Natural Product Synthesis

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Concise Stereoselective Synthesis of (−)-Podophyllotoxin by an Intermolecular Iron(III)-Catalyzed Friedel–Crafts Alkylation**

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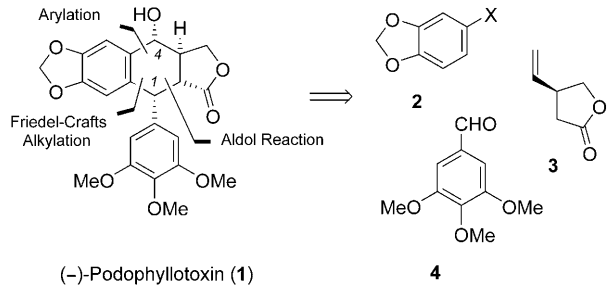
Owing to their diverse biological activities, in particular their cytotoxicity and antiviral properties, podophyllotoxin (**1**) and its derivatives are important members of the lignane class of natural products.[1] The biological profile of these compounds, which has inspired the design of new drugs, has been investigated intensively. The biological activity of podophyllotoxin has generated strong interest in the development of synthetic routes to this natural product.[2] Since the first synthesis of enantiomerically pure (−)-podophyllotoxin (**1**) by Meyers and co-workers[3] in a 24-step sequence, another five syntheses of the enantiomerically pure natural product have been reported.[4,5] Many additional studies have been concerned with the development of formal total syntheses and syntheses of racemic podophyllotoxin.[2] In all synthetic approaches to podophyllotoxin, the modular generation of the tetracyclic backbone and the brevity of the sequence are of central importance. We report herein a six-step total synthesis of enantiomerically pure (−)-podophyllotoxin with an iron(III)-catalyzed Friedel–Crafts alkylation as a key step. Apart from the use of a terminal alkene as an aldehyde equivalent, no protecting-group manipulations were required in the entire synthetic sequence.

Our retrosynthesis involved the disconnection of the target molecule into the three similarly sized fragments **2**, **3**, and **4** (Scheme 1).[6] We planned to use an intramolecular arylation to complete the tetracyclic core. Possible cyclization



Scheme 1. Retrosynthetic disconnection of (−)-podophyllotoxin (**1**) into fragments **2**, **3**, and **4**.

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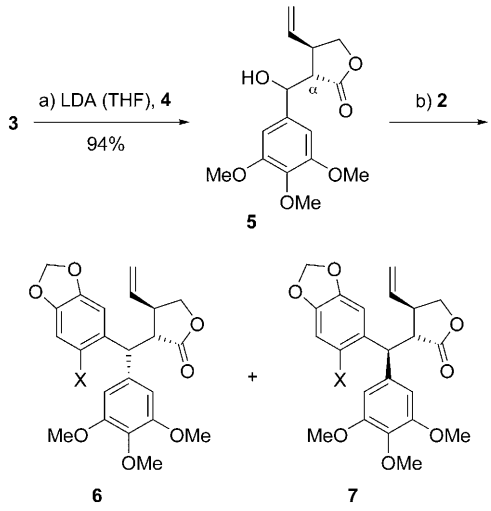
methods included a Heck reaction, a Nozaki–Hiyama coupling, and a classical Lewis acid mediated hydroxyalkylation. A diastereoselective intermolecular Friedel–Crafts alkylation was designed as the pivotal step, which should establish the stereogenic center at C1.

In accordance with the outlined plan, the synthesis commenced with the Taniguchi lactone (**3**), which is accessible in enantiomerically pure form from 2-butyne-1,4-diol in two steps with a subsequent conventional resolution[7] or in six steps through an enantioselective iridium-catalyzed allylation.[8] An aldol reaction with aldehyde **4** afforded **5** with excellent stereoselectivity with respect to the stereogenic center at the α position of the lactone (Scheme 2). The fact



Scheme 2. Aldol reaction und subsequent intermolecular Friedel–Crafts alkylation: a) LDA (1.1 equiv), THF, −78 °C, 30 min, then **4** (1.1 equiv), −78 °C, 3 h, 94% (d.r. 52:48); b) see Table 1. LDA = lithium diisopropylamide.

that the simple diastereoselectivity was low, as expected, was of no relevance, as the hydroxy group was substituted with an aryl group in the next step in a S_N1-type alkylation. To this end, **5** was treated with 1,3-benzodioxole (**2a**, X = H) and other derivatives **2** under acid catalysis. On the basis of our previous studies on diastereoselective Friedel–Crafts alkylation reactions with chiral benzylic carbenium ions,[9] we expected the stereoisomer **6** to be the predominant product.

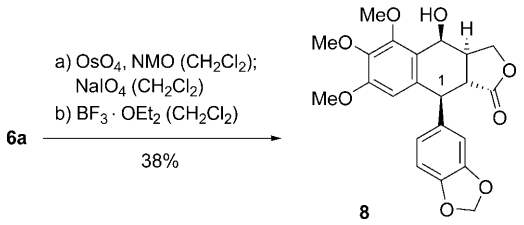
Whereas the reaction of **2a** with **5** proceeded smoothly under the usual reaction conditions ($HBF_4 \cdot OEt_2$ in CH_2Cl_2) with good diastereoselectivity to give product **6a** (d.r. 85:15; Table 1, entry 1), the analogous reactions of the substituted derivatives **2b** (X = Br), **2c** (X = OTf), and sesamol (**2d**, X = OH) failed (Table 1, entries 2–4). Only *O*-allyl-protected

sesamol **2e** underwent the desired reaction to afford products **6e** and **7e** (d.r. = 84:16; Table 1, entry 5). The discovery that this last reaction was also promoted by a catalytic amount of $Bi(OTf)_3$ (Table 1, entry 6)[10] prompted us to evaluate Bi catalysis with substrates **2b**–**2d**. Under these conditions, sesamol (**2d**) was transformed diastereoselectively into the desired product **6d** (d.r. 90:10; Table 1, entry 9); no conversion was observed with **2b** and **2c** (entries 7 and 8). Further optimization studies led to the identification of $FeCl_3$,[11] which outperformed even $AuCl_3$ (Table 1, entry 10), as the optimum catalyst for the transformation of **5** into **6d** (entry 11).[12] The product **6d** was formed with high diastereoselectivity in nearly quantitative yield (d.r. 94:6; Table 1, entry 11).

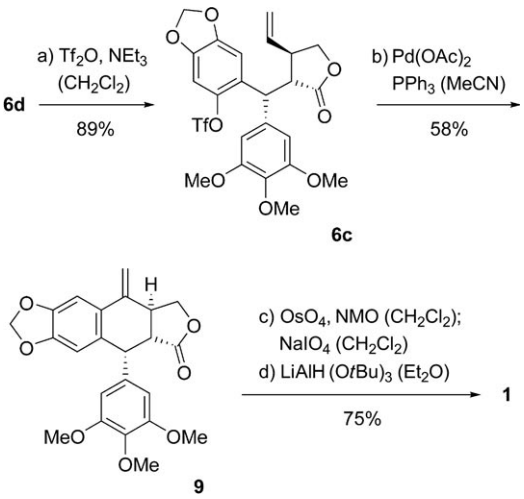
For the completion of the synthesis, different cyclization methods were evaluated. Unfortunately, an attempted Lewis acid catalyzed ring closure, which would have given rise to the shortest possible sequence, did not afford the desired product. Although oxidative cleavage of the terminal alkene to provide the aldehyde proceeded smoothly, electronic and conformational factors[13] prohibited the envisaged cyclization onto the 1,3-benzodioxole substituent. Instead, under a variety of conditions (one example is shown in Scheme 3), cyclization always occurred by electrophilic attack at the trimethoxyphenyl substituent to generate the podophyllotoxin isomer **8**.

Reactions of triflate **6c**, which can be prepared readily from alcohol **6d** (Scheme 4), were more successful. A Heck reaction[14] led to the desired cyclized product **9**.[15] An attempted Nozaki–Hiyama coupling reaction[16] investigated as an alternative cyclization procedure (after oxidative cleavage of the terminal alkene to give the corresponding aldehyde) did not lead to podophyllotoxin. Olefin **9** was converted smoothly by dihydroxylation and periodate cleavage into podophyllotoxon,[17] which was reduced diastereoselectively to **1** by a previously reported procedure.[18]

All physical properties of synthetic (−)-podophyllotoxin (**1**), which was obtained from the Taniguchi lactone (**3**) in 35% overall yield, were identical to those of the natural product. The synthesis illustrates that a stereogenic center in the β position to an ester or lactone moiety can be constructed highly diastereoselectively through a Lewis acid catalyzed S_N1 reaction if a stereogenic center is already present in the α position.



Scheme 3. Undesired regioselectivity in the BF_3-catalyzed cyclization of **6a**: a) OsO_4 (5 mol%), NMO (3 equiv), CH_2Cl_2, 20°C, 4 h, then $NaIO_4$ (2 equiv), 30 min, 92%; b) $BF_3{\cdot}OEt_2$ (10 equiv), CH_2Cl_2, −78°C, 3 h, 41%. NMO = *N*-methylmorpholine *N*-oxide.



Scheme 4. Completion of the total synthesis of (−)-podophyllotoxin (**1**): a) Tf_2O (1.5 equiv), NEt_3 (2 equiv), CH_2Cl_2, 0°C, 1 h, 89%; b) $Pd(OAc)_2$ (10 mol%), PPh_3 (0.3 equiv), K_2CO_3 (3 equiv), MeCN, 80°C, 20 h, 58%; c) OsO_4 (5 mol%), NMO (3 equiv), CH_2Cl_2, 20°C, 4 h, then $NaIO_4$ (2 equiv), 30 min, 95%; d) $LiAlH(OtBu)_3$ (10 equiv), Et_2O, −78→20°C, 18 h, 79% (d.r. 98:2). Tf = trifluoromethanesulfonyl.

Table 1: Optimization of the reaction conditions for the diastereoselective Friedel–Crafts alkylation.

Entry	X	**2**	Acid (mol%)	Solvent	*T* [°C]	*t* [min]	Yield [%][c]	d.r.[d] **6/7**
1[a]	H	**2a**	HBF_4 (400)	CH_2Cl_2	20	45	76	85:15
2[a]	Br	**2b**	HBF_4 (400)	CH_2Cl_2	20	45	–	–
3[a]	OTf	**2c**	HBF_4 (400)	CH_2Cl_2	20	45	–	–
4[a]	OH	**2d**	HBF_4 (400)	CH_2Cl_2	20	45	–	–
5[b]	OAllyl	**2e**	HBF_4 (125)	CH_2Cl_2	−78→20	15	97	84:16
6[b]	OAllyl	**2e**	$Bi(OTf)_3$ (10)	$MeNO_2$	20	80	94	77:23
7[b]	Br	**2b**	$Bi(OTf)_3$ (10)	$MeNO_2$	20	80	–	–
8[b]	OTf	**2c**	$Bi(OTf)_3$ (10)	$MeNO_2$	20	120	–	–
9[b]	OH	**2d**	$Bi(OTf)_3$ (10)	$MeNO_2$	20	80	95	90:10
10[b]	OH	**2d**	$AuCl_3$ (10)	$MeNO_2$	20	60	98	90:10
11[b]	OH	**2d**	$FeCl_3$ (5)	CH_2Cl_2	20	60	99	94:6

[a] HBF_4 (4 equiv) and the corresponding nucleophile **2** (10 equiv) were dissolved in CH_2Cl_2, and alcohol **5** (50 mM in CH_2Cl_2) was added dropwise over a period of 30 min with a syringe pump. [b] Compound **2** (4 equiv) was used in the solvent indicated. [c] Yield of the isolated product. [d] The diastereomeric ratio was determined by ^1H NMR spectroscopy of the crude product. Tf = trifluoromethanesulfonyl.

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[1] M. Gordaliza, P. A. García, J. M. Miguel del Corral, M. A. Castro, M. A. Gómez-Zurita, *Toxicon* **2004**, *44*, 441–459.
[2] For reviews, see: a) R. S. Ward, *Phytochem. Rev.* **2003**, *2*, 391–400; b) R. S. Ward, *Nat. Prod. Rep.* **1999**, *16*, 75–96; c) R. S. Ward, *Synthesis* **1992**, 719–730; d) R. S. Ward, *Tetrahedron* **1990**, *46*, 5029–5041.

[3] R. C. Andrews, S. J. Teague, A. I. Meyers, *J. Am. Chem. Soc.* **1988**, *110*, 7854 – 7858.
[4] For the synthesis of enantiomerically pure (+)- or (−)-podophyllotoxin, see: a) R. Van Speybroeck, H. Guo, J. van der Eycken, M. Vandewalle, *Tetrahedron* **1991**, *47*, 4675 – 4682; b) E. J. Bush, D. W. Jones, *J. Chem. Soc. Chem. Commun.* **1993**, 1200 – 1201; E. J. Bush, D. W. Jones, *J. Chem. Soc. Perkin Trans. 1* **1996**, 151 – 155; c) S. B. Hadimani, R. P. Tanpure, S. V. Bhat, *Tetrahedron Lett.* **1996**, *37*, 4791 – 4794; d) D. B. Berkowitz, S. Choi, J.-H. Maeng, *J. Org. Chem.* **2000**, *65*, 847 – 860; e) A. J. Reynolds, A. J. Scott, C. I. Turner, M. S. Sherburn, *J. Am. Chem. Soc.* **2003**, *125*, 12108 – 12109.
[5] For the synthesis of (−)-epipodophyllotoxin, see: U. Engelhardt, A. Sarkar, T. Linker, *Angew. Chem.* **2003**, *115*, 2591 – 2593; *Angew. Chem. Int. Ed.* **2003**, *42*, 2487 – 2489, and references therein.
[6] During our study, a formal total synthesis of (±)-podophyllotoxin was reported in which a Heck reaction was used for an intramolecular arylation: F. Mingoia, M. Vitale, D. Madec, G. Prestat, G. Poli, *Tetrahedron Lett.* **2008**, *49*, 760 – 763.
[7] a) K. Kondo, F. Mori, *Chem. Lett.* **1974**, 741 – 742; b) F. Ishibashi, E. Taniguchi, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4361 – 4366.
[8] C. Gnamm, S. Förster, N. Miller, K. Brödner, G. Helmchen, *Synlett* **2007**, 790 – 794.
[9] a) D. Stadler, T. Bach, *Chem. Asian J.* **2008**, *3*, 272 – 284; b) D. Stadler, F. Mühlthau, P. Rubenbauer, E. Herdtweck, T. Bach, *Synlett* **2006**, 2573 – 2576; c) F. Mühlthau, D. Stadler, A. Goeppert, G. A. Olah, G. K. S. Prakash, T. Bach, *J. Am. Chem. Soc.* **2006**, *128*, 9668 – 9675.
[10] P. Rubenbauer, T. Bach, *Tetrahedron Lett.* **2008**, *49*, 1305 – 1309.
[11] For recent reviews on iron catalysis, see: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217 – 6254; b) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363 – 3367; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317 – 3321.
[12] P. Rubenbauer, T. Bach, *Adv. Synth. Catal.* **2008**, *350*, 1125 – 1130.
[13] Besides the thermodynamic preference for the formation of isomer **8** with a pseudoequatorial aryl group at C1, the higher nucleophilicity of the trimethoxyphenyl group may favor attack at the activated aldehyde carbon atom.
[14] a) H. A. Dieck, R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 1133 – 1136; b) R. F. Heck, *Org. React.* **1982**, *27*, 345 – 390; c) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009 – 3066; d) K. Olofsson, H. Sahlin, M. Larhed, A. Hallberg, *J. Org. Chem.* **2001**, *66*, 544 – 549.
[15] For the synthesis of (−)-4-deoxy-4-methylenepodophyllotoxin (**9**) from (−)-podophyllotoxin, see: E. Roulland, P. Magiatis, P. Arimondo, E. Bertounesque, C. Monneret, *Bioorg. Med. Chem.* **2002**, *10*, 3463 – 3471.
[16] a) Y. Okude, S. Hirano, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1977**, *99*, 3179 – 3181; b) T. Hiyama, K. Kimura, H. Nozaki, *Tetrahedron Lett.* **1981**, *22*, 1037 – 1040; c) G. C. Hargaden, P. J. Guiry, *Adv. Synth. Catal.* **2007**, *349*, 2407 – 2424; d) R. L. Halterman, C. Zhu, *Tetrahedron Lett.* **1999**, *40*, 7445 – 7448.
[17] For the synthesis of (−)-podophyllotoxon from (−)-podophyllotoxin, see: P. H. Höfert, R. Matusch, *Helv. Chim. Acta* **1994**, *77*, 771 – 777.
[18] H. Yamaguchi, M. Arimoto, S. Nakajima, M. Tanoguchi, Y. Funaka, *Chem. Pharm. Bull.* **1986**, *34*, 2056 – 2060.

