60.90, 56.25, 46.94, 46.08, 27.90. Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48 (1H, s), 6.57 (1H, s), 6.20 (2H, s), 6.02 (1H, s), 5.99 (1H, s), 4.49 (1H, d, J = 5.4 Hz), 4.23−4.12 (1H, m), 3.88−3.70 (1H, m), 3.77 (3H, s), 3.73 (6H, s), 3.42 (1H, dd, J = 5.4, 12.8 Hz), 3.13−3.06 (1H, m), 2.85 (1H, brs), 1.31 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 198.44, 170.25, 153.33, 153.16, 147.99, 141.48, 137.54, 134.41, 126.69, 108.55, 106.65, 105.90, 102.14, 81.78, 62.48, 60.92, 56.23, 47.42, 45.81, 28.04.

Scheme 6. Michael Addition with Aryl Lithium



15: Ar = 3,5-Difluoro-phenyl, yield: 74%
16: Ar = 3,5-Dimethyl-4-Methoxylphenyl, yield: 71%

the *trans*-isomer in the mixture of 1,3-diol **10** was oxidized. In our previous research, we found that acetonitrile was a good solvent for reactions with substrates that might form an intramolecular hydrogen bond.[9] By utilization of acetonitrile as solvent, we finally got the desired ketone **12** in 82% yield. The *tert*-butyl group was then removed by treatment with 4 N HCl in acetonitrile, and the resulting product was directly converted to the methyl ester.[10] After reduction of the ketone moiety with super hydride,[8] a lactonization furnished podophyllotoxin **1** in 93% yield.[6d]

The flexibility of our strategy could be demonstrated by utilization of another aryl lithium as nucleophile in the key conjugate addition/enolate alkylation process. We found that even 1-bromo-3,5-difluorobenzene could be used in this step with 74% yield.

In summary, we have developed a highly practical, efficient, and stereoselective strategy for the total synthesis of podophyllotoxin. This route leads to podophyllotoxin **1** in only 12 steps with 29% overall yield. A notable feature of this synthetic strategy is the use of a cascade addition−alkylation to ensure the key C1−C2 stereochemistry that is pivotal for the synthesis of podophyllotoxin. This work also lays a foundation for the synthesis of representative of the podophyllotoxin family as well as analogues that are of interest for medicinal chemistry. Modification of ring systems presented in podophyllotoxin is possible by our synthetic procedure. Synthesis of analogues is currently underway in our laboratory.

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Supporting Information Available: General experimental details and ^{1}H NMR, ^{13}C NMR, MS, and HRMS spectra of all key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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