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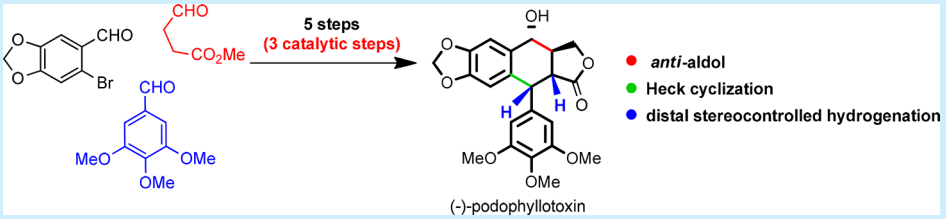
Catalytic Enantioselective Synthesis of (−)-Podophyllotoxin

Saumen Hajra,*[,†] Sujay Garai,[†,‡] and Sunit Hazra[‡,§]

[†]Centre of Biomedical Research (CBMR), Sanjay Gandhi Postgraduate Institute of Medical Sciences Campus, Raebareli Road, Lucknow 226014, UP, India

[‡]Department of Chemistry, Indian Institute of Technology Kharagpur (IIT Kharagpur), Kharagpur 721302, WB, India

Supporting Information



ABSTRACT: The first catalytic enantioselective total synthesis of (−)-podophyllotoxin is accomplished by a challenging organocatalytic cross-aldol Heck cyclization and distal stereocontrolled transfer hydrogenation in five steps from three aldehydes. Reversal of selectivity in hydrogenation led to the syntheses of other stereoisomers from the common precursor.

Podophyllotoxin **1** and its natural analogues (Figure 1) isolated from *Podophyllum* species have been extensively studied over the last two centuries for their significant biological profile and structural diversity.[1] This bioactive molecule is used for the treatment of genital warts and serves as a synthetic precursor for the chemotherapeutic drugs etoposide **2a** and teniposide **2b**, widely used as type II topoisomerase inhibitors for the treatment of testicular and lung cancer, leukemia, lymphoma, and Kaposi's sarcoma.[2] In addition, the natural isomeric lignans of **1** exhibit important bioactivities. The IGF-1R inhibitory molecule picropodophyllin **4** exhibits strong activity toward hepatocellular carcinoma, chemoresistant ovarian cancer cells, Ewing's sarcoma cells, and human lung cancer cell lines.[3] SAR studies and structural modification of **1** has produced other potent drugs. Thus, there have been constant efforts from synthetic chemists for the asymmetric synthesis of these compounds for the last 60 years.[4,5] In 1988, the first asymmetric total synthesis of **1** was reported by Meyer's group in 24 steps.[5a] Since then, several elegant strategies have been developed for its asymmetric synthesis involving either chiral auxiliary, chiral pool, or resolution strategies.[5b−h] However, the catalytic and enantioselective concise total synthesis of **1** has so far remained an unmet challenge. Herein, we report the first catalytic enantioselective synthesis of (−)-podophyllotoxin **1**, (−)-isopodophyllotoxin **1′**, (−)-picropodophyllin **4**, (+)-isopicropodophyllin **3′**, (+)-isopicropodophyllone **3**, and a formal total synthesis of (+)-podophyllotoxin **ent-1** from a common intermediate.

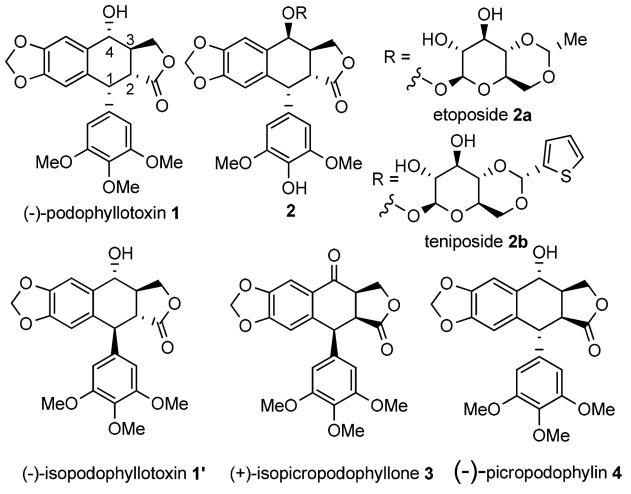


Figure 1. (−)-Podophyllotoxin and its stereoisomeric compounds.

Construction of a general backbone to access different stereoisomeric compounds is strategically attractive but synthetically challenging. Our primary goal was to achieve a common intermediate that will later be diversified to access different isomeric aryl tetralin lignans. Podophyllotoxin **1** bears four contiguous stereocenters with the relative stereochemistry of $cis_{1,2}$-$trans_{2,3}$-$trans_{3,4}$. We proposed the structure of an enantiopure dihydronaphthalene **5** as a common intermediate and hypothesized that it might undergo distal stereocontrol hydrogenation, governed by the C4-OR stereochemistry, and lead to **1** (Scheme 1), whereas proximal stereocontrol by the lactone methylene unit during hydrogenation was anticipated to provide isopicropodophyllin *viz*. **3**. The intermediate **5** could easily be synthesized from lactone **6**, which could be obtained by the *anti*-aldol reaction of 6-bromopiperonal **7** and methyl 4-oxobutanoate **8** followed by the chemoselective reduction−lactonization.

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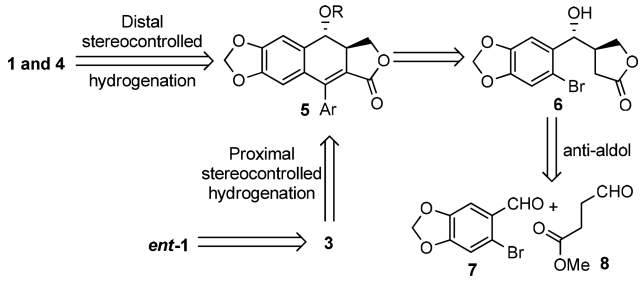
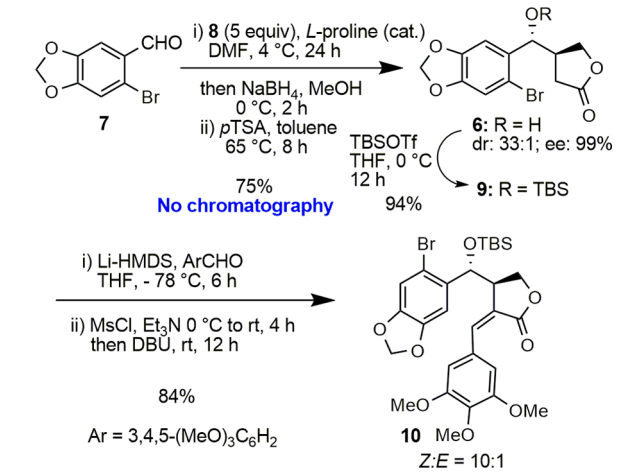
Scheme 1. Unified Retrosynthesis of (−)-Podophyllotoxin and Its Isomers



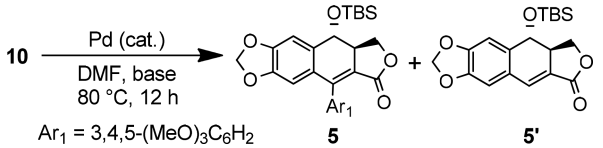
In our previous report, we observed that organocatalytic cross aldol reaction with electron-rich aldehyde was difficult to achieve.[6] Further, the scarcity of literature reports on the same made our synthesis tougher.[6b,7] Initially we found the aldol reaction of piperonal gave only a trace amount of the aldol product; however, the use of 6-bromopiperonal gave the desired lactone with low yield (20%) but with excellent selectivity (dr 24:1, ee 95%).[6c] The self-aldol reaction of **8** was found to be the major factor behind this low yield of the attempted cross-aldol reaction. Any attempt to match the reactivity between **7** and **8** was not successful. Finally, the use of excess (5 equiv) donor aldehyde **8** (which is in contrary to traditional organocatalytic aldol procedure) and its portionwise addition helped to achieve lactone **6** in 1 g scale with high yield (75%) and excellent selectivity (dr 33:1, ee 99%; Scheme 2).

Scheme 2. Synthesis of *Z*-Benzylidene Lactone 10



The choice of protecting group was crucial for our synthesis as it would later direct the distal stereoselectivity. Among different protecting groups, we found TBSOTf in THF was the most effective one. The Li-HMDS-mediated second aldol reaction of **9** with 3,4,5-trimethoxybenzaldehyde and subsequent treatment of the crude aldol adduct with MsCl and base produced the corresponding *Z*-benzylidene lactone **10** as a major diastereoisomer. Next, we examined the conditions for intramolecular Heck reaction (Table 1).[8] The presence of a substantially bulky *ortho*-substitution of bromoarene and the conformationally congested tethered trisubstituted *Z*-alkene made the attempted Heck reaction quite challenging. Desilylated **10** during the Heck coupling provided either a naphthalene derivative as a major product or a complex reaction mixture. Among different Pd catalysts employed,

Table 1. Optimization for Intramolecular Heck Reaction[a]



entry	catalyst	ligand	base	yield (%) 5	yield (%) 5′
1	$Pd(OAc)_2$	Ph_3P	TEA	15	nd
2	$PdCl_2PPh_3$	Ph_3P	K_2CO_3		
3	Pd_2dba_3	none	TEA	22	21
4	Pd_2dba_3	none	DIPEA	34	22
5	Pd_2dba_3	Ph_3P	DIPEA	61	12
6	Pd_2dba_3	Ar_3P	DIPEA	67	7
7[b]	Pd_2dba_3	Ar_3P	DIPEA	84	5
8[c]	**Pd_2dba_3**	**Ar_3P**	**DIPEA**	**84**	**5**

[a]Conditions: 0.05 g of substrate **10** in 0.5 mL of DMF, 20 mol % of catalyst, 2 equiv of base, ligand (2 × catalyst mol %). [b]10 mol % of catalyst used. [c]5 mol % of catalyst used. Ar_3P = tri(*o*-tolyl)phosphine.

Pd_2dba_3 was found to be the most effective one. Reaction without any ligand produced the desired product **5** in low yield along with the C1 dearylated Heck product **5′** (Table 1, entries 3−4). Gratifyingly, the use of a suitable ligand and base produced **5** as the major product and the suppression of catalyst loading gave better yield by inhibiting the side products formation (entries 6−8).

The final crucial step of our synthetic strategy was the stereocontrolled reduction of **5**. To achieve this, we attempted a Pd/C catalyzed hydrogenation. Reaction in MeOH showed the high proximal selectivity providing **12** (entry 1, Table 2). Variation in the solvent, catalyst, and temperature had little effect on the proximal selectivity. Bulky catalysts such as $RhCl(PPh_3)_3$ and $[Ir(cod)(PCy_3)(py)]PF_6$ produced no reaction (See SI for details). Thus, it was quite challenging to get the distal stereocontrol product **11**. However, catalytic transfer hydrogenation (CTH)[9] with HCO_2NH_4 in MeOH was quite interesting and provided better distal selectivity (entry 5 vs entry 1, Table 2). This led us to study the effect of solvent in CTH. Delightfully, we observed a linear correlation of distal selectivity with the increase in linear chain length of primary alcohols (entries 5−10 and Figure 2). Ultimately, we achieved higher distal stereocontrol effect over proximal effect with HCO_2Na in 1-pentanol (entry 14). This is the first report of selectivity switching by using solvent dependent substrate stereocontrolled CTH (entry 14 vs entry 5). A controlled amount of added water in HCO_2Na-mediated CTH was found to be very crucial for the reaction and the distal selectivity, as there was no reaction without water and excess water lowered the selectivity (entry 15).

The above observations indicated a probable coordination of solvent with Pd catalyst (Scheme 3). This coordination, in turn, generated a bulky solvent coordinated active catalytic species **C**, which is responsible for the increase in distal selectivity. This mechanism is in line with the CTH mechanism proposed by the Elsevier and Cazin groups.[9c−e] When the CTH was performed in CD_3OD a substantial amount of deuterium incorporation was observed in **11**/**12** (see the SI for details). The abundance ratios of D-H and H−H insertion in **11**/**12** were 1.01 and 1.52, respectively (Scheme 3).

The lower value of D-incorporation or, in other words, the higher value of dihydrogen insertion in the case of HCO_2NH_4

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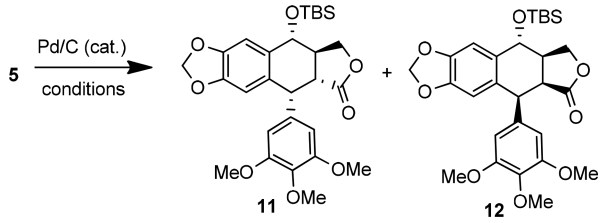
Table 2. Catalytic Hydrogenation of Compound 5 (Selected Optimization Conditions)[a]



entry	solvent	H source	temp (° C)	time (h)	11/12[b]
1	MeOH	H_2/1 atm	27	12	1:10
2	EtOH	H_2/1 atm	27	12	1:1.7
3	*n*-propanol	H_2/1 atm	27	12	1:10
4	toluene/EtOH	H_2/1 atm	27	12	1:2.5
5	MeOH	HCO_2NH_4	40	6	1:3
6	EtOH	HCO_2NH_4	40	6	1:1.5
7	1-propanol	HCO_2NH_4	40	6	1:1.5
8	1-butanol	HCO_2NH_4	40	6	1:1.4
9	1-pentanol	HCO_2NH_4	40	6	1:1
10	1-hexanol	HCO_2NH_4	40	6	1:1
11	2-propanol	HCO_2NH_4	40	6	1:2.5
12[c]	1-pentanol	HCO_2NH_4	40	6	1.2:1
13[d]	1-pentanol	HCO_2Na	40	12	1.5:1
14[e]	**1-pentanol**	**HCO_2Na**	**40**	**12**	**1.5:1**
15[f]	1-pentanol	HCO_2Na	40	12	1.15:1

[a]Conditions: 0.02 g of substrate **5** in 1 mL solvent, 20% catalyst (by wt.), 30 equiv formate. [b]Determined by the ^{1}H NMR analysis of the crude reaction mixture. [c]1-pentanol/H_2O (5:1) used. [d]10 equiv H_2O used. [e]20 equiv H_2O used. [f]30 equiv H_2O used.

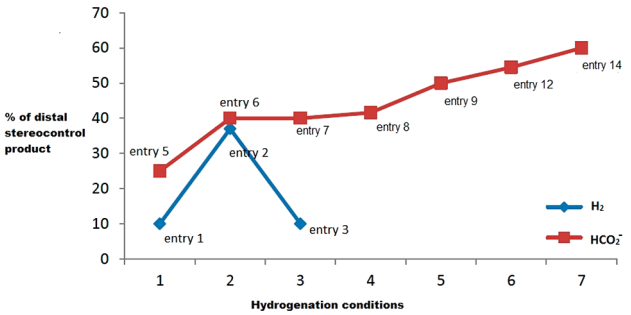
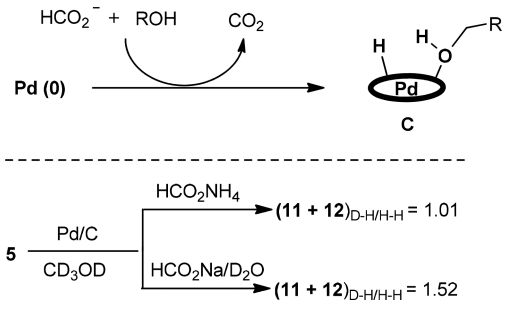


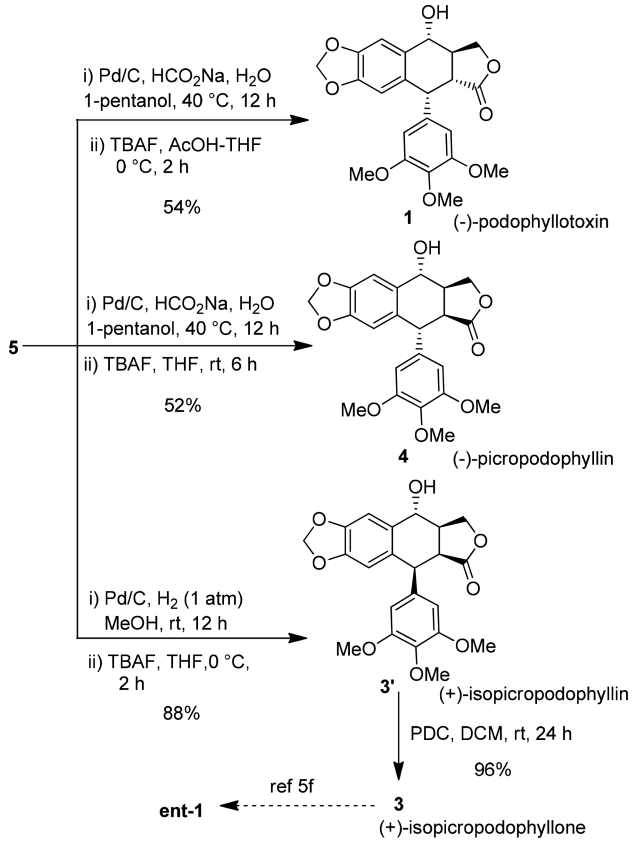
Figure 2. Graphical presentation for the comparison of distal selectivity between CTH and hydrogenation.

Scheme 3. Plausible Mechanism for the Effect of ROH in CTH



indicates the possibility of a competing H-transfer from NH_4^+ vs CD_3OD. This deuterium incorporation further confirmed that one of the H-transfers takes place from the ROH which probably coordinates with the catalyst. Thus, Pd/C-catalyzed distal stereocontrolled hydrogenation of **5** with HCO_2Na in 1-pentanol followed by TBS deprotection of the crude reduced product with TBAF−AcOH accomplished the total synthesis of (−)-podophyllotoxin **1** in 27% overall yield over five steps (Scheme 4). The spectral and analytical data of the synthesized

Scheme 4. Total Synthesis of (−)-Podophyllotoxin, (−)-Picropodophyllin, (+)-Isopicropodophyllin, and (+)-Isopicropodophyllone



compound **1** was in good agreement with that of the natural product.[5d,h] Desilylation of the crude hydrogenated product obtained from **5** with TBAF instead of TBAF-AcOH at room temperature gave directly (−)-picropodophyllin **4** in good yield via in situ isomerization at C2. Pd/C-catalyzed proximal stereocontrolled hydrogenation with hydrogen (H_2 balloon) in MeOH followed by sequential TBAF mediated desilylation of **5** afforded the (+)-isopicropodophyllin **3′**. PDC oxidation of **3′** completed the total synthesis of another natural product, (+)-isopicropodophyllone **3**. The synthesized **3** can easily be transformed to **ent-1** following the steps reported in the literature[5f] completing a formal total synthesis of (+)-podophyllotoxin (Scheme 4). Hence, changing our chiral catalyst to D-proline would lead to (−)-podophyllotoxin **1** with high diastereoselectivity via the isopicropodophyllone intermediate.

As an appended application, we also investigated the reductive Heck reaction of **10** instead of the two-step Heck reaction and hydrogenation sequence. Surprisingly, compound **10** did not respond to the reductive Heck reaction, but after desilylation, it responded to the Pd_2dba_3 catalyzed reductive Heck reaction with sodium formate and afforded (−)-isopodophyllotoxin **1′** in good yield (64%; Scheme 5).

In conclusion, the first catalytic enantioselective total synthesis of (−)-podophyllotoxin has been accomplished in

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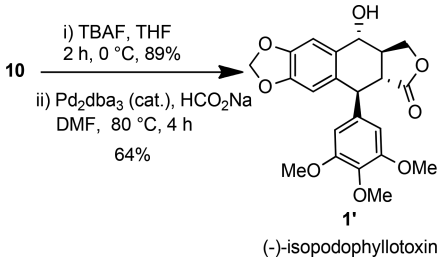
Scheme 5. Total Synthesis of (−)-Isopodophyllotoxin



only five steps starting from commercially available 6-bromopiperonal with an overall yield of 27% and 99% of ee, along with the total synthesis of (−)-picropodophyllin, (−)-isopodophyllotoxin, (+)-isopicropodophyllin, and (+)-isopicropodophyllone and a formal total synthesis of (+)-podophyllotoxin. The hydrogenation studies reported herein imply that even with the same catalyst, distal and proximal stereoselectivity can be achieved by altering the hydrogen source and solvent. The advantage of our strategy lies in the utilization of three catalytic steps out of five steps employed as well as in use of the common intermediate to synthesize other stereoisomers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03236.

Experimental details for all reactions and analytic details for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: saumen.hajra@cbmr.res.in. Fax: (+91)-522-2668995. Tel: (+91)-522-2668861.

ORCID

Saumen Hajra: 0000-0003-0303-4647

Present Address

§(S.H.) Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 5650871, Japan

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Professor Tarun K. Sarkar (former Professor of Chemistry, IIT Kharagpur) on the occasion of his 70th birthday.

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